NATIONAL PROTOCOLS
for
Adult Hematological Malignancies and Bone Marrow Transplantation

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ABBREVIATIONS

aGVHD	Acute Graft Versus Host Disease
AIHA	Autoimmune Hemolytic Anemia
AITL	Angioimmunoblastic T-Cell Lymphoma
ALCL	Anaplastic Large-Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
ALL	Acute Lymphoblastic Leukemia
ALLO-HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
Allo-SCT	Allogeneic Stem Cell Transplantation
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplantation
BL	Burkitt's Lymphoma
BM	Bone Marrow
BMA	Bone Marrow Aspiration
BMT	Bone Marrow Transplantation
BSC	Best Supportive Care
BTM	B-thalassemia major
BV	Brentuximab Vedotin
CBC	Complete Blood Count
CCyR	Complete Cytogenetic Response
cGVHD	Chronic Graft Versus Host Disease
cHL	Classical Hodgkin's Lymphoma
CHR	Complete Hematologic Response
CID	Congenital Immunodeficiency Diseases
CLL	Chronic lymphatic leukemia
CML	Chronic Myeloid Leukemia
CMML	Chronic Myelomonocytic Leukaemia
CNS	Central Nervous System
CR	Complete Remission
CR1	First Complete Remission
CR2	Second Complete Remission
CSA	Cyclosporine-A
CSF	Cerebrospinal Fluid
CSFs	Colony Stimulating Factors
CT	Computerized Tomography
Cy	Cyclophosphamide
DLBCL	Diffuse Large B-Cell Lymphoma
EATL	Enteropathy-Associated T-Cell Lymphoma
EBMT	European Group for Blood and Marrow Transplantation
ECG	Electrocardiogram

ELN	European Leukemia Net
ENKTCL	Extranodal Natural Killer/T-Cell
ESA	Erythropoiesis-Stimulating Agents
ESR	Erythrocyte Sedimentation Rate
ET	Essential Thrombocytosis
FA	Fanconi's Anemia
FDP	Fibrinogen Degradation Product
FFP	Fresh Frozen Plasma
FISH	Fluorescence in Situ Hybridization
FLC	Free Light Chain
FLIPI	Follicular Lymphoma International Prognostic Index
FN	Febrile Neutropenia
FNA	Fine-Needle Aspiration
FU	Fluorouracil
GCB	Germinal Center B-Cell
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GS	Gleason Score
GVHD	Graft Versus Host Disease
H.S.	Herpes Simplex
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCL	Hairy Cell Leukemia
HCT	Hematocrit
HCV	Hepatitis C Virus
HD	Hodgkin's Disease
HDT/ASCT	High-Dose Therapy/Autologous Stem Cell Transplantation
HLA	Human Leukocyte Antigen
HLH	Hemophagocytic Lymphohistocytosis
HSTCL	Hepatosplenic T-Cell Lymphoma
HU	Hydroxyurea
IMD	Inherited Metabolic Disorders
IPSS	International Prognostic Scoring System
ISRT	Involved-Site Radiation Therapy
ISS	International Staging System
IT	Intrathecal Therapy
ITP	Immune Thrombocytopenia
JMML	Juvenile Myelomonocytic Leukemia
KFT	Kidney Function Test
LBL	Lymphoblastic Lymphoma
LDH	Lactate Dehydrogenase
LDT	Lymphocyte Doubling Time

LFT	Liver Function Test
LN	Lymph Node
LP	Lumbar Puncture
LPL	Lymphoplasmacytic Lymphoma
LV	Leucovorin
MALT	Mucosa-Associated Lymphoid Tissue
MCL	Mantle Cell Lymphoma
mCRC	Metastatic Colorectal Cancer
MCyR	Major Cytogenetic Response
MDS	Myelodysplastic Syndrome
minCyR	Minimal Cytogenetic Response
MM	Multiple Myeloma
MMR	Major Molecular Response
MPNs	Myeloproliferative Neoplasms
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MUD	Matched Unrelated Donor
MZL	Marginal Zone Lymphomas
NHL	Non-Hodgkin Lymphoma
NMZL	Nodal MZL
noCyR	No Cytogenetic Response
NOS	Not Otherwise Specified
PB	Peripheral Blood
PB/BM	Peripheral Blood/Bone Marrow
PBSC	Peripheral Blood Stem cell
PCP	Pneumocystis Pneumonia
PCyR	Partial Cytogenetic Response
PET	Positron Emission Tomography
PMBL	Primary Mediastinal Large Lymphoma
PMF	Primary Myelofibrosis
PR	Partial Remission
PRCA	Pure Red Cell Aplasia
PT	Prothrombin Time
PTCLs	Peripheral T-Cell Lymphomas
PV	Polycythemia Vera
RA	Refractory Anemia
RAEB	Refractory Anemia with Excess Blasts
RARS	Refractory Anemia with Ringed Sideroblasts
RBC	Red Blood Cell
RCMD	Refractory Cytopenia with Multilineage Dysplasia
R-ISS	Revised International Staging System
RT	Radiation Therapy
RT-PCR	Real Time-Polymerase Chain Reaction
SAA	Severe Aplastic Anemia
SLL	Small Lymphocytic Lymphoma

SMZL	Splenic MZL
TBI	Total Body Irradiation
TKI	Tyrosine Kinase Inhibitors
TLC	Total Leukocyte Count
TLS	Tumor Lysis Syndrome
TRAP	Tartrate-Resistant Acid Phosphatase
WBC	White Blood Cell
WHO	World Health Organization

1. CHRONIC MYELOID LEUKEMIA (CML)

Evaluation at diagnosis

1. Complete blood and differential counts
2. Bone marrow aspiration
3. Conventional BM cytogenetic study
4. Quantitative FISH study for Philadelphia chromosome
5. Quantitative real-time RT-PCR study for bcr/abl:abl ratio
6. Biochemical studies: Liver and kidney functions, serum uric acid
7. HLA typing for patients less than 20 years old with good EBMT score

Phases of CML

- Chronic phase: PB/BM blasts <10%

	Accelerated Phase (AP)	Blast Phase (BP)
Blast%	10-19%	≥ 20%
Others	PLT <100 x 10^9/L* or >1000 x 10^9/L**	Extra-medullary involvement
	CCA/Ph+*** on ttt	

* Unrelated to therapy
** Unresponsive to therapy
***CCA/Ph+ = Clonal Chromosome Abnormalities in Ph+ cells

Definitions of responses in CML patient

1. Complete Hematologic response (CHR): WBC<10 X10^9/L; basophils <5%; absence of myelocytes, promyeloctes and myeloblasts in differential count; PLT <450 X109/L; and nonpalpable spleen
2. Cytogenetic responses:
   - Complete cytogenetic response (CCyR): no Ph+ metaphase
   - Partial cytogenetic response (PCyR): 1-35% Ph+ metaphases
   - Major cytogenetic response (MCyR): 0-35% Ph+ metaphases (CCyR + PCyR)
   - Minor cytogenetic response (mCyR): 36-65 Ph+ metaphases
   - Minimal cytogenetic response (minCyR): 66-95 Ph+ metaphases
   - No cytogenetic response (noCyR): >95 Ph+ metaphases
3. Molecular responses:
   - Major molecular response (MMR): Ratio of bcr-abl to abl (by QRT-PCR) < 0.1%
   - Deep MR: MR4.0 (0.01%), MR4.5 (0.0032%), MR5 (0.001%)
   - Molecularly undetectable leukemia (previously known as complete molecular response): with specification of the number of the control gene transcript copies and assay sensitivity.

Therapy for Chronic Phase

Initial treatment with Hydroxyurea to reduce the TLC till the availability of imatinib therapy and cytogenetic results

First Line Therapy for CML-CP

1. IMATINIB

Dose: 400 mg once daily PO lifelong (for responding patients)

Duration of Imatinib therapy

Currently, it is recommended that a patient with CML who is tolerating well and responding optimally to imatinib treatment continues indefinitely, at the standard recommended dose.

Eligibility Criteria for Imatinib first-line therapy

ALL OF THE FOLLOWINGS:

1. Chronic myeloid leukemia
2. Philadelphia chromosome (by conventional cytogenetic study and/or FISH)
3. First chronic phase of disease
4. Age: All patients above 16 years
5. Female in the child bearing period should use a contraceptive method

2. NILOTINIB (FIRST-LINE)

MOH Approved

Dose: 300 mg twice daily PO lifelong (for responding patients)

A panel of 10 expert hematologists from different sites:
Nilotinib 1st line treatment for CP-CML: 600 mg (300 X2)
For any of the following

1. All patients with age <45 years
2. Females in childbearing age wishing for future pregnancies
3. Patients in accelerated phase
4. Patients with high-risk score (Sokal/EUTOS).

STUDIES TO BE DONE TO EVALUATE THE RESPONSE TO IMATINIB THERAPY (ELN 2013)

1. CBC every month till CHR then every 2-3 months thereafter.
2. Conventional BM cytogenetic study (% of Ph chromosome) at 3rd and 6th month then every 6 months till achievement of CCyR, then only in the case of suspected disease progression.
3. Quantitative real-time RT-PCR study for *bcr/abl: abl* ratio every 3 months till the achievement of MMR; then every 6 months.
4. **FISH** is not generally recommended to monitor patients.
5. Mutation analysis in case of treatment failure or disease progression.

CRITERIA OF OPTIMAL RESPONSE TO IMATINIB FIRST-LINE THERAPY (ELN GUIDELINES 2013)

Continue imatinib if:

- At third month: Ph+ ≤35% (MCyR) and/or BCR-ABL ≤ 10%.
- At 6th month: Ph + 0% (CCyR) and/or BCR-ABL < 1%, and/or
- At 12th month: BCR-ABL ≤ 0.1% (MMR)
- Then at any time: BCR-ABL1 ≤ 0.1% (MMR)

CRITERIA OF "WARNING" TO IMATINIB FIRST-LINE THERAPY (ELN GUIDELINES 2013)

Continue imatinib with more frequent monitoring (every 1-2 months) if:

At third month: Ph+ 36-95% (m/minCyR) and/or BCR-ABL > 10%.

At 6th month: Ph + 1-35% (PCyR) and/or BCR-ABL=1-10%.

At 12th month: BCR-ABL= 0.1-1%.

Then at any time: Clonal cytogenetic abnormalities in Ph- cells (CCA/Ph-): -7, or 7q.

2nd line Therapy of imatinib refractory patients (resistant/intolerant)

DEFINITION OF IMATINIB REFRACTORINESS

- **Imatinib resistance:** failure to achieve or loss of previously achieved milestones of response to imatinib therapy (see above)
- **Imatinib intolerance:** inability to tolerate adequate dose of imatinib due to persist G3/4 toxicities

CRITERIA OF FAILURE OF RESPONSE TO IMATINIB THERAPY AND NEED TO SHIFT TO SECOND-LINE THERAPY (ELN GUIDELINES 2013)

Shift to second-line TKI if at:

- **Third month of imatinib therapy**: Non CHR, and/or Ph+ > 95% (noCyR).
- **6th month of imatinib therapy:** Ph + > 35% (<PCyR) and/or BCR-ABL> 10%.
- **12th month of imatinib therapy:** Ph + > 0 (<CCyR) and/or BCR-ABL >1%.
- **Then at any time:**
  - Loss of CHR/CCyR
  - Confirmed loss of MMR: in two consecutive tests, of which one with BCR ABL ≥1%
  - Mutations
  - CCA/Ph +

STUDIES TO BE DONE BEFORE SECOND-LINE

1. Complete blood and differential counts
2. Bone marrow aspiration (? phase of disease)
3. Conventional BM cytogenetic study
4. Quantitative real-time RT-PCR study for bcr/abl:abl ratio
5. Biochemical studies: Liver and kidney functions, serum uric acid
6. Mutation analysis
   a. Mutations resistant to nilotinib: Y253H, F359C/V, V379I, E255K/V
   b. Mutations resistant to Dasatinib: F317L, V299L, Q252H.
   c. Mutations resistant to both drugs: T315I (indicated for BMT only)
7. ECG (sp. QT interval), echocardiography, chest X-ray (to exclude pleural effusions)
8. HLA typing for transplant-eligible patients

DRUGS USED FOR 2ND LINE THERAPY IN CHRONIC PHASE

1. Nilotinib 400 mg BID (Avoid food 2 hours before and 1 hour after a dose).
2. *Dasatinib 100 mg daily (no effect of food).*

CHOICE OF 2ND LINE THERAPY

Both are MOH approved

	Nilotinib 400 X2	Dasatinib 100 X1
Avoid with	• Uncontrolled DM • Hx of pancreatitis • Hepatic disease, • PAD	• Lung disease (Asthma, COPD) • GIT bleeding • CHF
Resistant mutations	Y253H; F359C/V; V379I; E255K/V	F317L; V299L; Q252H
Patient preference	Twice per day on an empty stomach.	Once per day

DURATION OF 2ND LINE THERAPY

Currently, it is recommended that a patient with CML who is tolerating well and responding optimally to second-line TKIs treatment continues indefinitely, at the standard recommended dose.

CRITERIA OF RESPONSE TO 2ND LINE THERAPY IN CHRONIC PHASE

EVALUATION TIME (MONTHS)	RESPONSE		WARNING
	SUBOPTIMAL	FAILURE	
Baseline	NA	NA	• Hematologic resistance to Imatininb • CCA/Ph+ • Mutations poorly sensitive to TKIs
3	Minor CgR (Ph+ 36-65%)	• No CgR (Ph+>95%) • New mutations	Minimal CgR (Ph+ 66-95%)
6	PCgR (Ph+ 1-35%)	• Minimal CgR (ph+ 66-95%) • New mutations	Minor CgR (Ph+ 36-65%)
12	Less than MMolR	• Less than PCgR (Ph+>35%) • New mutations	

Discontinuation of TKI therapy

Outside Clinical trials, Consider Stopping TKI After Full discussion and understanding of the patient **ONLY IF ALL THE FOLLOWING** 10 Criteria and pre-requisites are fully satisfied:

Patient/disease

1. Age **≥18** years.
2. **CP-CML**: No prior history of AP or BP-CML.
3. **No history of resistance** to any TKI.

Laboratory

5. Prior evidence of quantifiable BCR-ABL1 transcript.
6. **Access to a reliable QPCR test** with a sensitivity of detection of **≥4.5 logs** that reports results on the IS and provides results **within 2 weeks.**
7. **Stable molecular response (MR^4 ; ≤0.01%^{IS})** for **≥2 years**, as documented on **at least four tests**, performed **at least three months** apart.
8. **Monthly molecular monitoring** for the first 6 months following discontinuation, **bimonthly** during months 7–24, and **quarterly** thereafter (indefinitely) for patients who **remain in MMR** (MR3; ≤0.1% IS).

Drug

4. On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for ≥ 3 years

9. Reporting any

- **Significant AE** related to treatment discontinuation, including TKI withdrawal synd.
- **Progression** to AP or BP-CML

10. Resumption of TKI, for patients with a loss of MMR:

- With a **monthly** molecular monitoring for the first 6 months following resumption of TKI and **every 3 months** thereafter (indefinitely).
- **For those who fail to achieve MMR after six months of TKI resumption**, mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 ms.

Take in consideration that ~50% of patients discontinuing TKI therapy will suffer from loss of response (MMR) and should re-initiate TKI therapy

Therapy for accelerated and blastic phases (ELN 2013)

AP and BP	THERAPY
In newly diagnosed, **TKI naïve** patients	• Imatinib 800 mg daily, or dasatinib 140 mg. • Then, allo-SCT is recommended for **all BP** patients and for the **AP patients who do not achieve** an optimal response. • Chemotherapy may be required before allo-SCT, to control the disease
As a progression from CP, in **TKI pretreated** patients	• Any TKI that were not used before progression • Chemotherapy is frequently required to make patients eligible to allo-SCT. • Then allo-SCT in all patients (except resistant BP).

Overall indications for BMT for CML

Time	Indications for Allo-HSCT
At diagnosis	Presenting in AP or BP (Pretreatment with a TKI is recommended.)
At time of Imatinib Failure	1. Progression to AP or BP (pretreatment with a second-generation TKI is recommended) 2. Carrying the T315 I mutation
Failure with 2nd generation TKI	In all patients

ALLO-HSCT IS APPLIED ONLY TO PATIENTS WHO:

1. By age and health conditions, are considered eligible for Allo-HSCT, with
2. Standard or myeloablative procedures
3. EBMT risk score ≤ 2
4. Have an HLA-identical sibling.

EBMT risk score:

- **1 point for each:** matched unrelated donor (MUD), AP, age 20-40 yr, male recipient/female donor, time from diagnosis to BMT >1year
- **2 points for each:** ABC/higher CP, age >40 years

CML and Pregnancy

Situation	Recommendations
At diagnosis	• Female patient in the childbearing period→ effective contraception should be suggested
Conception should be only scheduled	• After achievement of a sustained ≥ MMR for ≥ 2 years • Discontinue TKI at the end of menstrual cycle
Monitoring during TKI discontinuation	• Proper, high quality monthly monitoring by RQ-PCR
Further therapy in pregnancy	• If remains in MMR/CMR→ No treatment • If RQ-PCR starts to rise → non-pegylated IFN* in 2nd trimester (PEG-IFN is less safe during pregnancy), • In 3rd trimester: Imatinib and nilotinib (and HU) can be used (limited placental transfer) • Dasatinib should not be used all through the pregnancy
After delivery	• Stop breast feeding **3-5 days before restarting imatinib**

*3-5 MIU/m2 every other day

2. CHRONIC LYMPHATIC LEUKEMIA (CLL) AND SMALL LYMPHOCYTIC LYMPHOMA (SLL)

Minimal Initial Diagnostic Work-up of CLL/SLL

1. Complete blood counts.
2. LFTs, KFTs, uric acid.
3. Bone marrow aspiration and biopsy.
4. BM or Pb Immunophenotyping.
5. Cytogenetic analysis (conventional & FISH).
6. Hemolytic screen: reticulocytic count, LDH, direct Coombs test, serum haptoglobin.
7. LN biopsy and immunohistochemistry (in case of SLL).
8. Viral Screen for HBV and HCV.

Criteria to start treatment

(1) A minimum of any one of the following ***disease-related symptoms*** must be present:

A) Weight loss ≥ 10 % in less than 6 months.

B) Fever > 38.5^0 C for ≥ 2 weeks.

C) Night sweats. D) Extreme fatigue (cannot perform usual activities).

(2) Progressive ***marrow failure***: development or worsening of anemia (Hb≤ 9 gm/dL) and/or thrombocytopenia (PLT <100 X 10^9/L)

(3) Autoimmune ***hemolytic anemia*** (AIHA) or ***immune thrombocytopenia***: poorly responsive to steroid therapy.

(4) Progressive ***splenomegaly*** (> 6 cm below costal margin)

(5) Massive node clusters or ***progressive lymphadenopathy*** (> 10 cm longest diameter).

N.B.

- ***High lymphocyte count*** as a sole parameter is not an indication to start treatment.
- ***Lymphocyte doubling time (LDT) < 6 months:*** is no more considered as an indication to start treatment.
- Complications like ***hyperviscosity or leukostasis*** are very rare and appear only at counts > 350 X 10^9/l (such a very high count is an indication to treat).

Treatment options for CLL/SLL:

Age	Treatment (if indicated)
>65	**First line regimens:** • ***Chlorambucil (Clb) ± steroid*** (only if AIHA or immune thrombocytopenia) or • ***Chlorambucil + Rituximab (Clb-R)*** every 3-4 w is an option according to local institutional guidelines • **COP (CVP) regimen** every 3w or • **CHOP regimen** every 3w Therapy is given till CR or a maximum response for a **max of 6 cycles.** **Second line regimens:** If progression occurs: • In >24 months → repeat the 1st line. • In <24 months →use alternative 1st regimens

Age	Treatment (if indicated)
Age ≤ 65	**First line regimens** • ***FCR regimen (if CD 20+)*** every 21-28 days or • ***FC regimen*** every 21-28 days or • ***CHOP regimen*** every 3 weeks or • ***R-CHOP regimen (if CD 20+)*** every 3 weeks Therapy is given till CR or a maximum response for **a max of 6 cycles** **Second line regimens** If progression occurs: • In >12 months → repeat the 1st line. • In <12 months → use the alternative1st regimens*: o R-Bendamustine (BR): every 28 days o DHAP: every 21 days o ICE: every 21 days o Gem-P: every 21 days o GDP: every 21 days o GV: every 21 days o GEM-OX: every 14 days Therapy is given till CR or a maximum response for a **max of 6 cycles**

FIRST-LINE REGIMENS FOR CLL/SLL

- **FCR regimen:** fludarabine 30 mg/m²/d (D 1-3), cyclophosphamide 300 mg/m²/d (D 1-3), Rituximab: Cycle 1: 375 mg/m2 D1, Cycles 2-6: 500 mg/m² D1
- **FC regimen:** fludarabine 30 mg/m²/d (D 1-3), cyclophosphamide 300 mg/m²/d (D 1-3)
- **CHOP regimen:** cyclophosphamide 750 mg /m² IV D1, Adriamycin 50 mg /m2 IV D1, Vincristine 1.4 mg /m² (max 2 mg) IV D1, Prednisone 100 mg PO D1-5.
- **R-CHOP regimen: as CHOP +** Rituximab: Cycle 1: 375 mg/m² D1, Cycles 2-6: 500 mg/m²
- **Clb:** Chlorambucil 0.3 mg/kg for days 1-5 every 21-28 days **± steroid (**only if AIHA or immune thrombocytopenia)
- **Clb-R:** Chlorambucil 10 mg/m² days 1-7, Rituximab: Cycle 1: 375 mg/m² D1, Cycles 2-6: 500 mg/m² D1
- **COP (CVP) regimen:** cyclophosphamide 750 mg /m² IV D1, Vincristine 1.4 mg /m² (max mg) IV D1, Prednisone 40-60 mg/m² PO D1-5.

SECOND-LINE REGIMENS FOR CLL/SLL

- **BR:** Bendamustine 90 mg/m² days 1-2, Rituximab: Cycle 1: 375 mg/m² D1, Cycles 2-6: 50 mg/m² D1
- **DHAP:** Dexamethasone 40 mg on days 1-4 plus cytarabine 2 g/m² every 12h for 2 doses day 2 plus cisplatin 100 mg/m² on day 1.

- **ICE:**
  - **Option 1:** Ifosfamide 2000 mg/m²/d iv over 2 h d1-3 (hours 0-2); Etoposide 100-150 mg/m²/d iv over 3 hrs after ifosfamide d 1-3 (hours 2-5); Carboplatin (AUC 5, max 800 mg) over 2 h after etoposide D1 only (hours 5-7); Mesna 25% of Ifosphamide dose iv 30 minutes before Ifosfamide, repeat 3, 6 and 9 hrs after Ifosfamide.
  - **Option 2:** Etoposide 100-150 mg/m² IV over 3 hrs Days 1–3; Carboplatin AUC = 5 (max dose 800mg) over 2 h Day 2 and Ifosfamide admixed with mesna both at a dose of 5 gm/m² via 24-hour continuous IV beginning day 2
- **Gem-P:** Gemcitabine 1000 mg/m² on days 1 and 8, cisplatin 100 mg/m² on day 1.
- **GDP:** Gemcitabine 1000 mg/m² on days 1 and 8, dexamethasone 40 mg on days 1-4, cisplatin 75 mg/m² on day 1.
- **GV:** Gemcitabine 1000 mg/m² plus vinorelbine 30 mg/m² on days 1 and 8.
- **GEM-OX:** Gemcitabine 1000 mg/m² plus oxaliplatin 100 mg/m² on day 1.
  Repeat every 14 d.

3. HAIRY CELL LEUKEMIA (HCL)

Minimal Initial Diagnostic Work-up

(1) Complete blood counts
(2) Bone marrow aspiration and biopsy.
(3) Tartrate-resistant acid phosphatase (TRAP) staining.
(4) Immunophenotyping (CD20, CD11c, CD25, CD 103)
(5) Cytogenetic analysis

Management

INDICATIONS FOR TREATMENT

- Hb level <10 gm/dl
- Platelet count < 100,000/ul
- ANC < 1000/ul with recurrent bacteremia or opportunistic infections.
- Symptomatic splenomegaly or lymphadenopathy

LINES OF TREATMENT

- **Cladribine:** (treatment of choice): 0.14 mg/kg SC daily for 5 days (single course) then monthly FU.
- Relapse ≥2 year after Cladribine → repeat cladribine
- **Current indications of splenectomy**:
    a) Massive painful splenomegaly
    b) Failure of Cladribine (<2 years)
- **Pre-splenectomy vaccination** for *Streptococcus pneumoniae, Haemophilus influenzae b (Hib), Neisseria meningitidis.*

4. MULTIPLE MYELOMA (MM)

Minimal Initial Diagnostic Work-up

- **History and physical examination**
- **Blood workup**
  - CBC with differential and platelet counts
  - BUN, creatinine, S. uric acid
  - Electrolytes, calcium/albumin, LDH
  - Serum quantitative immunoglobulins
  - Serum protein electrophoresis and immunofixation
  - β_2-microglobulin
  - Serum free light chain assay
  - 24-hr urinary protein
  - Urinary Bence-Jones protein
  - ESR, CRP
  - Skeletal survey (by plain X-rays)
  - Unilateral bone marrow aspirate and biopsy (with bone marrow IHC or flow cytometry)
  - Bone Marrow Cytogenetics with **FISH** evaluation for **high risk MM:** del17p, t(4;14), t(14;16) and Chromosome 1p abnormalities

Criteria for Diagnosis

INTERNATIONAL MYELOMA WORKING GROUP DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA (2014)

- Clonal **BM plasma cells*** ≥10% or **biopsy-proven bony or extramedullary plasmacytoma***

And

- Any one or more of the following *myeloma defining events:*

Evidence of end organ damage	Any one or more of the following biomarkers of malignancy
• **Hypercalcemia:** serum Ca >1 mg/dL higher than ULN or >11 mg/dL • **Renal insufficiency:** CrCl<40 mL per min† or serum creatinine >2 mg/dL • **Anemia:** Hb>2 g/dL below the lower limit of normal, or Hb <10 g/dL • **Bone lesions:** ≥1 osteolytic lesions on skeletal radiography, CT, or PET-CT**	• **Clonal BM plasma cell*** ≥60% • **Involved: uninvolved serum free light chain (FLC) ratio** ≥100 with involved FLC ≥100 mg/L • **>1 focal lesions** on MRI studies (Each lesion must be ≥5 mm in size).

*Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used

** If BM has <10% plasma cells, >1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

INTERNATIONAL MYELOMA WORKING GROUP DIAGNOSTIC CRIT FOR SMOULDERING MULTIPLE MYELOMA (2014)

Both criteria must be met:

- **Serum monoclonal protein** (IgG or IgA) ≥30 g/L or **urinary monoclonal prot** mg per 24 h and/or clonal **bone marrow plasma cells 10–60%**
- **Absence of** myeloma defining events or amyloidosis

Staging of MULTIPLE MYELOMA

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
I	Serum beta-2 microglobulin < 3.5 mg/dl Serum albumin ≥ 3.5 mg/dl	ISS stage I and standard-risk chromosomal cytogenetic ab by FISH and LDH ≤ ULN
II	Not stage ISS I or III	Not stage R-ISS I or III
III	Serum beta-2 microglobulin ≥ 5.5 mg/dl	Stage III ISS and either high-risl cytogenetic abnormalities by > ULN

Response Criteria by International Myeloma Working Group [IMWG

Stringent complete response (sCR): CR as defined below plus

- Normal FLC ratio and
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

Complete response (CR):

- Negative immunofixation on the serum and urine and
- Disappearance of any soft tissue plasmacytomas and
- ≤5% plasma cells in bone marrow

Very Good Partial response (VGPR):

- Serum and urine M-protein detectable by immunofixation but not on el or
- ≥90% reduction in serum M-protein plus urine M-protein level <100 mg p

Partial response (PR):

- ≥50% reduction of serum M-protein and reduction in 24-h urinary M-prot or to <200mg per 24h
- If the serum and urine M-protein are unmeasurable, a ≥50% decrease i difference between involved and uninvolved FLC levels is required in pl protein criteria
- If serum and urine M-protein are unmeasurable, and serum free light as unmeasurable, ≥50% reduction in plasma cells is required in place of M provided baseline bone marrow plasma cell percentage was ≥30%
- In addition to the above listed criteria, if present at baseline, a ≥50% re size of soft tissue plasmacytomas is also required

Stable Disease (SD):

Not meeting criteria for CR, VGPR, PR or progressive disease (PD).

Progressive Disease (PD): requires any one or more of the followings:

- Increase of ≥25% from baseline in:
  - Serum M-component and/or (the absolute increase must be ≥0.5 g/dl)
  - Urine M-component and/or (the absolute increase must be X200 mg/24 h
  - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be ≥10 mg/dl.
  - In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, BM plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%).
- Appearance of a new lesion(s), ≥50% increase from nadir in maximal perpendicular diameters [SPD] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis.
- ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease.

Clinical relapse: requires one or more of the following criteria:

- Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice.
- Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression).
- Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD of the measurable lesion.
- Hypercalcemia (>11 mg/dL).
- Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions.
- Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and *attributable to myeloma.*
- Hyper-viscosity related to serum paraprotein.

Management of multiple myeloma

	Transplant-eligible	Transplant-ineligible
Definition	ALL of the followings: 1. Age ≤ 65 years 2. Good performance status 3. Adequate organ function 4. No significant comorbidities	ONE of the followings: 1. Age > 65 years 2. Poor performance status 3. Inadequate organ function 4. Significant comorbidities
Aim of therapy	**Curative potential**	**Palliative**
First-line therapy	**4 courses of VCD or Cy-Dex or VAD (choice as per Each institutional guidelines) VRD** can be an option IF other therapy options are available and affordable for salvage in case of relapse → • **CR/VGPR**: refer to ASCT • PR: 2 more cycles of VCD or VAD till Best Response then refer to ASCT • NR or PD: 2nd line therapy	**MP or MPT** till max response or CI
After VGPR/CR	ASCT	Follow-up till progression
Maintenance after ASCT	• **Lenalidomide** can be considered (as per Each institutional guidelines) for maintenance post-auto (may be less active in high-risk MM): 10 mg daily PO for 21 days every month for a max of 2-3 years • **Thalidomide:** 100 mg daily PO for 1 year	NA
Second-line therapy	• THAL-dex • Len-Dex • DCEP regimen X 4-6 cycles • Consider Bendamustine combinations	If progression occurs: • In >12 months→ repeat MP or MPT • In <12 months→THAL-Dex

ASCT AS PLANNED PART OF "FRONTLINE THERAPY"

Recommendations:

1. ASCT is strongly considered in "front-line therapy for MM" → improved RRs (CR≥90%) c OS with TRM <5%.
2. Standard conditioning regimen is Melphalan 200 mg/m2 (NO TBI).
3. Stem cell purging… NOT recommended.
4. PBSCs > BM: easy & rapid.
5. Pre-ASCT induction: Thal/Dex, Vel/Dex, VTD, Len/dex.
6. Planned tandem ASCT: Only if did NOT attain at least VGPR after 1st SCT, otherwise investigational!

Consider Allo-SCT in highly-selected young patients with high-risk myeloma if auto deemed inappropriate (no second auto-SCT).

INDICATIONS OF RADIOTHERAPY:

1. Symptomatic osteolytic lesions
2. Significant osteolytic lesions in weight-bearing bone (for fear of pathological fracture)
3. Spinal cord compression
4. Symptomatic extramedullary plasmacytoma
5. Solitary plasmacytoma (as a definitive therapy)

DETAILS OF THERAPY

VCD Regimen (option 1): **every 3 weeks**

- **Bortezomib:** 1.3 mg/m² IV or SC d1, 4, 8 and 11
- **Cyclophosphamide:** 300 mg/m²/ day IV on d1, 8, and 15
- **Dexamethasone:** 40 mg d1, 4, 8,15

VCD Regimen (option 2): **every 4 weeks**

- **Bortezomib:** 1.3 mg/m² IV or SC weekly for 4 weeks
- **Cyclophosphamide:** 300 mg/m²/ day IV weekly for 4 weeks
- **Dexamethasone:** 40 mg weekly for 4 weeks

VRD (RVD) regimen: **every 21 days**

- **Bortezomib:** 1.3 mg/m² IV or SC, on days 1, 4, 8, 11 (or on days 1, 8, 15).
- **Lenalidomide:** 15 mg to 25 mg PO daily, on days 1 through 14
- **Dexamethasone:**
  - **40 mg** IV or PO daily, on days 1, 8, 15 (or on days 1 through 4) or:
  - **20 mg** IV or PO daily on days 1, 2, 4, 5, 8, 9, 11, and 12

VAD Regimen: **every 4 weeks**

- **Vincristine:** 0.4 mg iv over 4-24 hr qd d1-4
- **Adriamycin:** 9 mg/m2 iv over 4-24 hr qd d1-4
- **Dexamethasone:** 40 mg IV (or PO) qd d1-4, 9-12, 17-20

Cy-Dex regimen: **every 21 days**

Option 1:

- **Cyclophosphamide:** 300 mg/m2/ day IV on d1, 8, and 15
- **Dexamethasone:** 40 mg IV (or PO) d1, 4, 8,15

Option 2:

- **Cyclophosphamide:** 1000 mg/m2 IV over 1h D1 only
- **Dexamethasone:** 40 mg IV (or PO) d1-4, 9-12

MP Regimen: **every 4 weeks**

- **Melphalan:** 8 mg/m2 P.O. day 1-4 or 8 to 10 mg/day for 7 days (lower doses may be needed in RF)
- **Prednisone:** 60 mg/m2 P.O. day 1-4 or 60 mg/day orally for 7 days

MPT Regimen: **every 4 weeks**

- **Melphalan:** 4 mg/m2/d po d1-7 qm x 6 cycles
- **Prednisone:** 40 mg/m2/d po d1-7 qm x 6 cycles
- **Thalidomide:** 100 mg po qd till disease progression
- **Prophylactic Enoxaparin** 40 mg sc qd during first 4 cycles of therapy

Thal-Dex regimen:

- **Thalidomide** is given orally at a single dose of 100 mg/d at bedtime for 2 weeks ar increased as tolerated by 50 mg/d every 2 weeks to a maximum dose of 200 mg/ Thalidomide dose is to be reduced to 50 to 100 mg/d if grade 2 or higher toxicity v encountered.
- **Dexamethasone** is given at a dose of 40 mg/d IV or orally on days 1 to 4, 9 to 12, a 20 (odd cycles) and 40 mg/d days 1 to 4 (even cycles), repeated monthly.
- **Low molecular weight heparin** is to be given prophylactically to all patients to redu incidence of deep venous thrombosis since the incidence of this complication hac been reduced by treatment with low-dose warfarin *(Bart Barlogie et al, NEJM, 200*

LEN-DEX Regimen: **every 4 weeks**

- **Lenalidomide**: 25 mg po qd d1-21
- **Dexamethasone** (LD): 40 mg/w

DCEP regimen:

- Dexamethasone 40 mg/d IV D1-4
- Cyclophosphamide: 400 mg/m^2/d IV D1-4
- Etoposide 40 mg/m^2/d IV D1-4
- Cisplatin 10 mg/m^2/d IV D1-4

} Mixed over 1000 cc NS 24-hour

Use of Bisphosphonate in multiple myeloma

INDICATIONS

1. For patients who have on plain radiograph(s), lytic destruction of bone
2. For patients with osteopenia but no radiographic evidence of lytic bon

DRUGS USED

Zoledronic acid 4 mg IV over 15 minutes **every 12 weeks.**

DURATION OF THERAPY

- Therapy with bisphosphonates be given **<u>every 3 months</u>** for a period of **two ye**
- At two years, the physician should seriously consider stopping bisphosphonate patients with responsive or stable disease, but their further use is at the discretic treating physician.
- For those patients in whom bisphosphonates were withdrawn after two years, t should be resumed upon relapse with new onset skeletal related events.

Treatment of multiple myeloma with renal impairment

- **Supportive care:** hydration, correction of hypercalcemia.
- **Start treatment immediately** to avoid deterioration of renal function/improve chance of renal recovery:
  - **High dose dex-based therapies:** highly active in patients with renal impairment
  - **Bortezomib plus dex** is recommended treatment for myeloma patients with renal impairment of any grade
  - **Lenalidomide:** feasible and effective treatment option in presence of renal impairment; dose adjustments based on renal function need to be implemented
- **Dosage Modifications of zoledronic acid with renal impairment:**
  - CrCl 50-60 mL/min: 3.5 mg
  - CrCl 40-49 mL/min: 3.3 mg
  - CrCl 30-39 mL/min: 3 mg
  - CrCl <30 mL/min: Not recommended

Treatment of hypercalcemia in multiple myeloma

Treatment of MM-related hypercalcemia should be started at a corrected serum Ca level >12 mg/dL:

- **Aggressive hydration** with 3-4 L /24 hrs
- **Nephrology consultation** ± dialysis
- **Intravenous diuretic** therapy (e.g. furosemide)
- **Dexamethasone:** 40 mg I.V. daily for 4 days
- **Prompt start of active chemotherapy**
- **Special therapy of hypercalcemia:**
  - **Without renal impairment:** Zoledronic acid 4 mg IV over 15 minutes
  - **Mild-to-moderate renal impairment** (CrCl 30 to 60 mL/min): Zoledronic acid with dose modification for the renal function (as before).
  - **Severe life-threatening hypercalcemia** (serum Calcium corrected for serum albumin > 12.5 mg/dl) associated with Disturbed Conscious Level and **severe renal impairment** (CrCl <30 mL/min):
    - **One dose of Denosumab** 120 mg SC can be given only ONCE, as bisphosphonates are not preferred in this setting

5.WALDENSTROM MACROGLOBULINEMIA (WM)

Minimal Initial Diagnostic Work-up

As in multiple myeloma + IgM level + blood viscosity level.

Lines of therapy

(1) Asymptomatic patients may be followed without specific therapy until symptoms develop.

(2) Hyperviscosity syndrome → plasmapheresis (1-2 sessions/week).

(3) **Symptomatic** patients should receive **chemotherapy** for **4-6 cycles:**

- **≤60 y:**
  - **Need for rapid tumor control** (high M-protein level >5 g/dL, symptomatic hyperviscosity, serum viscosity >4-6 cp):
    - **BDR:** ONLY as per local institutional guidelines. Otherwise for initial 1-2 cycles then other regimens (as RCD or CPR) are valid options.
  - **No need for rapid tumor control:**
    - **RCD**
    - **CPR**
- **>60 yr:**
  - **BR**
  - **FR**
  - **FC**
  - **Oral Chlorambucil**: with comorbidities

DETAILS OF REGIMENS

- **BDR.** Bortezomib1.3 mg/m² days 1, 4, 8, 11; Dexamethasone 40 mg IV days 1, 4, 8, 11; Rituximab 375 mg/m² IV day 1; Repeat cycle every 21 days.
- **RCD:** Rituximab 375 mg/m² IV day 1; Cyclophosphamide 100 mg/m² PO BID day 1-5; Dexamethasone 20 mg days 1; Repeat cycle every 21 days
- **CPR:** Cyclophosphamide 1000 mg/m² IV day 1, Prednisone 100 mg/day PO d1-5; Rituximab 375 mg/m² IV day 1; Repeat cycle every 21 days.
- **FR:** Fludarabine 25 mg/m²/d x5 days; Rituximab 375 mg/m² IV day 1; Repeat cycle every 28 days.
- **FC:** Fludarabine 25 mg/m² x 3 days; Cyclophosphamide250 mg/m² x 3 days; Repeat cycle every 21 days.
- **BR:** Bendamustine 90 mg/m² days 1-2, Rituximab 375 mg/m² D1. Repeat cycle every 21-28 days.
- ***Chlorambucil (oral):*** *as in CLL*

6. MYELOPROLIFERATIVE NEOPLASMS (MPNS)

6.1. Polycythemia Vera (PV)

WHO CRITERIA FOR DIAGNOSIS OF PV (2016)

Diagnosis of PV requires:

- Meeting either all three major criteria or
- The first two major criteria and one minor criterion.

Major criteria:

1. Hb >16.5 g/dl (men) or >16 g/dl (women) or HCT >49% (men) or >48% (women)
2. BM trilineage myeloproliferation with pleomorphic megakaryocytes
3. Presence of JAK2 mutation

Minor Criteria:

1. Subnormal serum erythropoietin level.

MINIMAL INITIAL DIAGNOSTIC WORK-UP

1. **Complete blood counts**
2. **Bone marrow aspiration and biopsy** with reticulin stain.
3. Cytogenetic studies to rule out CML
4. Serum erythropoietin level.
5. JAK2 mutation test.

RISK FACTORS FOR THROMBOSIS IN PV

one of the followings:

1. Age > 60 years
2. History of previous thrombosis
3. Cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, smoking, and congestive heart failure. Contraceptive pills).

N.B.) The role of extreme thrombocytosis (platelet count > 1500 × 10^9/L) as a risk factor for thrombosis in PRV is uncertain.

MANAGEMENT STRATEGY

1. **Low-risk patients:** Phlebotomy (venesection) to maintain hematocrit < 45%±Low-dose aspirin (75-100 mg daily) to reduce the incidence of major thrombotic events
2. **High-risk patients** and patients with poor compliance to phlebotomy or with progressive myeloproliferation (increasing splenomegaly or very high leukocyte or PLT): Hydroxyurea (10-30mg/kg/day) + low-dose aspirin (75-100 mg daily) to reduce the incidence of major thrombotic events.
3. **During pregnancy** (with indication of therapy): Interferon 3 MU 3 times/week or Peg-Interferon 90-120 Ugm/week till delivery.

6.2. Essential Thrombocytosis (ET)

WHO CRITERIA FOR DIAGNOSIS OF ET (2016)

Diagnosis of essential thrombocythemia requires:

- Meeting either all four major criteria or
- First three major criteria and one minor criterion

Major criteria:

1. Platelet count ≥450 × 10^9/L
2. BM biopsy: megakaryocyte proliferation with large and mature morphology
3. Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm
4. Presence of JAK2, CALR or MPL mutation

Minor Criteria:

1. Presence of a clonal marker (e.g. abnormal karyotype) or Absence of evidence for reactive thrombocytosis

MINIMAL INITIAL DIAGNOSTIC WORK-UP

1. Complete blood counts
2. Bone marrow aspiration and biopsy with reticulin stain.
3. Cytogenetic studies to rule out CML
4. JAK2 mutation test.
5. Serum Iron and ferritin levels

RISK FACTORS FOR THROMBOSIS IN ET

one of the followings:

1. Age > 60 years
2. History of previous thrombosis
3. Cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, smoking, and congestive heart failure).

N.B.) Extreme thrombocytosis (platelet count > 1500 × 10^9/L) is a risk factor for bleeding.

PRIMARY MANAGEMENT STRATEGY

1. **High-risk patients: Hydroxyurea** 10-30mg/kg/day (to maintain PLT <500 × 10^9/L) + Low-dose **aspirin** (75-100 mg daily).
2. **Low-risk patients:** Low-dose **aspirin** (75-100 mg daily).
3. **During pregnancy** (with indication of therapy): Interferon 3 MU 3 times/week or Peg-Interferon 120-160 Ugm/week till delivery.

ET with resistance / intolerance to hydroxyurea

Criteria for definition; **any of these:**

- After 3 months of > 2g/day of HU → Platelets >600,000/μL.
- At any dose of HU →
  - Platelets >400,000/μL and WBC <2,500/μL or Hb <10 g/dL
  - Presence of leg ulcers or other unacceptable mucocutaneous manifestations.
  - Hydroxyurea-related fever

Indications of Anagrelide (Thrombonorm 0.5 mg capsule) for ET:

1. Second-line therapy in patients with ET who are resistant/intolerant to HU.
2. Combined use of HU and anagrelide when the dose of HU required to maintain platelet count at the target level causes hematological or other kind of toxicities.

Dose of anagrelide:

- Dose: 1-3 mg (2-6 capsules) daily

Recommendations for therapy in PV and ET:

		PV	ET
Target		HCT ≤45%	PLT ≤450 X 10^9/L
For all patients		1. Low-dose aspirin (unless contraindicated)	
		2. Venesection	
For high-risk patients	**1st line**	Hydroxyurea (HU)	
	2nd line	1. Interferon	
			2. Anagrelide (alone or in combination with HU)

ACCELERATED AND BLASTIC PHASES: treated as AML

PV/ET IN PREGNANCY

High-risk pregnancy: presence of any of the following factors

1. Previous thrombosis/hemorrhage in the mother
2. Previous pregnancy-related complications attributable to PV/ET
3. Severe preeclampsia, abruptio placentae, and unexplained recurrent first trimester fetal loss, IUGR, intrauterine death

Management of PV/ET in pregnancy

All Patients	In High-risk ADD
Venesection to target HCT <45% (PV)	Non-peg IFN control HCT or e reme thrombocytosis (PLT > 1,500 X 109 / L).
Low-dose aspirin throughout pregnancy	Stop aspirin with previous or current major bleeding
Prophylactic LMWH after delivery X 6 ws	LMWH throughout pregnancy
Hydroxyurea and anagrelide should be avoided ;Peg-IFN is less safe	

6.3. Primary myelofibrosis (PMF)

WHO CRITERIA FOR DIAGNOSIS OF PMF (2016)

Diagnosis of PMF requires meeting:

- Meeting either all three major criteria or
- The first two major criteria and all three minor criteria.

Major criteria:

1. BM biopsy: Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis
2. Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm

3. Presence of JAK2, CALR or MPL mutation

Minor Criteria:

1. Presence of a clonal marker (e.g. abnormal karyotype) **or** Absence of evidence for reactive bone marrow fibrosis
2. Presence of anemia or palpable splenomegaly
3. Presence of leuko-erythroblastosis or increased LDH

MINIMAL INITIAL DIAGNOSTIC WORK-UP

(1) Complete blood counts
(2) Bone marrow aspiration
(3) Bone marrow biopsy with trichrome and silver reticulin stains.
(4) Cytogenetic studies to rule out CML
(5) JAK2 mutation test.
(6) Serum LDH level

PATIENT RISK STRATIFICATION (IPSS)

Poor prognostic factors (one point for each): age >65, constitutional symptoms, Hb <10 gm/dL, TLC > 25 x 10^9/L, circulating blasts ≥ 1%, PLT<100 x 10^9/L, RBC transfusion need, Unfavorable karyotype [+8, -7/7q-, i(17q), inv(3), -5/5q, 12p-, or 11q23 rearrangements].

- Low risk (0 point)
- Intermediate I (1 point)
- Intermediate II (2 points)
- High risk (≥ 3 points)

LINES OF THERAPY

(1) **Symptomatic or progressively worsening anemia→**Androgen (Danazol) ± low dose steroids (prednisone 15-20 mg daily) + erythropoietin (if Epo level < 500 mU/ml).

(2) **Progressive symptomatic splenomegaly, thrombocytosis, or leukocytosis→** low-dose hydroxyurea (500-1500 mg daily).

(3) **Patients with intermediate or high-risk MF**:

Consider Ruxolitinib: As per local institutional guidelines OR ONLY if other measures fail to control progressive Huge splenomegaly or constitutional symptoms. 15-20 mg PO twice daily (for PLT >200 X 10^9/L); or 15 mg PO twice daily (for PLT= 100-200 X 10^9/L)

(4) **High-risk patients < 50 y:** Allogeneic stem cell transplantation if HLA matched donor available.

(5) **Accelerated and blastic phases:** treated as AML

7. ACUTE MYELOID LEUKEMIA (EXCEPT PROMYELOCYTIC LEUKEMIA)

Investigations at diagnosis

- CBC, BMA, Immunophenotyping
- Cytogenetics, FISH studies.
- Molecular: FLT3-ITD, NPM, CEBPA.
- CSF examination in AML FAB-M4 or FAB- M5.

Risk status based on validated cytogenetics and molecular abnormalities

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
Favorable-risk	Core binding factor: inv(16) or t(16;16) or t(8;21) t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	CBF with c-kit mutation
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)	Normal cytogenetics: with FLT3-ITD mutation TP53 mutation

Treatment Schedule

Pre-phase: for high WBC counts by hydroxyurea PO 1000-3000 mg (total dose) daily to reduce WBC count to <100,000 $X10^9$/L

Treatment Phase	Treatment
Induction	***(3+7) regimen***
Consolidation	***One more course*** of (3+7) regimen
Post-remission therapy	• 4 courses of high-dose Ara-C *(HIDAC) regimen then* • Patient is eligible for BMT → refer to ***BMT*** program
Monthly FU	By CBC + BM (if indicated)
Relapsed/refractory patients	*Salvage* therapy: - HAM - FLA-IDA or FLA-ADRIA or FLA-M - A-Triple V

FOR ELDERLY AML:

- Standard therapy if FIT.
- Unfit elderly patients are treated with 2+5, COAP ± Adria regimen, low-dose ara-C, oral etoposide or BSC.
- **Single-agent Hypomethylating agents** are not supported (ONLY IF included in the local institutional guidelines).

PATIENTS <18 YEARS OLD WITH AML

Should be treated with pediatric AML protocols as ADE (details are included in the National Protocols for Pediatric Hematologic Malignancies)

Details of regimens

(3+7) REGIMEN

- **Anthracycline:** Daunorubicin 60 mg/m² or Doxorubicin 45 mg/m² or Idarubicin 10-12 mg/m² for 3 days (D 1-3).
- **ARA-C:** 100 mg/m²/day continuous IVI for 7 days (D 1-7).
- **In patients with significant cardiac comorbidities:** anthracycline can be substituted by Mitoxantrone (12 mg/m² for 3 days) or Etoposide (100 mg/m² for 3-5 days).

(2+5) REGIMEN

- **Anthracycline:** Daunorubicin 60 mg/m² or Doxorubicin 45 mg/m² or Idarubicin 10-12 mg/m² for 2 days (D 1-2).
- **ARA-C:** 100 mg/m²/day continuous IVI for 5 days (D 1-5).
- **In patients with significant cardiac comorbidities:** anthracycline can be substituted by Mitoxantrone (12 mg/m² for 2 days) or Etoposide (100 mg/m² for 3-5 days).

HIDAC REGIMEN

- **H**igh-dose **A**RA-C: 1-1.5 gm/m² (3 hrs infusion) /12 hrs D 1-3

HAM REGIMEN

- **H**igh-dose **A**RA-C 1-1.5 gm/m² (3hrs infusion) /12 hrs D 1-3 and
- **M**itoxantrone 12 mg/m² I.V. D 3-5.

FLA-IDA (OR FLA-ADRIA OR FLA-M) REGIMEN (FOR SALVAGE THERAPY)

- **Fl**udarabine: 25 mg/m² (1/2 hr IV) daily for 4 days (4 hours before start of ARA-C)
- **A**ra-C: 2 gm/m² (4 hrs infusion) daily for 4 days
- **Ida**rubicin 10 mg/m² (or **Adria**mycin 45 mg/m² or **M**itoxantrone12 mg/m²) IV for 3 days

A-TRIPLE V REGIMEN

- **A**ra-C 100 mg/m²/day continuous IVI for 7 days
- **V**P16 (Etoposide) 100 mg/m²/day for 5 days
- **V**incristine 0.8-1.2 mg/m² (max 2 mg) Day 10
- **V**inblastine 6 mg/m² (max 10 mg) Day 12

PALLIATIVE CHEMOTHERAPY FOR END-STAGE RELAPSED/REFRACTORY OR ELDERLY AML

- **Oral Etoposide:**50-100 mg PO daily for 14-21 days every month for 6-12 months.
- **Oral Hydroxyurea (for AML):** 1000-3000 mg PO daily according to WBC count.

- **Low-dose Cytarabine (Ara-C):** 20 mg/m² SC for 2 weeks every month for 6 months.
- **COAP ± Adria regimen:**
  - Cyclophosphamide: 100 mg/m² for 5 d.
  - Vincristine: 1.5 mg/m² on d 1
  - Cytosine arabinoside: 100 mg/m² for 5 d
  - Prednisone: 100 mg/d for 5 d
  - ± Adriamycin 35 mg/m² d1

INDICATIONS FOR ALLOGENEIC BMT FOR AML

Up to the age of 60 years, with available fully HLA-identical donor:

- **All patients in first complete remission (CR1)** except cases with t(15;17), t (8; 21), or inv (16)
- **All patients in second or subsequent CR.**

8.ACUTE PROMYELOCYTIC LEUKEMIA (AML M_3)

Coagulopathy

AML (M_3) is characterized by high risk of coagulopathy, which is defined as:

- Fibrinogen level < 150 mg/dl or
- Two of the following:
  - Fibrinogen 150-200 mg/dl
  - FDP
  - PT 3 seconds longer than control

MANAGEMENT OF COAGULAOPATHY

1. Keep PLT count > 50 000
2. FFP 15 ml/kg (max infusion rate = 200 ml/hr)
3. Fibrinogen (2 gm I.V.) may be given instead of plasma if available.

Risk stratification of APL

- Low-risk disease (WBC count ≤ 10,000/mcL)
- High-risk disease (WBC > 10,000/mcL).

Treatment of AML (M_3)

		Low risk APL (PETHEMA/AIDA regimen)	High risk APL (European APL regimen)
Induction		• **ATRA *capsule:* 45** mg/m²/day orally divided into two doses, starting on day **zero** Continued till **morphologic CR** • **Idarubicin:** 10-12 mg/m²/day (or **Adriamycin** 45 mg/m²/day or **Daunorubicin** 60 mg/m²/day) for 4 days (1, 3, 5, 7).	
		-----	**ARA-C** 100-200 mg/m²/day continuous IVI for 7 days (D 1-7).
Consolidation (4w cycle) for CR patients	**All cycles**	**ATRA** 45 mg/m²/d x 15 days with each 4-wk cycle of chemotherapy	
	Cycle 1	• **Idarubicin** 5 mg/m²/day (or **Adriamycin** 20 mg/m²/day or **Daunorubicin** 25 mg/m²/day) on days 1-4	• **Daunorubicin** 60 mg/m2/day (or **Adriamycin** 45 mg/m²/day) on days 1-3 plus • **ARA-C** 100-200 mg/m²/day continuous IVI for 7 days (D 1-7).
	Cycle 2	**Mitoxantrone** 10 mg/m²/day (or **Adriamycin** 45 mg/m²/day or **Daunorubicin** 60 mg/m²/day) on days 1-3	• **Daunorubicin** 45 mg/m²/day (or **Adriamycin** 35 mg/m²/day) on days 1-3 plus • **HD ARA-C:** 1 g/m² every 12h on days 1-4 • **5 doses of intrathecal CT**
	Cycle 3	**Idarubicin:** 10-12 mg/m² (or **Adriamycin** 45 mg/m² or **Daunorubicin** 60 mg/m²) on day 1 only	---

MAINTENANCE TREATMENT

ATRA + CT: *for 2 years*

- ATRA: 45 mg/m² P.O. daily for 2 weeks every 3 months for 2 years.
- 6-MP: 60 mg/m² PO in the morning before breakfast
- MTX: 20 mg /m² IM once weekly.

Monitoring of PML-RARα by peripheral blood RT-PCR starting after the end of consolidation:

- Low-risk: every 6 months for 2 years
- High-risk: every 3 months for 3 years

TREATMENT OF PATIENTS WITH RELAPSED DISEASE OR PERSISTENTLY POSITIVE PML/RARa FUSION GENE AFTER INDUCTION THERAPY

1. Salvage regimens

a. ***HAM regimen:***
   - **H**igh-dose **A**RA-C 1 gm/m² (3hrs infusion) /12 hrs D 1-3 and
   - **M**itoxantrone 12 mg/m² I.V. D 3-5.

b. ***FLA-IDA (FLA-ADRIA or FLA-M) regimen:***
   - **Fl**udarabine: 25 mg/m² (1/2 hr infusion) daily for 4 days (4 hours before start of ARA-C)
   - **A**ra-C: 2 gm/m² (4 hrs infusion) daily for 4 days
   - **Adria**mycin: 45 mg/m² (or **Ida**rubicin10 mg/m² or **M**itoxantrone12 mg/m²] IV for 3 days

c. ***A-triple V regimen:***
   - **A**ra-C 100 mg/m²/day continuous IVI for 7 days,
   - **V**P16 (Etoposide) 100 mg/m²/day for 5 days,
   - **V**incristine 0.8-1.2 mg/m² (max 2 mg) Day 10, and
   - **V**inblastine 6 mg/m² (max 10 mg) Day 12.

Or

2. Arsenic Trioxide: IV over 250 cc D5% or NS over 2 hours

- Induction therapy: 0.15 mg/kg daily until BM remission
- Consolidation therapy: should begin 3-6 weeks after completion of induction therapy at a dose of 0.15 mg/kg daily for 25 doses over a period up to 5 weeks (5 days/week).

Followed by:

3. ALLOGENEIC BMT (available donor) or ASCT (no donor in Molecular CR) in transplant eligible patients

PALLIATIVE CHEMOTHERAPY FOR END-STAGE RELAPSED/REFRACTORY OR ELDERLY APL

- **COAP ± Adria regimen:**
  - Cyclophosphamide: 100 mg/m² for 5 d.
  - Vincristine: 1.5 mg/m² on d 1

- Cytosine arabinoside: 100 mg/m^2 for 5 d
- Prednisone: 100 mg/d for 5 d

± Adriamycin 35 mg/m^2 d1

- **Oral Etoposide:** 50-100 mg PO daily for 14-21 days every month for 6-12 months.
- **Oral Hydroxyurea (for AML):** 1000-3000 mg PO daily according to WBC count.
- **Low-dose Cytarabine (Ara-C):** 20 mg/m^2 SC for 2 weeks every month for 6 months.

4- Cytogen

ALL with adverse c **biological features:**

- Ph+ A L (rapid ection, to TKI therapy)
- t(4;1 ALL
- t(1;19)+
- Other high genetics (complex ≥5 unrelated clonal abnormalities)

5- **Cerebro-spinal f d examination**

6- **MRD marker(s): Leukemia associated immunophenotype (LAIP):**

•MRD-based risk classification

7- **Other w rk up:**

- Coagulation profile
- TLS panel
- Test for liver and kidney function
- Radiology:
  - Chest x ray (CT if abnormal)
  - Abdomen and pelvic U/S
  - Echocardiogram
- Screen for active infection if febrile

Prognostic factors

(1) AT DIAGNOSIS	Favorable features	Unfavorable features
Age	15-20 yrs	>50 yrs
WBC (B-lineage)	<30 000/µL	>30 000/µL
Immunophenotype	Thymic T-ALL	- Pro B-ALL - Early T-ALL - Mature T-ALL
Cytogenetics & Molecular genetics	-Normal diploid karyotype -Hyperdiploid karyotype	-t(9;22)/BCR-ABL (ph+) -Ph-like (CLRF2+ or IKZF1+) -t(4;11)/ALL1-AF4

(2) RESPONSE TO TREATMENT	Favorable features	Unfavorable features
Time to CR	CR <2-4 ws	CR >2-4 w
MRD after induction	$<10^{-3}$-10^{-4}	$>10^{-3}$-10^{-4}
MRD during consolidation	$<10^{-4}$ or negative	$>10^{-4}$ or increasing

Treatment options for ALL

Risk	Age ≤40 yrs	40-60 yrs	>60 yrs
Standard risk	Dana Farber Protocol	• ***Standard***-risk Holzer protocol with maintenance arm • ***No BMT***	***COAP*** only
High risk	• Dana Farber Protocol + • Allo-BMT	• ***High-risk*** Holzer protocol • No allo BMT	***COAP*** only
Ph+ ALL	• Dana Farber Protocol + • Imatinib + • Allo-BMT	• ***High-risk*** Holzer protocol + • ***Imatinib*** • Allo BMT (If <50 y)	***COAP*** only
Mature B-ALL & Burkitt's NHL	***6 full blocks*** (A1B1A2B2A3B3) ± ***BMT***	***4 incomplete blocks*** (without HD MTX) (a1b1a2b2)	

PREPHASE (IN ALL PROTOCOLS)

for high WBC counts and/or massive organomegaly

- Vincristine: 1.2 mg/m² (max. 2 mg) IV D1
- Prednisone: 60 mg/m² D1-7

HOELZER PROTOCOL (AGE >25 YEARS)

Hoelzer Protocol: for standard-risk patients

Treatment Phase	Treatment
Phase I induction	• **VCR:** 2 mg I.V. D1, 8, 15, 22 • **DNR:** 45 mg/m² I.V. D1, 8, 15, 22 • **L-Asp:** 5000 U/m² /other day D15–33 • **Prednisone:** 60 mg /m² P.O D1-28 • **MTX:** 15 mg intrathecal D1
Phase II induction	• **Cyclophosphamide:** 650 mg/m² D 1, 14, 28 • **ARA-C:** 75 mg/m² D 3-6, and D 9-12, D 16-19; and D 23-26
Cranial prophylaxis	• **Cranial irradiation:** 24 Gy • **MTX:** 15 mg intrathecal is given as 4 doses (twice/w)
Phase I consolidation	• **VCR:** 2 mg I.V. D1, 8, 15, 22 • **ADR:** 25 mg/m² I.V D1, 8, 15, 22 • **Prednisone:** 60 mg /m² P.O D1-28 • **Triple intrathecal (D1):** ARA-C 40 mg, MTX 15 mg, dexamethasone 4 mg
Phase II consolidation	• **Cyclophosphamide:** 650 mg/m² D 1 • **ARA-C: 75** mg/m² D3, 4, 5, 6 and D 9, 10, 11, 12 then **100** mg /m² D25, 26, 27, 30 • **VP16:** 100 mg / m² D 25, 26, 27, 30 • **Triple intrathecal (D1):** ARA-C 40 mg, MTX 15 mg, dexamethasone 4 mg
Maintenance	• ***6-Mercaptupurine:* 60** mg/m² /day P.O. for 2 years • ***Methotrexate:*** 20 mg /m² IM once weekly for 2 years
Relapsed dis	FLA-IDA (or FLA-Adria or FLA-M) regimen

Hoelzer Protocol: for high-risk patients

Treatment Phase	Treatment
Phase I induction	• **VCR:** 2 mg I.V. D1, 8, 15, 22 • **DNR:** 45 mg/m² I.V. D1, 8, 15, 22 • **L-Asp:** 5000 U/m² /day D15–28 • **Prednisone:** 60 mg /m² P.O. D1-28 • **MTX:** 15 mg intrathecal D1
Phase II induction	• **Cyclophosphamide:** 650 mg/m² D 1, 14, 28 • **ARA-C:** 75 mg/m² D 3-6, and D 9-12, D 16-19; and D 23-26
Post-induction therapy	**HLA-typing→** • No identical donor → two courses of **HAM** regimen then refer for autologous BMT Or • Identical donor available → refer for **allogeneic** BMT
Relapsed dis	FLA-IDA (or FLA-Adria or FLA-M) regimen

Hoelzer Protocol: High-risk protocol in Ph+ ALL (> 25 y)

- As the previous Hoelzer High-risk protocol +
- Imatinib 400 mg daily throughout the treatment +
- Allogeneic BMT

Hoelzer Protocol for Ph-like ALL

- As Ph+ ALL with substitution of imatinib by Dasatinib (100 mg daily)

DANA FARBER PROTOCOL (AGE< 25 Y)

Phase I induction

- **Methylprednisolone** 8 mg/m²qid or **Prednisone** 10 mg/m² qid **(for 29 days)**
- **Vincristine** 2 mg IV [may be replaced by Vinblastine 10 mg IV for proximal muscle weakness or unacceptable neuropathy] (Hold dose if ileus develops) **(D 1,8,15,22)**
- **Doxorubicin** 30 mg/m² IV [Replace with Amascarine 85mg/ m²if EF <50%] **(D 1 , 2)**
- **Methotrxate** 1.5 gm/m² in D5W over one hour **(D 3)**
  [Leucovorine: give 36 hs after start of MTX 15 mg/m² /6hs add to at least 150 ml solvent (4 doses). Check MTX level after 24 hs; if > 0.1 uM/L→ give another 2 doses of leucovorine (15 mg/m²)]
- **L-Asparaginase** 25,000 IU/m² IM **(D 5)**
- **Intrathecal therapy:**
  - **D 1** LP ara-C 40 mg IT
  - **D 15** LP mtx 12 mg + ara-C 40mg+hydrocortisone 15 mg (or Dexa 4 mg)
  - If initial CSF +ve, continue IT chemo twice weekly using D15 doses until CSF clear **× 3**

Phase II induction + CNS Therapy

- **Vincristine** 2 mg IV [If unacceptable neuropathy switch to Vinblastine 10 mg IV] **(D 1)**
- **Doxorubicin** 30 mg/m² IV **(D 1)**
- **6MP** 50 mg/m²/d **× 14 days**-hold for ANC<500 or plt<50 or AST>8× normal or direct bili> 2 (Take at bedtime without milk)
- **Intrathecal therapy:**
  - **D 1, 4, 8, 11** LP mtx 12 mg+ ara-C 40mg+hydrocortisone 15 mg (or Dexa 4 mg)
  - D29 induction LP may be used as D1 LP for CNS phase.
- **Cranial RT:** (Delete if pts to undergo allo-SCT using TBI.)
  - For pts. Who present without CNS disease at diagnosis:
    - Total dose: 1800 cGy. Fraction dose: 180cGy (10 fractions)
  - For pts. Who present with CNS disease at diagnosis:
    - Total dose: 2400 cGy. Fraction dose: 240 cGy (10 fractions)
  - Radiation should start as close to Day 1 as possible.

Intensification Therapy (10 Cycles) [Phase III] (Each cycle = 3 week)

- **Dexamethasone** 9 mg/m² PO or IM bid **(D1→D5)**
- **Vincristine** 2 mg IV [If unacceptable neuropathy switch to Vinblastine 10 mg IV] **(D 1)**
- **6MP** 50 mg/m²/d **(D1→D14)**
- **Doxorubicin** 30 mg/m² IV, until 300 mg/m² total dose. **For Cycles 1→7 (D 1)**
  *Replace with Amascrine 85 mg/m² if EF <50%
- **L-Asparaginase** 12,500 IU/m²/dose **(D1,8,15)**
- **Methotrxate** 20 mg/m² IV push or IM **one day after L-ASP for Cycles 8,9&10. (D2,9,16)**
- **Intrathecal therapy:**
  - LP mtx 12 mg+ ara-C 40mg+ hydrocortisone 15 mg (or Dexa 4 mg) → **D1, Cycle 6** only

Continuation Therapy-24 Cycles [Phase IV] = 72 Weeks (to two years post CR)

- **Dexamethasone** 6 mg/m² PO or IM bid **(D1→D5)**
- **Vincristine** 2 mg IV *[If unacceptable neuropathy switch to Vinblastine 10 mg IV]* ***(D 1)***
- ***6MP*** *50 mg/m²/d* **(D1→D14)**
- **Methotrxate** 30 mg/m² IV push or IM **-hold the day IT MTX given, Max dose 40 mg if XRT (D1)**
- **Intrathecal therapy:**
  - LP mtx 12 mg + ara-C 40mg+hydrocortisone 15 mg (or Dexa 4 mg) → **D1 / 18 weeks**

IMATINIB DFCI PROTOCOL FOR PH-POSITIVE ALL (AGE < 25 YEARS)

Phase I induction:

- **Imatinib** 400 mg PO daily for 16 days **(start D -2 →D 14)**
- **Methylprednisolone** 8 mg/m²qid or Prednisone 10 mg/m² qid, **(for 29 days)**
- **Vincristine** 2 mg IV [may be replaced by Vinblastine 10 mg IV for proximal muscle weakness or unacceptable neuropathy] (Hold dose if ileus develops) **(D 1,8,15,22)**
- **Doxorubicin** 30 mg/m² IV **(D 1 , 2)**
- **Methotrexate*** 1.5 gm/m² **(D 3)**

[**Leucovorine**: give 36 hs after start of MTX 15 mg/m² /6hs add to at least 150 ml solvent (4 doses). Check MTX level after 24 hs; if > 0.1 uM/L→ give another 2 doses of leucovorin (15 mg/m²).]

- **L-Asparaginase** 25,000 IU/m² **(D 5)**
- **Intrathecal therapy:**
  - D 1 LP ara-C 40 mg IT
  - D 15 & 29 LP mtx 12 mg + ara-C 40mg+hydrocortisone 15 mg (or Dexa 4 mg)
  - If initial CSF+, continue IT chemo twice weekly using D15 doses until CSF clear × 3

Phase II: CNS Therapy:

- **Imatinib** 400 mg PO daily **(D 1→D 14)**
- **Vincristine** 2 mg IV [If unacceptable neuropathy switch to Vinblastine 10 mg IV] **(D 1)**
- **Doxorubicin** 30 mg/m² IV **(D 1)**
- **6MP** 50 mg/m²/d **× 14 days**-hold for ANC <500 or plt<50 or AST>8× normal or direct bili> 2
- **Intrathecal therapy:**
  - **D 1,4,8,11** LP mtx 12 mg/ ara-C 40mg/hydrocortisone 15 mg (or Dexa 4 mg)
  - **D29** induction LP may be used as D1 LP for CNS phase.
- **Cranial RT:** (Delete if pts to undergo allo-SCT using TBI.)
  - For pts. who present without CNS disease at diagnosis:
    - Total dose: 1800 cGy. Fraction dose: 180cGy (10 fractions)
  - For pts. who present with CNS disease at diagnosis:
    - Total dose: 2400 cGy. Fraction dose: 240 cGy (10 fractions)
  - Radiation should start as close to Day 1 as possible.

Intensification Therapy (10 Cycles) [Phase III] *(Each cycle = 3 weeks):*

- **Imatinib** 400 mg PO daily, for 14 days **(D 1→D 14)**
- **Dexamethasone** 9 mg/m²PO or IM bid **(D1→D5)**
- **Vincristine** 2 mg IV [If unacceptable neuropathy switch to Vinblastine 10 mg IV] **(D 1)**
- **6MP** 50 mg/m²/d **(D1→D14)**
- **Doxorubicin** 30 mg/m² IV, until 300 mg/m² total dose. **For Cycles1→7 (D 1)**
  *Replace with Amascrine 85 mg/m² if EF <50%
- **L-Asparaginase** 12,500 IU/m²/dose **(D1,8,15)**
- **Methotrxate** 30 mg/m² IV push or IM **one day after L-ASP for Cycles 8, 9 & 10. (D2,9,16)**
- **Intrathecal therapy:**
  - LP mtx 12 mg/ ara-C 40mg/hydrocortisone 15 mg → **D1, Cycle 6** Only

Continuation Therapy-24 Cycles [Phase IV] = 72 Weeks *(to two years post CR):*

- **Dexamethasone** 6 mg/m² PO or IM bid **(D1→D5)**
- **Vincristine** 2 mg IV [If unacceptable neuropathy switch to Vinblastine 10 mg IV] **(D 1)**
- **6MP** 50 mg/m²/d **(D1→D14)**
- **Methotrxate** 30 mg/m² IV push or IM **- hold the day IT MTX given, Max dose 20 mg if XRT (D1→D3)**
- **Intrathecal therapy:**
  - LP mtx 12 mg + ara-C 40mg + hydrocortisone 15 mg (or Dexa 4 mg) → **D1 / 18 weeks**

DFCI PROTOCOL FOR PH-LIKE ALL

As in Ph+ ALL with substitution of imatinib by Dasatinib (100 mg daily)

ALTERNATIVE REGIMEN

Hyper-CVAD/MA regimen

Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (cycle A), alternating with high-dose methotrexate and cytarabine (cycle B):

Cycle A: Courses 1, 3, 5, & 7			
Cyclophosphamide	300 mg/m² (bid)	i.v. (2-3 h inf) with Mesna Uroprotection	D 1-3
Vincristine,	2 mg	i.v.	D 4, 11
Doxorubicin	50 mg/m²	i.v. (2h inf)	D 4
Dexamethasone	40 mg/d	i.v. or p.o.	D -4, 11-14

Cycle B: Courses 2, 4, 6, & 8			
Methotrexate*	1000 mg/m²	i.v. (24 h inf)	D 1
Cytarabine	3000 mg/m² (bid)	i.v. (2 h inf)	D 2, 3
Methylprednisolone	50 mg (bid)	i.v.	D 1-3

* With Leucovorin rescue

All courses with G-CSF support, repeated every 3 (or 2 if count recovery allows) weeks.

CNS prophylaxis			
Methotrexate	12 mg*	i.th.	D 2
Cytarabine	100 mg	i.th.	D 8

* 6 mg via the Ommaya reservoir

- Of each course for all 8 courses
- Patients with a high risk for CNS disease (lactate dehydrogenase level >600 U/L), or with a proliferative index ≥ 14% receives 16 i.th. treatments. Patients with low risk receives 4, those with unknown risk 8 i.th. treatments

Maintenance			
Mercaptopurine	1000 mg/m²	i.v. (1 h inf)	Daily x5 every month
Methotrexate	10 mg/m²	i.v. (1 h inf)	Daily x5 every month*
Vincristine	2 mg	i.v.	Monthly
Prednisone	200 mg	p.o.	Daily x5 every month**

Except for patients with mature B-ALL and those with Ph+ ALL eligible for allo-SCT.
* With Mercaptopurine
**With Vincristine

In patients with Ph+ ALL and Ph-like ALL: Imatinib and Dasatinib are added to hyper-CVAD/MA regimen respectively

COAP ± Adria regimen

- Cyclophosphamide: 100 mg/m² for 5 d.
- Vincristine: 1.5 mg/m² on d 1
- Cytosine arabinoside: 100 mg/m² for 5 d
- Prednisone: 100 mg/d for 5 d
- ± Adriamycin 35 mg/m² d1

Patients ≤25 years old with ALL

Can be treated with pediatric ALL protocols as Total XV (details are included in the National Protocols for Pediatric Hematologic Malignancies)

Mature-B ALL and & Burkitt's NHL protocol

Patient's Age	Treatment
Age ≤ 50	**Give 2 full blocks** (A1+B1) → • ***CR*** (low risk) → continue for **another 4** full blocks (A2+B2+A3 + B3)→ **no** further therapy. Or • ***No CR*** (high-risk) → continue for **another 4** full blocks (A2+B2+A3 + B3) till CR → **refer to BMT** program
Age > 50	**Give 4 *incomplete* blocks** (without high-dose methotrexate) → no further therapy.
Relapsed disease	FLA-IDA (or FLA-Adria or FLA-M) regimen

DETAILS OF BLOCK THERAPY

Block A:

- ***VCR:*** 2 mg I.V. D1
- ***MTX:*** 3 gm /m² D1
- ***Ifosphamide:*** 800 mg/m² D1-5
- ***VP16:*** 100 mg/m² D4, 5
- ***ARA-C:*** 150 mg/m² D4, 5
- ***Dexamethasone:*** 10 mg/m²D1-5
- ***Triple intrathecal*** (D1& 5): ARA-C 40 mg, MTX 15mg, dexamethasone 4 mg

Block A:

- ***VCR:*** 2 mg I.V. D1
- ***MTX:*** 3 gm /m² D1
- ***Cyclophosphamide:*** 200 mg/m² D1-5
- ***Doxorubicin:*** 25 mg/m² D4, 5
- ***Dexamethasone:*** 10 mg/m² D1-5
- ***Triple intrathecal*** (D1& 5): ARA-C 40 mg, MTX 15mg, dexamethasone 4 mg

Patients <18 years old with Mature-B ALL and & Burkitt's NHL

Should be treated with pediatric Mature-B ALL and & Burkitt's NHL protocols (details are included in the National Protocols for Pediatric Hematologic Malignancies)

FOLLOW-UP

- The follow-up of asymptomatic patients should include blood cell counts and routine chemistry during maintenance therapy; usually every month during the first 2 years to adjust treatment accordingly.
- Thereafter, follow-up should be 3-monthly in years 1, 2 and 3, then half-yearly in the 4th and 5th year.

- For evaluation of MRD, bone marrow aspiration is required 3-monthly. It is also desirable in Ph+ MRD to search for MRD (BCR-ABL) and, if possible, for mutations to switch to another TKI inhibitor.

Treatment of relapsed or refractory ALL (all types)

OVERALL EVALUATION OF THE CLINICAL SITUATION SHOULD TAKE INTO ACCOUNT:

1- Disease-specific factors (B-ALL or T-ALL, BCR-ABL1 status),

2- Patient factors (age, performance status, organ function and presence of extramedullary disease, in particular CNS),

3- Previous therapy (with particular reference to prior allograft, anthracycline dose)

4- Specific toxicities of prior treatment, which might guide therapeutic selection (e.g. osteonecrosis, vinca alkaloid neuropathy and specific infectious complications such as fungal infections).

TREATMENT WITH A CURATIVE AIM INVOLVES ACHIEVEMENT OF CR FOLLOWED BY ALLOGENEIC SCT:

- Long duration of first CR (>2 years): re-induction with a standard induction regimen—such as that used for original treatment—may be used
- Short first CR or primary refractory disease is a very high-risk situation

THE MOST COMMONLY USED SALVAGE REGIMENS ARE:

A. HAM regimen

- **H**igh-dose **A**RA-C 1-1.5 gm/m² (3hrs infusion) /12 hrs D 1-3 and
- **M**itoxantrone 12 mg/m²I.V. D 3-5.

B. FLA-IDA (or FLA-ADRIA or FLA-M) regimen (for salvage therapy)

- **Fl**udarabine: 25 mg/m² (1/2 hr IV) daily for 4 days (4 hours before start of ARA-C)
- **A**ra-C: 2 gm/m² (4 hrs infusion) daily for 4 days
- **Ida**rubicin 10 mg/m² (or **Adria**mycin 45 mg/m² or **M**itoxantrone12 mg/m²) IV for 3 days

C. A-triple V regimen

- **A**ra-C 100 mg/m²/day continuous IVI for 7 days
- **V**P16 (Etoposide) 100 mg/m²/day for 5 days
- **V**incristine 0.8-1.2 mg/m² (max 2 mg) Day 10
- **V**inblastine 6 mg/m² (max 10 mg) Day 12

- **Ph+ ALL patients:** should be offered the new generations of TKIs, according to the results of mutational analysis of their BCR-ABL1 transcripts. Patients who have lost response to Imatinib will receive Nilotinib or Dasatinib

STEM CELL TRANSPLANTATION FOR ALL:

- **AlloSCT in CR1** significantly improves OS and EFS in **high-risk** patients/MRD+ patients and is the best post-remission option for Ph+ ALL and MLL-rearranged ALL

- **All patients in CR ≥2** are candidates for **alloSCT**
- **Conditioning regimens** are age-adapted with full allo versus RIC for elderly patients or patients unfit for full conditioning

PALLIATIVE CHEMOTHERAPY FOR END-STAGE RELAPSED/REFRACTORY OR ELDERLY ALL:

- **Oral Etoposide:** 50-100 mg PO daily for 14-21 days every month for 6-12 months.
- **Vincristine and steroids**.
- **COAP ± Adria regimen**
    - Cyclophosphamide: 100 mg/m^2 for 5 d.
    - Vincristine: 1.5 mg/m^2 on d 1
    - Cytosine arabinoside: 100 mg/m^2 for 5 d
    - Prednisone: 100 mg/d for 5 d
    - ± Adriamycin 35 mg/m^2 d1

10.MYELODYSPLASTIC SYNDROME (MDS)

New WHO classification

MYELODYSPLASTIC SYNDROMES

a) Refractory anemia (RA):
- With ringed sideroblasts (RARS)
- Without ringed sideroblasts

b) Refractory cytopenia (MDS) with multilineage dysplasia (RCMD)

c) Refractory anemia (MDS) with excess blasts (RAEB)

d) 5q- Syndrome

MYELODYSPLASTIC/MYELOPROLIFERATION DISEASES

a) CMML

b) Atypical CML

c) Juvenile myelomonocytic leukemia

Initial Investigations

- CBC, BMA/B AND IRON STAIN,
- Immunophenotyping including CD55 and CD59
- Cytogenetics

International Prognostic Scoring System (IPSS) for MDS:

	IPSS score				
	0	0.5	1	1.5	2
BM blast %	<5%	5-10%	-	11-20%	21-30%
Cytogenetics*	Good	IM	Poor	-	-
Cytopenias**	< 1	2-3	-	-	-

* CYTOGENETIC CLASSIFICATION

Good Prognosis	Intermediate Prognosis	Poor Prognosis
• Normal	• Single miscellaneous abn. • Double abn.	• Complex abn
• -Y only • Del 20q only	• Trisomy 8 (+8)	• Any ch 7 abn.

** TYPES OF CYTOPENIA

- HB < 10 gm/dL
- ANC < 1500/cmm
- PLT < 100 000/cmm

Treatment options for MDS

	Lower risk	Higher risk
IPSS risk	Low + Int. I (score ≤1)	Int. II + high (score >1)
For anemia	• Transfusions • Erythropoietin (if HB<10 gm/dl and serum Epo level <200 mU/ml)	• Transfusions
Immunosuppression (CSA + std ± ATG	• Age <60 years • Karyotype: NCG, +8 • HLDR15+ • Marrow hypoplasia • PNH clone.	-----
Del (5q)	Lenalidomide	-----
Chemotherapy	-----	**Age ≤55 yr:** • Intensive chemotherapy (3+7) **Age >55 yr:** • Low-dose Ara-C± ADR • Hypomethylating agents
Allo-SCT	For refractory/progressive transfusion-dependent patients	**For patients ≤55 yr** having an HLA-identical donor

TREATMENT DETAILS

Type of therapy	Treatment
Supportive measures	• Blood transfusion • PLT transfusion • Antibiotics • Erythropoietin ± G-CSF • Immunosuppression: CSA + Std ± ATG
(3+7) regimen	• Daunorubicin 45 mg/m² D 1-3 • ARA-c 100 mg/m² I.V D 1-7.
Low-dose chemotherapy	• Low dose Ara-C 20 mg/m² SC daily D 1-14 ± • Adriamycin (or daunorubicin) 30 mg (total dose) D 1 & 8
Hypomethylating agents	**These are options ONLY IF included in the local institutional guidelines** • **Azacitidine:** 75 mg/m² SC D1-7 every 4 weeks. • **Decitabine:** 20 mg/m² IV over 1-hr daily for 5 days, every 4 weeks.

11.LYMPHOMAS

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

WHO 2016: MATURE B-CELL NEOPLASMS

WHO 2016: MATURE B-CELL NEOPLASMS
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable ○ *Splenic diffuse red pulp small B-cell lymphoma* ○ *Hairy cell leukemia-variant*
Lymphoplasmacytic lymphoma ○ Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma ○ *Pediatric nodal marginal zone lymphoma*
Follicular lymphoma ○ In situ follicular neoplasia ○ Duodenal-type follicular lymphoma
Pediatric-type follicular lymphoma
Large B-cell lymphoma with IRF4 rearrangement
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma ○ In situ mantle cell neoplasia

Diffuse large B-cell lymphoma (DLBCL), NOS ○ Germinal center B-cell type ○ Activated B-cell type
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV+ DLBCL, NOS
EBV+ mucocutaneous ulcer
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8+ DLBCL, NOS
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
High-grade B-cell lymphoma, NOS
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
HHV8+ DLBCL, NOS
Burkitt-like lymphoma with 11q aberration
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements
High-grade B-cell lymphoma, NOS

WHO 2016: MATURE T-CELL AND NK-CELL NEOPLASMS

WHO 2016: MATURE T-CELL AND NK-CELL NEOPLASMS
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV+ T-cell lymphoma of childhood
Hydroa vacciniforme–like lymphoproliferative disorder
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Indolent T-cell lymphoproliferative disorder of the GI tract
Hepatosplenic T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders • Lymphomatoid papulosis • Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8+ T-cell lymphoma
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma
Nodal peripheral T-cell lymphoma with TFH phenotype
Anaplastic large-cell lymphoma, ALK+
Anaplastic large-cell lymphoma, ALK−
Breast implant–associated anaplastic large-cell lymphoma

WHO 2016: HODGKIN LYMPHOMA

Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma

WHO 2016: POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD

WHO 2016: HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease

11.1. Aggressive Lymphomas

11.1.1. DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Biopsy

- An incisional or excisional lymph node biopsy
- When a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques may be sufficient for diagnosis.
- FNA alone is not acceptable as a reliable diagnostic tool for NHL. However, it may be sufficient to establish a relapse.
- Expert hematopathology review. Re-biopsy if material is nondiagnostic.
- Adequate immunophenotyping to establish diagnosis is mandatory (see appendix).
- Cytogenetic or molecular biologic analysis may be necessary in certain cases.

Diagnostic Issues

- *Subtypes include DLBCL(NOS), DLBCL coexistent with follicular lymphoma of any grade, DLBCL coexistent with gastric MALT lymphoma, DLBCL coexistent with nongastric MALT lymphoma, follicular lymphoma grade 3, Intravascular large B-cell* lymphoma, DLBCL associated with chronic inflammation, ALK-positive DLBCL, EBV-positive DLBCL of the elderly, and T-cell- histiocyte-rich large B-cell lymphoma.
- These subtypes are treated the same as DLBCL
- Although GCB subtype is associated with an improved outcome compared to non-GCB subtype, treatment remains the same for both the subtypes and cell-of-origin should not be used to guide the selection of therapy.
- No guidelines are available for the treatment of patients with "double-hit" lymphomas with concurrent *MYC* and *BCL2* rearrangements. Additional data on the management of these high-risk disease subtypes is needed.

Workup

- A thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms.
- Laboratory assessments should include standard blood work including CBC, a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH) and serum beta-2-microglobulin levels.
- Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome, including measurements of uric acid level.
- HBV and HCV testing
- Adequate trephine biopsy with or without bone marrow aspiration.
- CT chest/abdomen/pelvis with oral and IV contrast (not in renal insufficiency) , and Echocardiography.
- PET-CT scans are optional, as they have a more clear-cut role in selected cases of DLBCL than in other lymphoid neoplasms.
- Lumbar puncture is recommended in patients with one or more of the following sites of involvement: paranasal sinus, testicular, epidural, HIV-associated lymphoma, bone marrow (with large cells) or the presence of 2 or more extranodal sites and elevated

LDH levels (Patients with these risk factors should also be considered for prophylactic chemotherapy for the CNS).

Treatment outline Recommendations

R-CHOP-21 is recommended as initial therapy

Stage I or II disease:

For patients with non-bulky (<10 cm) stage I or II disease:

- R-CHOP (3 cycles) with IFRT or R-CHOP (6 cycles) with or without IFRT is recommended.
- IFRT is recommended for patients who are not candidates for chemotherapy.

Patients with bulky disease (10 cm or greater)

- 6 cycles of R-CHOP with or without locoregional RT (category 1).

For patients with advanced stage disease:

- Treatment with R-CHOP-21 (category 1) is recommended.
- In selected cases, RT to bulky sites may be beneficial (category 2B).

The following regimens as first-line therapy options for very frail patients or those with poor left ventricular function may be used:

- R-miniCHOP (for frail patients over 80 years of age)
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) + rituximab
- CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisone) + rituximab
- CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) + rituximab

For Patients at increased risk for developing CNS relapse, consider CNS prophylaxis with 4 to 8 doses of intrathecal methotrexate and/or cytarabine, or 3-3.5 g/m^2 of systemic methotrexate.

For patients with concurrent presentation of parenchymal involvement of the CNS, systemic methotrexate (3–8 g/m^2) should be incorporated as part of the treatment plan;

For patients with concurrent leptomeningeal disease, 4 to 8 doses of intrathecal methotrexate and/or liposomal cytarabine and/or 3 to 3.5 g/m^2 systemic methotrexate should be incorporated.

When administering high-dose methotrexate, patients should be pre-treated with hydration and alkalinization, and then receive leucovorin rescue beginning 24 hours after the beginning of the methotrexate infusion. Renal and hepatic function must be monitored. Full recovery of blood counts should be confirmed prior to initiating the next cycle of R-CHOP. Systemic methotrexate with leucovorin rescue has been safely incorporated into R-CHOP-21, with methotrexate administered on day 15 of the 21-day R-CHOP cycle.

Response Assessment and Follow-up Therapy

- Patients who are receiving induction therapy should undergo evaluation prior to receiving RT, including all positive studies, or after 3-4 cycles of chemotherapy.
- End of treatment restaging is performed upon completion of treatment.
- Stage I/II disease: After end of treatment restaging, follow-up at regular intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter) is recommended for patients with CR.
- PET or CT is not recommended for routine surveillance for patients who have achieved a CR to initial therapy and are recommended only if clinically indicated.
- For patients with stage III-IV disease who achieve remission to initial therapy, CT scans are to be done no more than once every 6 months for up to 2 years after completion of treatment, with no ongoing routine surveillance imaging after that time, unless it is clinically indicated.
- When surveillance imaging is performed, CT scan is preferred over PET/CT for the majority of patients.

What to do next:

Stage I-II

- If interim restaging demonstrates a CR, the planned course of treatment is completed.
- If the interim restaging demonstrates a PR:
  - Treatment with a higher dose of RT is appropriate.
  - Alternatively, a repeat biopsy can be obtained and if positive, the patient can proceed to second-line therapy followed by HDT/ASCR.
  - The choice between these two options is often made on clinical grounds. RT is appropriate for patients not eligible for HDT/ASCR. Higher dose RT is also a reasonable choice if there is a very good PR.
- Patients with refractory or primarily progressive disease are managed as refractory or relapsed disease.

Stage III-IV

- *If interim staging (after 2–4 cycles of R-CHOP-21) demonstrates a CR and PR, the* planned course of R-CHOP to a total of 6 cycles is completed.
- Observation is preferred for patients with CR.
- RT to initially bulky disease or first-line consolidation with HDT/ASCR can be considered in selected high-risk patients with high-IPI risk.
- Patients with PR (after completion of initial therapy) and those with no response to treatment or progressive disease are treated as described below for relapsed or refractory disease.

Relapsed or Refractory Disease

- *HDT/ASCR is the treatment of choice for patients with relapsed or refractory disease* that is chemosensitive at relapse.

- Patients with relapsed or refractory DLBCL who are candidates for HDT/ASCR should be treated with second-line chemotherapy, with or without rituximab (depending on whether the patient was refractory to prior rituximab regimens).
- Suggested regimens (with or without rituximab) include the following (in preparation for autologous bone marrow transplantation):
    - DHAP (dexamethasone, cisplatin, cytarabine),
    - ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin)
    - GDP (gemcitabine, dexamethasone, cisplatin)
    - Gem-Ox (gemcitabine and oxaliplatin)
    - Gem-Cis (gemcitabine and cisplatin)
    - ICE (ifosfamide, carboplatin and etoposide)
    - MINE (mitoxantrone, ifosfamide, mesna, etoposide)
- Patients with CR or PR to second-line chemotherapy regimen should be considered for further consolidation with HDT/ASCR (category 1 for patients with CR) with or without RT.
- IFRT before HDT/ASCR has been shown to result in good local disease control and improved outcome. Additional RT can be given before or after stem cell rescue to sites with prior positive disease.
- The option of allogeneic stem cell transplantation, may also be considered in some cases.
- Patients who are not eligible for HDT/ASCR should be treated with single-agent e.g. weekly vinblastine, or multiagent chemotherapy regimens such as dose-adjusted EPOCH, CEPP (cyclophosphamide, etoposide, prednisone and procarbazine), GDP or Gem-Ox.
- Patients with progressive disease after three successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients who have experienced a long disease-free interval.

Palliative chemotherapy for End-stage R/R HL and NHL:

- **Oral Etoposide:** 50-100 mg PO daily for 14-21 days every month for 6-12 months.
- **Oral Cyclophosphamide:** 100-150 mg PO daily for 14-21 days every month for 6-12 months.
- **Vinblastine:** 10 mg IV every 1-2 weeks for 6 months.

11.1.2. PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMBL)

- PMBL is a distinct subtype of NHL that histologically can be indistinguishable from DLBCL.
- Age-adjusted IPI is of limited value in determining the prognosis of PMBL at diagnosis.

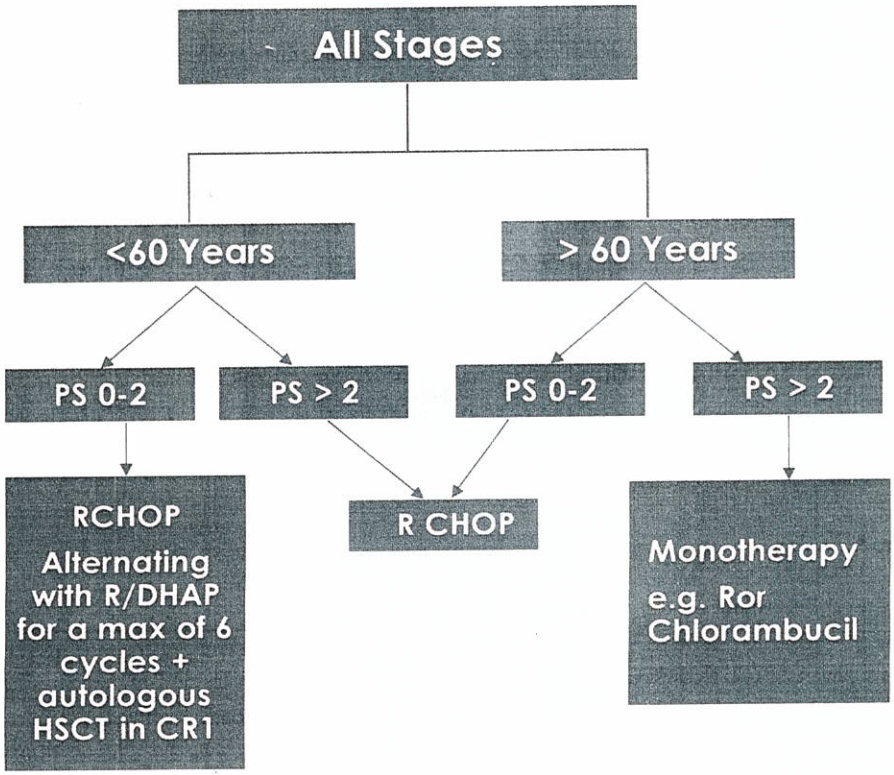
- The following regimens are included as options for first-line therapy:
  - R-CHOP (6 cycles) + RT
  - Dose-adjusted R-EPOCH (6 cycles) + RT for persistent local disease
  - R-CHOP (4 cycles) followed by ICE (3 cycles) with or without RT (category 2B)

11.1.3. MANTLE CELL LYMPHOMA (MCL)

Biopsy, Diagnosis, and Work up

- As above
- Add:
  - Cyclin-D1 (by IPT) and t(11;14) (by FISH)
  - Endoscopy/colonoscopy as it is essential for confirmation of stage I-II disease
  - Lumbar puncture (for blastic variant or CNS symptoms)
  - Beta-2-microglobulin

Treatment outline recommendations for MCL



11.1.4. PERIPHERAL T-CELL LYMPHOMAS (PTCLS)

- PTCLs include primary nodal and primary extranodal subtypes.
- The present guidelines cover the systemic subtypes of primary nodal peripheral T-cell lymphomas.

- Primary nodal PTCLs include PTCL-not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL), both fusion protein ALCL anaplastic lymphoma kinase positive (ALCL ALK+) and ALCL anaplastic lymphoma kinase negative (ALCL ALK−), and angioimmunoblastic T-cell lymphoma (AITL).
- Primary extranodal PTCL subtypes comprise enteropathy-associated T-cell lymphoma (EATL), extranodal natural killer/T-cell lymphoma (ENKTCL), and hepatosplenic T-cell lymphoma (HSTCL).
- Primary leukemic PTCL subtypes (i.e. T-cell prolymphocytic leukaemia, T-cell large granular lymphocytic leukaemia, adult T-cell leukaemia/lymphoma and aggressive NK-cell leukaemia) as well as primary cutaneous T-cell lymphomas are not covered here and are covered separately.

Diagnosis

Table 1, bellow, summarizes the immunophenotypes of the PTCL entities along with their TCR rearrangement features and putative cell of origin.

Table 1. Nodal and extranodal PTCL subtypes—cell of origin and related phenotypes

	PTCL entity	Immunophenotypic features	TCR	Presumed cell of origin
Nodal	PTCL-NOS	CD4>CD8, frequent antigen loss (CD5, CD7), CD30+/−, CD56+/−, subset FTH features, cytotoxic granules+/−	αβ, rarely γδ	Variable, mostly T-helper cell
	AITL	CD4+, CD10+/−, BCL+/−, CXCL13+, PD1+, ICOS+/−, SAP+/, CCR5+/−, hyperplasia of FDC, EBV+ B blasts	αβ	FTH
	ALCL ALK+	ALK+, CD30+, EMA+, CD25+, cytotoxic granules+, CD4+/−, CD3+/−	αβ	Cytotoxic T-cell
	ALCL ALK-	ALK−, CD30+, EMA+, CD25+, cytotoxic granules+, CD4+/−, CD3+/−	αβ	Cytotoxic T-cell
Extranodal	EATL, type 1	CD8(+)/−, CD56−, HLA-DQ2/-DQ8	αβ	Intra-epithelial T cells (αβ), pre-existing enteropathy
	EATL, type 2	CD8+, CD56+, HLA-DQ2/-DQ8	γδ or αβ	Intra-epithelial T cells or NK, no pre-existing enteropathy
	NKTCL	CD2+, CD56+, surface CD3−, cytoplasmic CD3ε+, gr B+, TIA-1+, perforin+, EBV+, LMP1	TCR in germline configuration, rarely αβ or γδ	NK, rarely cytotoxic T cells
	HSTCL	CD3+, CD56+/−, CD4−, CD8+/−, CD5−, TIA1+, gr M+, gr B−, perforin−	γδ, rarely αβ	Cytotoxic T cell of the innate immune system

PTCL, peripheral T-cell lymphomas; PTCL-NOS, PTCL-not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALCL ALK+, anaplastic large-cell lymphoma anaplastic lymphoma kinase positive; ALCL ALK-, ALCL anaplastic lymphoma kinase negative; EATL, enteropathy-associated T-cell lymphoma; NKTCL, natural killer/T-cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; FTH, follicular T helper; FDC, follicular dendritic cell; EMA, epithelial membrane antigen; HLA, human leukocyte antigen; EBV, Epstein-Barr virus; TCR, T-cell receptor; NK, natural killer.

Prognostic indices

For clinical practice purposes, the IPI is therefore still the recommended tool.

Treatment

Nodal PTCL (PTCL-NOS, AITL, ALCL ALK$^+$, ALCL ALK$^-$):

First-line treatment

- Treatment strategies should be adapted according to factors such as age, IPI, and co-morbidity that define a patient's eligibility for dose-intensified approaches.
- In nodal PTCL, a dose-dense **CHOEP schedule followed by autoSCT** in chemosensitive and transplant-eligible patients represents an evidence-based approach.
- In low-risk (low-/low-intermediate IPI) ALCL ALK+ patients, consolidation with autoSCT is not recommended.
- The few patients with truly localised (stage I) disease should receive a shortened chemotherapy schedule (e.g. 3 courses), followed by local radiotherapy.
- Frail patients not eligible for intensive chemotherapy schedules may be considered for less toxic approaches such as monotherapy schedules, e.g. with gemcitabine.

Relapse

- Except for CD30+ ALCL, there is no specific standard of care for relapsed/refractory nodal PTCL (other than that of other aggressive NHL, mentioned before).
- The only globally approved salvage treatment in PTCL is the anti-CD30 antibody conjugate brentuximab vedotin (BV) administered in the setting of relapsed systemic ALCL (regardless of the ALK status).
- For relapsed/ refractory nodal PTCL other than ALCL, in fit patients, combination chemotherapy regimens such as DHAP or ICE can be attempted in chemosensitive patients with an available donor, aiming at alloSCT as a potentially curative modality. In unfit patients, monotherapy with gemcitabine is generally well-tolerated.

SUPPORTIVE TREATMENT FOR AGGRESSIVE LYMPHOMA PATIENTS

Tumor Lysis Syndrome

- **High-risk features**
  - Histologies of Burkitt Lymphoma and Lymphoblastic Lymphoma;
  - Elevated WBC
  - Bone marrow involvement
  - Pre-existing elevated uric acid
  - Ineffectiveness of allopurinol
  - Renal disease or renal involvement by tumor
- **Laboratory hallmarks of TLS:**
  - High potassium
  - High uric acid
  - High phosphorous
  - Low calcium

- **Symptoms of TLS**
  - Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.
  - If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.
- **Treatment of TLS**
  - TLS is best managed if anticipated and treatment started prior to chemotherapy.
  - Centerpiece of treatment includes:
    - Rigorous hydration
    - Management of hyperuricemia
    - Frequent monitoring of electrolytes and aggressive correction is Essential
    - Allopurinol beginning 2-3 days prior to chemotherapy and continued for 10-14 days

Management of HBV and HCV during Anti-CD20 Antibody Therapy

Hepatitis B virus (HBV)

- Hepatitis B surface antigen (HBsAg), antibody (HBsAB), and Hepatitis B core antibody (HBcAb) testing,
- Quantitative hepatitis B viral load by PCR only if one of the screening tests is positive
- Prophylactic antiviral therapy with entecavir (Baraclude tab, 0.5 mg PO daily before starting chemotherapy) is recommended for any patient who is HBsAg-positive and receiving anti-lymphoma therapy. In cases of HBcAb positivity, prophylactic antiviral therapy is preferred; however, if there is a concurrent high-level hepatitis B surface antibody, these patients may only be monitored with serial hepatitis B viral load.
- Avoid lamivudine (epzicom) due to risks of resistance development.
- Monitor hepatitis B viral load with PCR monthly through treatment and every 3 months thereafter
  - If viral load is consistently undetectable, treatment is considered prophylactic
  - If viral load fails to drop or previously undetectable PCR becomes positive, consult hepatologist and discontinue antiCD20 antibody therapy
- Maintain prophylaxis up to 12 mo (usually 3 mo) after oncologic treatment ends.
- Consult with hepatologist for duration of therapy in patient with active HBV

Hepatitis C virus (HCV)

- Patients should be initially treated with chemoimmunotherapy regimens according to the usual guidelines for NHL.
- Liver functional tests and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for development of hepatotoxicity.
- Antiviral therapy should be considered in patients in complete remission after completion of lymphoma therapy.

Appendix

INTERNATIONAL PROGNOSTIC INDEX

ALL PATIENTS

Prognostic Factors	Prognostic Groups	
Age >60 years	Low	0 or 1
Serum LDH > normal	Low intermediate	2
Performance status 2-4	High intermediate	3
Stage III or IV	High	4 or 5
Extra-nodal involvement >1 site		

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX

PATIENTS ≤ 60 YEARS

Prognostic Factors	Prognostic Groups	
Stage III or IV	Low	0
Serum LDH > normal	Low/intermediate	1
Performance status 2-4	High/intermediate	2
	High	3

REVISED-IPI

All PATIENTS

Prognostic Factors	Prognostic groups	
Age >60 years	Very Good	0
Serum LDH > normal	Good	1-2
Performance status 2-4	Poor	3-5
Stage III or IV		
Extra-nodal involvement >1 site		

AN ARBOR STAGING SYSTEM

I. Involvement of a single lymphatic region (I) or localized involvement of single extra-lymphatic organ or site (IE).

II. Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localized involvement of a single extra-lymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm (IIE).

III. Involvement of lymphatic regions on both side of the diaphragm.

IV. Diffuse or disseminated involvement of one or more extra-lymphatic organs with or without lymphatic involvement.

RESPONSE ASSESSMENT OF NHL (NOT INCLUDING PET)

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
Cru (unconfirmed)	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	50% decrease	50% decrease	Irrelevant
	Decrease in liver/spleen	50% decrease	50% decrease	Irrelevant
Relapse/ Progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

11.2. Highly Aggressive Lymphomas

11.2.1. Adult Burkitt`s Lymphoma

Diagnosis

- Tissue diagnosis and staging is time-sensitive
- Histology and immunophenotyping
- For proper staging
    - Bilateral bone marrow biopsies (due to patchy distribution)
    - CT (neck, chest, abdomen, pelvis)
    - PET (whole body)
    - Lumbar puncture +/- MRI brain if CSF involvement

Staging and Risk Assessment

- **St. Jude Staging System**

Stage	Description
I	• A single tumor (extranodal) • Single anatomic area (nodal) **with the exclusion** of mediastinum or abdomen
II	• A single tumor (extranodal) regional node involvement • Two or more nodal areas on the **same side** of the diaphragm • Two single (extranodal) tumors **with or without** regional node on the same side of the diaphragm • A primary gastrointestinal tract tumor with or without mesenteric nodes, **grossly and completely excised**
III	• Two single tumors (extranodal) on **opposite sides** of the diaphragm • Two or more nodal areas **above and below** the diaphragm • All of the primary **intrathoracic** tumors (mediastinal, pleural, thymic) • All extensive primary **intra-abdominal** disease • All **paraspinal** or **epidural** tumors, regardless of the other tumor site(s)
IV	• **Any of the above with** initial CNS and/or bone marrow involvement (<25% malignant)

- Groups are stratified by: extent of disease, staging, and relative risk of relapse, with treatment intensity based on group designation

Group	Description
A	• Completely resected Stage I • Completely resected abdominal Stage II lesions
B	All cases not eligible for Group A or Group C
C	• Any CNS involvement and/or bone marrow involvement (>25% blasts) ***CNS involvement signifies:** •Any L3 blasts in CSF •Cranial nerve palsy (if not explained by extracranial tumor) •Clinical spinal cord compression •Isolated intra-cerebral mass •Parameningeal extension: cranial and/or spinal

Treatment

- Chemotherapy: Cornerstone of treatment + intra thecal therapy
- Surgery: Limited role
  - To perform complete resection of GI tumor, allowing for restaging of disease (i.e. less intensive chemo)
- Radiation: restricted to emergency situations
  - Mediastinal disease, cord compression
  - Palliative pain control
  - BMT (Relapse)

- **Chemotherapy**
  - Because of its aggressive behavior, BL should be treated with intensive multiagent regimens
  - Treatment should be given in experienced centers.
  - No specific regimen can be recommended, and different chemotherapy protocols can be used.
  - The intensity of the treatment may be adapted according to the stage or other risk factors.
  - Hyper-CVAD with rituximab, DA-EPOCH-R regimens or Burkitt-ALL regimen (see before) may be used

- **Potential Emergencies**
  - Upper airway obstruction possible with some jaw tumors
  - Permanent paraplegia can arise if not treated within 24-48 hours: may arise anyway

- Vision may be lost with intraorbital tumor
- Pericardial tamponade, respiratory compromise or oliguria with serous effusions – worsened by hydration
- Renal failure from hyperuricemia with large tumors
- Inferior vena caval obstruction: pulmonary embolus
- Hypoglycemia or hypercalcemia (rare)

- CNS prophylaxis to reduce the high risk of CNS relapse must be given.
- Tumor lysis syndrome prophylaxis should be started immediately at diagnosis to prevent spontaneous tumor lysis.
- **At relapse**, HDT with ASCT or allogeneic transplantation should be considered in patients achieving a second response to salvage regimens for aggressive lymphomas (see before).

11.2.2. Lymphoblastic lymphoma

- Lymphoblastic lymphoma (LBL) and acute lymphoblastic leukemia (ALL) are considered to be the same disease with different clinical presentation.
- LBL is arbitrarily defined by the presence of enlarged LN (frequently a mediastinal mass) and <20% lymphoblasts in the BM, contrasting with >20% in ALL.
- As in ALL, there is a high risk of CNS infiltration at diagnosis, so CNS should be evaluated with CSF examination including flow cytometry.
- Conventional regimens for NHL result in a short DFS. Intensive NHL protocols improve the results.
- LBL should be exclusively treated in experienced centers with ALL-like regimens (see ALL protocols).
- CNS prophylaxis with intrathecal chemotherapy, high-dose MTX or Ara-C, or irradiation reduces the high risk of CNS relapse.

11.3. Indolent Lymphomas

11.3.1. FOLLICULAR LYMPHOMA

Diagnosis

- Diagnosis should be based on an excisional lymph node biopsy.
- Core biopsies should only be carried out in patients without easily accessible lymph nodes (e.g. retroperitoneal bulk).
- Fine-needle aspirations are inappropriate for a reliable diagnosis.
- The histological report should give the diagnosis according to the World Health Organization (WHO) classification.
- Grading of lymph node biopsies is carried out according to the number of blasts/high power field (Table 1).
- FL grade 3B (with sheets of blasts) is considered an aggressive lymphoma and treated accordingly, whereas grades 1, 2, and 3A should be treated as indolent disease.

Table 1. Grading of follicular lymphoma

Grade	Description
1	≤5 blasts/high power field
2	6–15 blasts/high power field
3A	>15 blasts/high power field, centroblasts with intermingled centrocytes
3B	>15 blasts/high power field, pure sheets of blasts

Staging and risk assessment

- Initial staging should be thorough, particularly for patients with early stages I and II (10%–15%) (Table 2).
- Initial work-up should include a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy (Table 3).
- Positron emission tomography–computed tomography (PET-CT) scan is not mandatory. In rare stage I/II cases, PET-CT scan may be useful to confirm localised stage I/II disease before localised radiotherapy.
- A complete blood count, routine blood chemistry including lactate dehydrogenase, β2-microglobulin and uric acid as well as screening tests for hepatitis B and C are required.
- The staging is carried out according to the Ann Arbor classification system with mention of bulky disease >5 cm when appropriate.

- For prognostic purposes, a 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI, Table 4) is used. A revised FLIPI 2 (incorporating β2-microglobulin, diameter of largest lymph node, bone marrow involvement and hemoglobin level) has been recently suggested.
- Biological parameters are still investigational for prognostic assessment and are not yet suitable for clinical decision-making.

Table 2. Ann Arbor classification

Stage	Area of involvement
I (I_E)	One lymph node region or extralymphatic site (I_E)
II (II_E)	Two or more lymph node regions or at least one lymph node region plus a single localised extralymphatic site(II_E) on the same side of the diaphragm
III (III_E, III_S)	Lymph node regions or lymphoid structures (e.g. thymus, Waldeyer's ring) on both sides of the diaphragm with optional localised extranodal site (III_E) or spleen (III_S)
IV	Diffuse or disseminated extralymphatic organ involvement
For all stages	
A	no symptoms
B	unexplained fever of >38°C, drenching night sweats; or loss of >10% body weight within 6 months

Table 3. Diagnostic work-up

History	B symptoms
Physical examination	Peripheral lymph nodes, liver, spleen
Laboratory work-up	Blood and differential count
	Optional: FACS, PCR for BCL-2 rearrangement
	LDH (suspected transformation), uric acid
	electrophoresis (optional: immune fixation)
	β2-microglobulin (FLIPI 2)
Serology	Hepatitis B, C and HIV serology
Imaging	Chest X-ray
	Abdominal ultrasound
	CT neck, chest, abdomen, pelvis
	MRT only in selected locations (CNS)
	Optional: PET
Bone marrow	Histology
	Cytology
	Optional: FACS, PCR for BCL-2 rearrangement
Toxicity	Electrocardiogram, cardiac ultrasound (before anthracyclines, ASCT)
	Creatinine clearance
	Optional: reproductive counselling in young patients

FACS, fluorescence-activated cell sorting; PCR, polymerase chain reaction; LDH, lactate dehydrogenase; FLIPI 2, Follicular Lymphoma International Prognostic Index 2; HIV, human immunodeficiency virus; MRT, magnetic resonance tomography; CNS, central nervous system; PET, positron emission tomography; ASCT, autologous stem-cell transplantation; BCL-2, B-cell lymphoma 2.

Table 4. 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI) risk factors

Parameter	Definition of risk factors	
	FLIPI 1	FLIPI 2
Nodal sites	*>4 lymph node regions*	*Long diameter of largest lymph node*
Age	Above 60 years	Above 60 years
Serum marker	Elevated LDH	Elevated β2-microglobulin
Stage	Advanced (III–IV according to Ann Arbor classification)	Bone marrow involvement
Haemoglobin	<12 g/dl	<12 g/dl

With 0–1 risk factors, low risk; 2, intermediate risk; 3–5, high risk.
LDH, lactate dehydrogenase.

Treatment of FL

First line

Stage I–II

- Radiotherapy (involved field, 24–36 Gy) is the preferred treatment having a curative potential.
- In selected cases, watchful waiting or rituximab monotherapy may be considered to avoid the side-effects of radiation (e.g. cervical: sicca syndrome; abdominal: myeloablative suppression).
- In stage I–II patients with large tumor burden or adverse prognostic features, systemic therapy as indicated for advanced stages should be applied; a radiation consolidation may be considered depending on tumor location and expected side-effects.

Stages III–IV

- Therapy should be initiated only upon the occurrence of symptoms including B symptoms, hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion, or rapid lymphoma progression.
- The current therapeutic approach is based on clinical risk factors, symptoms and patient perspective (Figure 1).
- Rituximab in combination with chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine should be used.
- CVP (cyclophosphamide, vincristine and prednisone) combination results in inferior PFS, but no impact on OS was observed between these chemotherapy regimens.
- Full courses of purine analogue-based schemes [FC (fludarabine and cyclophosphamide) or FM (fludarabine and mitoxantrone)] are not recommended due to higher hematological toxicities.
- In case of (histological or clinical) characteristics of transformation to aggressive lymphoma, an anthracycline-based regimen should be preferred.
- Four prospective first-line trials, two salvage trials and a systematic meta-analysis confirmed an improved overall response, PFS and OS if rituximab was added to chemotherapy.
- In patients with positive hepatitis B serology, prophylactic antiviral medication is strongly recommended.
- Myeloablative consolidation followed by autologous stem-cell transplantation (ASCT) is not recommended in first-line therapy of responding patients.

ph node >

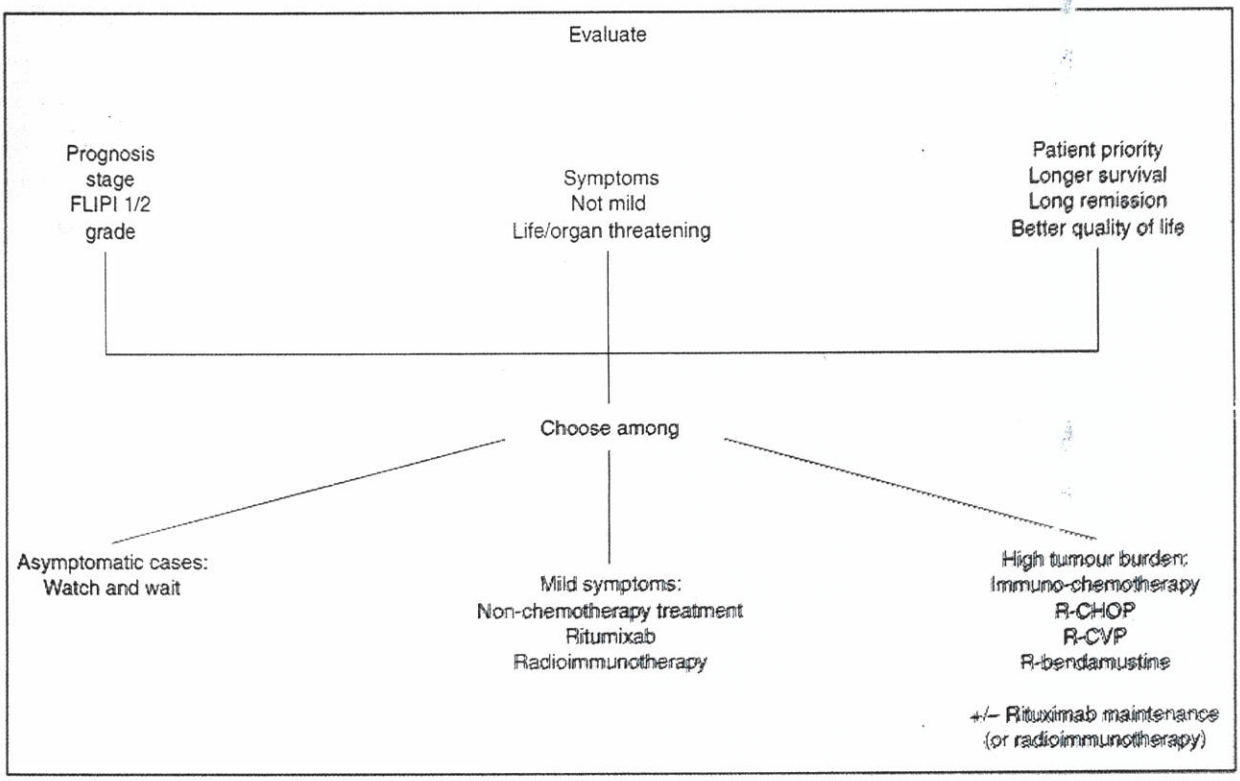


Figure 1. Therapeutic algorithm for Follicular lymphoma

Relapsed disease

- A repeated biopsy is strongly recommended to rule out a secondary transformation into aggressive lymphoma, and to consider Pet/Ct scan to guide for biopsy site.
- As at first presentation, observation is an accepted approach in asymptomatic patients with low tumor burden.
- Selection of salvage treatment depends on efficacy of prior regimens. In early relapses (<12–24 months), a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP or vice versa). Rituximab should be added if the previous antibody-containing scheme achieved >6 months duration of remission
- In symptomatic cases with low tumor burden, a rituximab monotherapy may be applied.
- Rituximab maintenance for up to 2 years has a favorable side-effect profile and, based on a systematic meta-analysis, substantially prolongs PFS and OS in relapsed disease even after antibody-containing induction in patients who have not received antibody as first-line therapy.
- High-dose chemotherapy with ASCT prolongs PFS and OS and should be considered, especially in patients with short-lived first remissions after rituximab-containing regimens.

- In selected younger patients with high-risk profile or relapse after ASCT, a potentially curative allogeneic stem-cell transplantation (preferably with dose-reduced conditioning) may be discussed.

Response evaluation

- Adequate radiological tests should be carried out midterm and after completion of chemotherapy. Patients with insufficient or lacking response [less than partial response (PR)] should be evaluated for early salvage regimens.
- No consensus could be reached on the routine application of PET-CT for response evaluation. Also, minimal residual disease (MRD) analysis by polymerase chain reaction at the end of the treatment should not guide therapeutic strategies outside clinical studies.

Long-term follow up

- History and physical examination every 3 months for 2 years, every 4–6 months for 3 additional years, and subsequently once a year with special attention to transformation and secondary malignancies including secondary leukaemia.
- Blood count and routine chemistry every 6 months for 2 years, then only as needed for evaluation of suspicious symptoms.
- Evaluation of thyroid function in patients with irradiation of the neck at 1, 2 and 5 years.
- Minimal adequate radiological or ultrasound examinations every 6 months for 2 years and annually thereafter. Regular CT scans are not mandatory, especially if abdominal ultrasound is applicable. PET-CT should not be used for surveillance.

11.3.2. MARGINAL ZONE LYMPHOMAS (MZL)

- MZL is defined as lymphoma where malignant lymphocytes derive from and infiltrate the marginal zone of lymphoid follicles.
- WHO 2008 Classification: 3 Subtypes
  - MZL of MALT
  - Nodal MZL (NMZL)
  - Splenic MZL (SMZL)
- Morphologically heterogeneous mainly small B centrocyte-like lymphocytes, variable plasma cell differentiation, CD 20 +, and CD 5, CD 10, CD 23, bcl-6, cyclin D1: negative.

11.3.2.1. MZL of MALT:

Initial work-up

- Routine basic CBC, biochemical studies
- CT chest, abdomen, and pelvis
- BM biopsy
- Gastroduodenal endoscopy
- H. pylori status: IHC, breath test, serology

Treatment

- **Localized Disease:**
  - Anti H. pylori triple therapy (a proton pump inhibitor, clarithromycin, amoxicillin, or metronidazole) for localized disease in the stomach
  - After 4-6 weeks, a breath test should be performed
  - Regression occur within 6 months of treatment, may be 12 months
  - Endoscopic follow up: 3-6 months, 6 months for 2 years
  - Other work-up / year
- **Localized disease which is H. Pylori negative, antibiotic resistant or non-gastric tumors:**
  - RTH (30-40 Gy) is widely used with excellent results
  - Watch and Wait: for localized non-symptomatizing disease.
- **Disseminated disease:**
  - Asymptomatic: watch and wait
  - When treatment is required: non-intensive immunochemotherapy like in follicular low-grade NHL
  - Transformation: like DLBCL

11.3.2.2. Splenic MZL (SMZL):

Diagnosis

- While splenic histology is not mandatory for diagnosis, it should be based on a combination of PB morphology, BM histology, immunophenotype, and cytogenetics

Treatment

- **Indications**
  - Painful splenomegaly
  - Significant cytopenia (HB<10gm/dl, platelet <80 000 ml)
  - Progressive lymphadenopathy
  - Extranodal involvement
  - **Splenectomy** is the historical treatment, not curative. Spleen should not be routinely removed, as it is not required for diagnosis and splenectomy is no longer the standard treatment
  - **Rituximab** is a better and relatively non-toxic treatment alternative to splenectomy for SMZL

11.3.2.3. Nodal MZL (NMZL):

- Only symptomatic NMZL patients should be treated.
- There is no standard therapy.
- It may be treated like follicular lymphoma.

11.4. Hodgkin's lymphoma

DIAGNOSIS

- Pathological diagnosis should be made according to the WHO classification from a sufficiently large surgical specimen or excisional lymph node biopsy
- In Classical HL (cHL), the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining while the detection of lymphocyte predominant cells is required for the diagnosis of NLPHL (Nodular Lymphocyte Predominant HL).
- The immunophenotype of the malignant cells in cHL and NLPHL differs significantly. In contrast to HRS cells that stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, LP cells are characterized by the expression of CD20 and CD45, but they lack CD15 and CD30.

STAGING AND RISK ASSESSMENT

- Work-up is shown in Table 1.
- Medical history and physical examination including the presence of B symptoms (fever, drenching night sweats, unexplained weight loss >10% of total body weight over 6 months) and other disease-related symptoms such as fatigue, pruritus and pain.
- Chest X-ray and a CT scan of neck, chest and abdomen are mandatory. In addition, a baseline PET should be carried out whenever this diagnostic tool is available.
- Given the high sensitivity of PET/CT for bone marrow involvement, a bone marrow biopsy is no longer indicated in patients undergoing PET/CT evaluation. However, bone marrow biopsy must be carried out if PET/CT is not available.
- Full blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein, alkaline phosphatase, lactate dehydrogenase, liver enzymes and albumin, and kidney function tests. Screening for hepatitis B, and hepatitis C is compulsory.
- Staging is carried out according to the Ann Arbor classification in consideration of defined clinical risk factors. Patients are allocated to three categories (limited, intermediate and advanced stages, Table 2).
- To identify patients at increased risk for acute and/or long-term complications, cardiac and pulmonary function tests should be carried out before the start of treatment.
- Since chemotherapy and radiotherapy (RT) can potentially cause permanent fertility damage, reproductive counselling must be offered to young patients of both genders before treatment.

TREATMENT OF cHL

limited-stage patients

- Combined modality treatment consisting of a brief chemotherapy followed by RT. Currently, two or three cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) (Table 3) followed by involved field RT (20 Gy IFRT) is considered standard of care for limited-stage HL. However, the current RT guidelines of the

International Lymphoma Radiation Oncology Group (ILROG) recommend involved-site RT (ISRT) after chemotherapy in limited stages.

- The question of whether RT can be omitted in patients with complete metabolic response at interim PET is currently a matter of debate. Therefore, interim PET-guided treatment in limited-stage HL is not recommended outside clinical studies.

Intermediate-stage patients

- Four cycles of ABVD followed by 30 Gy IFRT is considered standard for intermediate-stage HL.
- In patients ≤60 years who are eligible for a more intensive treatment, this standard is challenged by a protocol consisting of two cycles of **BEACOPP escalated regimen** (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone in escalated dose) (Table 4) followed by two cycles of ABVD and 30 Gy IFRT.
- The question of whether RT is dispensable in intermediate stage patients with complete metabolic response at interim PET is unanswered. Trials addressing this issue are ongoing.

Advanced-stage patients

- Advanced-stage HL is treated with chemotherapy alone. Additional RT is confined to patients with residual disease after chemotherapy.
- Patients ≤60 years are treated with either six to eight cycles of ABVD followed by localised RT of residual disease larger than 1.5 cm or six cycles of BEACOPP escalated followed by localized RT of PET-positive residual lesion larger than 2.5 cm.
- In patients >60 years, the BEACOPP regimen should not be given, as an increased rate of treatment-related mortality has been observed. Thus, ABVD represents the standard regimen for older HL patients who are fit enough for treatment with multi-agent chemotherapy.
- Given a lack of mature prospective data, treatment stratification on the basis of early interim PET cannot be considered standard as yet.

Relapsed disease

- For most patients with refractory or relapsed HL, the treatment of choice consists of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT).
- Salvage regimens such as dexamethasone/high-dose Ara-C/cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/carboplatin/etoposide (ICE) (see before) are given to reduce the tumor burden and mobilize stem cells before high-dose chemotherapy and ASCT.

- A subset of low-risk patients relapsing after primary treatment with two cycles of chemotherapy followed by RT can be successfully salvaged with a second, more intensive conventional chemotherapy such as BEACOPP escalated.
- In some patients with localised late relapse, salvage RT alone appears to be sufficient.
- In patients with multiple relapses who have no other treatment options, the use of palliative single agent chemotherapy with gemcitabine, vinblastine, and/or regional RT.

TREATMENT OF NLPHL

Stage IA without risk factors

- 30 Gy IFRT alone is the standard treatment for stage IA NLPHL patients without risk factors.

Other stages

- Usually, NLPHL is treated identically to cHL in all stages except for stage IA without risk factors.

Relapsed NLPHL patients

- Even more importantly than in cHL, a renewed biopsy should be obtained in patients with suspected NLPHL relapse before salvage therapy is initiated, since transformation into aggressive non-Hodgkin's lymphoma must be excluded.
- Localised NLPHL relapses can be effectively treated with rituximab alone.
- Patients with more advanced disease at relapse often require a more aggressive salvage therapy possibly combined with an anti-CD20 antibody.

RESPONSE EVALUATION

- Interim response evaluation by contrast-enhanced CT should be carried out after completion of chemotherapy/before RT in limited and intermediate stages and after four cycles of chemotherapy as well as before RT in advanced stages.
- In advanced-stage and relapsed patients, interim PET appears to be a useful tool to identify poor-risk individuals. However, interim PET-guided treatment cannot be considered standard except for the decision of whether patients with advanced HL receiving BEACOPP-escalated require RT.
- Final staging should be carried out after completion of treatment. Physical examination, laboratory analyses and contrast enhanced CT are mandatory. In addition, PET should be carried out at final staging whenever this diagnostic tool is available

FOLLOW UP

- Additional evaluation of thyroid function (thyroid-stimulating hormone) after irradiation of the neck at one, two and at least five years is recommended.
- Furthermore, testosterone and estrogen levels should be monitored, particularly in younger patients who had intensive chemotherapy.

- CT scans and previously pathologic radiographic tests must be carried out once to confirm the remission status. Thereafter, surveillance scans are not indicated unless clinical symptoms occur.
- Patients should be asked for symptoms indicating the existence of long-term toxicity, particularly of heart and lung. Cancer screening should be conducted regularly due to the increased risk of hematological and solid secondary malignancies after HL treatment.

Table 1. Diagnostic work-up in Hodgkin's lymphoma

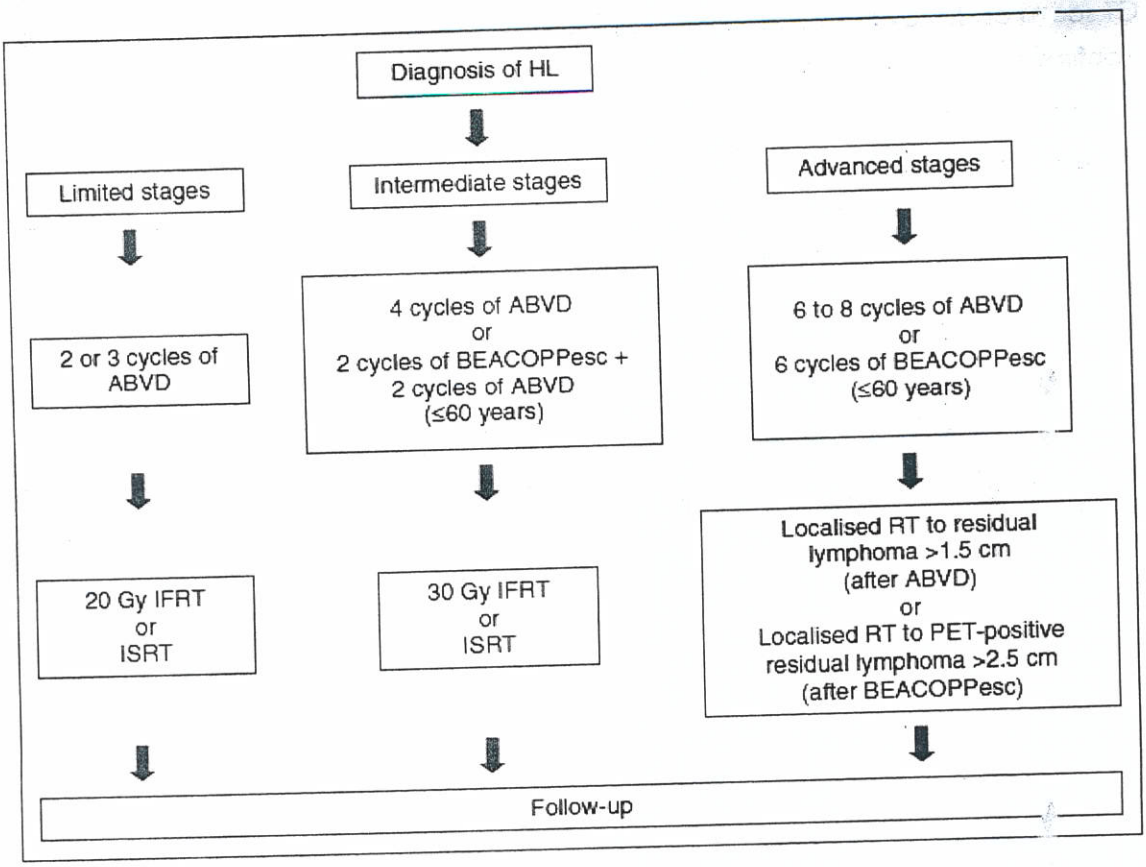
Diagnosis
Lymph node biopsy (or a biopsy from another organ with suspected affection)
Staging and risk stratification
Medical history and physical examination
X-ray of the chest
Contrast-enhanced CT scan of neck, chest and abdomen
PET
Full blood cell count and blood chemistry
HBV, HCV and HIV screening
Pre-treatment examinations
ECG
Echocardiography
Pulmonary function test
Reproductive counselling (in younger patients)
Serum pregnancy test (in younger female patients)

CT, computed tomography; PET, positron emission tomography; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; ECG, electrocardiography.

Table 2. Definition of Hodgkin's lymphoma risk groups according to the European Organisation for Research and Treatment of Cancer /Lymphoma Study Association and the German Hodgkin Study Group

Treatment group	EORTC/LYSA	GHSG
Limited stages	CS I–II without risk factors (supra-diaphragmatic)	CS I–II without risk factors
Intermediate stage	CS I–II with ≥1 risk factors (supra-diaphragmatic)	CS I, CS IIA with ≥1 risk factors; CS IIB with risk factors C/D, but not A/B
Advanced stages	CS III–IV	CS IIB with risk factors A/B, CS III/IV
Risk factors	(A) Large mediastinal mass	(A) Large mediastinal mass
	(B) Age ≥50 years	(B) Extranodal disease
	(C) Elevated ESR	(C) Elevated ESR
	(D) ≥4 nodal areas	(D) ≥3 nodal areas

Elevated ESR: >50 mm/h without B symptoms, >30 mm/h with B symptoms.
Large mediastinal mass: more than one-third of the maximum horizontal chest diameter.
B symptoms: fever, night sweat, unexplained weight loss >10% over 6 months.
EORTC: European Organisation for Research and Treatment of Cancer; LYSA: Lymphoma Study Association; GHSG: German Hodgkin Study Group; CS: clinical stage; ESR: erythrocyte sedimentation rate.



Therapeutic algorithm for newly diagnosed Hodgkin's lymphoma.

Table 3. The adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) regimen

Adriamycin	25 mg/m^2	i.v.	Days 1 + 15
Bleomycin	10 mg/m^2	i.v.	Days 1 + 15
Vinblastine	6 mg/m^2	i.v.	Days 1 + 15
Dacarbazine	375 mg/m^2	i.v.	Days 1 + 15

Recycle: day 29.

Table 4. The bleomycin/etoposide/adriamycin/cyclophosphamide/ vincristine/ procarbazine/ prednisone in escalated dose (BEACOPPescalated) regimen

Bleomycin	10 mg/m^2	i.v.	Day 8
Etoposide	200 mg/m^2	i.v.	Days 1–3
Adriamycin	35 mg/m^2	i.v.	Day 1
Cyclophosphamide	1250 mg/m^2	i.v.	Day 1
Vincristine	1.4 mg/m^2 (maximum: 2 mg)	i.v.	Day 8
Procarbazine	100 mg/m^2	p.o.	Days 1–7
Prednisone	40 mg/m^2	p.o.	Days 1–14
G-CSF		s.c.	From day 8

Recycle: day 22.
G-CSF, granulocyte colony-stimulating factor.

11.5. Chemotherapeutic regimens for lymphomas

CHOP +/- R	**Day 1:** Rituximab 375mg/m^2 **Day 1:** Cyclophosphamide 750 mg/m^2, doxorubicin 50mg/m^2, and vincristine 1.4mg/m^2 IV bolus (max dose 2mg) **Days 1–5:** Prednisone 40mg/m^2. **Repeat every 3 weeks for 6-8 cycles.**
mini-CHOP +/- R	**Day 1:** Rituximab 375mg/m^2 **Day 1:** Cyclophosphamide 400mg/m^2, doxorubicin 25mg/m^2, and vincristine 1mg **Days 1–5:** Prednisone 40mg/m^2. Repeat every 3 weeks for 6-8 cycles.
CEPP +/- R	**Day 1:** Rituximab 375mg/m^2 **Days 1 and 8:** Cyclophosphamide 600mg/m^2 IV **Day 1-3:** Etoposide IV 70mg/m^2 IV **Days 1–10:** Procarbazine 60mg/m^2 PO and prednisone 60mg/m^2 PO. Repeat every 28 days
CNOP +/- R	**Day 1:** Rituximab 375mg/m^2 **Day 1:** Cyclophosphamide 750mg/m^2 IV, mitoxantrone 10mg/m^2 IV, and vincristine 1.4mg/m^2 IV (max dose 2mg) **Days 1–5:** Prednisone 50mg/m^2 PO. Repeat cycle every 3 weeks for 6 cycles (max 8 cycles).
CEOP +/-R	**Day 1:** Rituximab 375mg/m^2 **Day 1:** Cyclophosphamide 750mg/m^2 IV, etoposide 50mg/m^2 IV, and vincristine 1.4mg/m^2 IV (max dose 2mg) **Days 1–5:** Prednisone 100mg PO **Days 2–3:** Etoposide 100mg/m^2 PO. Repeat cycle every 3 weeks
CVP +/- R	**Day 1:** Rituximab 375mg/m^2 IV, cyclophosphamide 750mg/m^2 IV, and vincristine 1.4 mg/m^2 IV (max 2mg) **Days 1–5:** Prednisone 40mg/m^2 PO. Repeat every 21 days.

DHAP	**Days 1–4:** Cisplatin 100mg/m² IV via 24-hour infusion, cytosine 2g/m² in 2 pulses each given 12 hours apart, and dexamethasone 40mg PO or IV. Repeat in 3–4 weeks.
ESHAP	**Days 1–4:** Etoposide 40–60mg/m² **Days 1–5:** Methylprednisolone 250–500mg IV **Day 5:** Cytarabine 2 gm/m² IV over 2–3 hours **Days 1–4:** Cisplatin 25mg/m² IV via 24-hour infusion Repeat every 3–4 weeks.
GDP	**Days 1 and 8:** Gemcitabine 1000 mg/m² IV over 30 minutes **Days 1–4:** Dexamethasone 40mg PO **Day 1:** Cisplatin 75mg/m² IV OR carboplatin at AUC = 5 IV over 30 minutes Repeat every 3 weeks.
GEM-OX	**Day 1:** Gemcitabine 1000 mg/m² and oxaliplatin 100mg/m². Repeat every 15 days if ANC >1 × 10^9/L and platelet count >100 ×10^9/L; if not, then every 3 weeks.
ICE **Option 1/2**	**Days 1–3**: Ifosfamide 2000 mg/m²/d iv over 2 h (hours 0-2), Mesna 25% of Ifosphamide dose IV 30 minutes before Ifosfamide, repeat 3, 6 and 9 hrs after Ifosfamide. **Days 1–3**: Etoposide 100-150 mg/m²/d iv over 3 hrs after Ifosfamide (hours 2-5) **Day 1:** Carboplatin (AUC 5, max 800 mg) over 2 h after Etoposide D1 only (hours 5-7)
ICE **Option 2/2**	**Days 1–3**: Etoposide 100-150 mg/m² IV over 3 hrs **Day 2:** Carboplatin AUC = 5 (max dose 800 mg) over 2 h **Day 2:** Ifosfamide admixed with mesna both at a dose of 5 gm/m² via 24-hour continuous IV beginning day 2. **On Days 5–12 (or days 7–14):** Filgrastim 5mcg/kg/day for cycles 1–2, increased to 10 mcg/kg/day following cycle 3 until completion of peripheral blood stem cell collection, ± Repeat every 14 days or when ANC >1000 cells/mcL and platelet count >50000/mcL.

MINE **For HL**	**Days 1–3:** Mesna 1.5g/m² and Ifosfamide 1.5g/m² **Day 1:** Mitoxantrone 10mg/m² **Days 1–3:** Etoposide 80mg/m² Repeat every 3 weeks for 2 cycles.
MINE **For NHL**	**Days 1–3:** Mesna 1.33g/m² and Ifosfamide 1.33g/m² **Day 1:** Mitoxantrone 8mg/m² **Days 1–3:** Etoposide 65mg/m² Repeat every 3 weeks for 2 cycles.
DA-EPOCH **+/- R**	**Day 1:** Rituximab 375mg/m² ***Days 2–4:*** *Doxorubicin 15mg/m² via continuous IV infusion, etoposide 65mg/m² via continuous IV infusion, and vincristine 0.5mg via continuous IV infusion* **Day 5:** Cyclophosphamide 750mg/m² IV **Days 1–14:** Prednisone 60mg/m² PO *Repeat every 21 days.*
CHOEP	***Days 1–4:*** *Etoposide 50mg/m²/day continuous IV infusion* + doxorubicin 10mg/m²/day continuous IV infusion + vincristine 0.4mg/m²/day continuous IV infusion **Days 1–5:** Prednisone 60mg/m² orally daily **Day 5:** Cyclophosphamide 750mg/m² IV over 15 minutes. Repeat cycle every 3 weeks for 6–8 cycles.
Ifosfamide + Gemcitabine + Etoposide + Vinorelbine (IGEV)	**Days 1–4:** Mesna 400mg/m² IV over 15 minutes prior to Ifosfamide dose and at 4 and 8 hours from the start of each Ifosfamide dose + Ifosfamide 2,000 mg/m² over 3 hours **Days 1 and 4:** Gemcitabine 800mg/m² IV over 30 minutes **Day 1:** Vinorelbine 20mg/m² IV over 5–10 minutes **Days 1–4:** Prednisone 100mg PO daily. Repeat cycle every 3 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (non-transplant candidates).

HyperCVAD +/- R	**Cycle 1, 3, 5, 7:** **Day 1:** Rituximab 375mg/m^2 **Days 1–3:** Cyclophosphamide 300mg/m^2 over 2 hours every 12 hours for 6 doses + mesna 600mg/m^2/day continuous IV infusion starting 1 hour before cyclophosphamide until 12 hours after completion **Day 4:** Doxorubicin 50mg/m^2 IV over 24 hours **Days 1–4 and Day 11–14:** Dexamethasone 40mg IV or PO **Days 4 and 11:** Vincristine 2mg IV. **Cycle 2, 4, 6, 8:** **Day 1:** Rituximab 375mg/m^2 **Day 1:** Methotrexate 200mg/m^2 IV over 2 hours, then 800mg/m^2 IV over 22 hours + leucovorin 50 mg IV every 6 hours beginning 12 hours after completion of methotrexate **Days 2 and 3:** Cytarabine 3,000mg/m^2 (1,000mg/m^2 for patients ≥60 years old) IV over 2 hours every 12 hours. **CNS Prophylaxis** **Day 2:** Methotrexate 12mg intrathecally **Day 7:** Cytarabine 100mg intrathecally.
FC	**Days 1-3:** Fludarabine (25 mg/m^2/d, ½ h IVI), cyclophosphamide (250 mg/m^2/d) Every 4 weeks
Gemcitabine + Vinorelbine	**Days 1 and 8:** Gemcitabine 1 gm/ m^2 Vinorelbine 20 mg/ m^2 Every 3 weeks
Gem-Ox	Gemcitabine 1000 mg/m^2 plus oxaliplatin 100 mg/m^2 on **day 1**. Every 15 days
Gem-Cis	Gemcitabine 1000 mg/m^2 on **days 1 and 8** plus cisplatin 100 mg/m2 on **day 1**; every 21d
BR	**Days 1–2:** Bendamustine 90 mg/m^2, **Day 1:** Rituximab 375 mg/m^2. Repeat every 28 days for up to 6 cycles.

Single agent therapy	
Bendamustine	**Days 1–2:** Bendamustine 120 mg/m^2 Repeat every 3 weeks (6-8 cycles).
Vinblastine	4-6 mg/ m^2 weekly until disease progression or intolerable toxicity
Rituximab	**Day 1:** Rituximab 375mg/m^2 IV during each cycle of chemotherapy for up to 8 infusions.
Rituximab	**Day 1:** Rituximab 375 mg/m^2 IV. Repeat every 7 days for 4 cycles.
Chlorambucil	Chlorambucil: 0.1 mg/kg/day for 45 days then on days 1–15, monthly for 4 months
Gemcitabine	1000 mg/m^2 IV infusion over 1-hour days 1, 8, and 15 every 4 weeks.
Oral Etoposide	50-100 mg PO daily for 14-21 days every month for 6-12 months.

Concurrent Presentation with CNS Disease	
Parenchymal	Systemic methotrexate 3g/m^2 or more on day 15 of a 21-day R-CHOP cycle that has been supported by growth factors.
Leptomeningeal	Methotrexate/cytarabine IT. Consider Ommaya reservoir placement and/or systemic methotrexate 3–3.5g/m^2.

12. POLICY FOR SUPPORTIVE TREATMENT OF ADULT HEMATOLOGICAL MALIGNANCIES

12.1. Use of hematopoietic colony stimulating factors (CSFs) in hematologic malignancies

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) RECOMMENDATIONS (2006)

1. **Primary prophylaxis:** is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For "dose-dense" regimens, CSF is required and recommended. Use CSF when the risk of FN is in the range of ≥20%.
2. **Primary prophylaxis (Special circumstances):** Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age > 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; BM involvement by tumor-producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate, even with regimens with FN rates of < 20%.
3. **Secondary prophylaxis:** is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
4. **Afebrile neutropenia:** CSF should not be routinely used.
5. **Febrile neutropenia:** CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 X 10^9/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.
6. **Dose intensity/density of chemotherapy:** should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data.
7. **Adjuncts to progenitor-cell transplantation:** Administration of CSF to mobilize PBPC often in conjunction with chemotherapy, and their administration after autologous, but not allogeneic, PBPC transplantation is the current standard of care.
8. **AML (initial or repeat induction chemotherapy):** CSF use following initial induction

therapy is reasonable, though there has been no favorable impact on remission rate, remission duration, or survival. Patients > 55 years of age may be most likely to benefit from CSF use.

9. **AML (CSF for priming effects):** Use of CSF for priming effects is not recommended.
10. **AML (Consolidation chemotherapy):** CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive post-remission chemotherapy.
11. **AML (in relapse):** CSF should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia.
12. **MDS:** Intermittent administration of CSF may be considered in a subset of patients with severe neutropenia and recurrent infection.
13. **ALL:** CSF administration is recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post-remission course, thus shortening the duration of neutropenia of < 1,000/mm^3 by approximately 1 week.
14. **Radiotherapy ± chemotherapy:** CSF should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSF may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.
15. **Older patients (≥65 y):** Prophylactic CSF for patients with lymphoma treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections.

12.2. Transfusion Policy

- **ABO/Rh compatible packed RBCs** should be given to maintain HB level ≥ 8 gm/dl and hematocrit ≥25%.
- **Prophylactic single donor ABO/Rh compatible platelet** transfusions will be given to maintain a platelet count >10 x 10^9/L in uncomplicated patients.
- **In patients with bleeding** (esp. in APL) or undergoing surgical procedures (e.g. central venous line insertion, lumbar puncture), a platelet count >30-50 x 10^9/L has to be maintained.
- **Leucodepleted blood products** should be given to AL, MDS, and SAA patients
- **Irradiated blood products** should be given to all HL patients (for life), AL patients (with HLA-matched or family-donated products), MDS patients (transplant candidates), SAA patients (with ATG therapy), patients undergoing HSCT (see SCT protocols), and all patients receiving purine analog therapy.

Threshold of transfusion HB (gm)	PLT (x 10^9/L)	Category	Leucodepleted RBCs	Irradiated Blood Components (#TA-GVHD)
<10 (symp.) <8 (asymp.)	<10	Solid tumors	No	No
		NHL	No	No
		HL	No	For Life
≤8	<10	AL	Yes (# allo-immunization)	Only with HLA-matched or family-donated products
		MDS	? yes	For transplant candidates
		SAA	? yes	With ATG
		HSCT	Yes (#CMV)	Yes
		Purine analogs	No	Yes

12.3. Use of erythropoiesis-stimulating agents (ESA) (e.g. erythropoietin) in Adult Patients with Cancer

ASCO/ASH CLINICAL PRACTICE GUIDELINES (2010)

- **Threshold for Initiating ESA Therapy** in Chemotherapy-Induced Anemia: Hb <10 g/dL
- **Thromboembolic Risk:** weigh the risks of thromboembolism in patients for whom erythropoietin are prescribed. Randomized clinical trials and systematic reviews of available randomized clinical trials demonstrate an increased risk of thromboembolism in patients receiving erythropoietin. Specific risk factors for thromboembolism have not been defined in these trials; therefore, clinicians should use caution and clinical judgment when considering use of these agents. Established, general risk factors for thromboembolic events include history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Some diseases and treatment regimens have also been associated with higher risk of venous thromboembolic events.
- **Starting and Modifying Doses:** erythropoietin 150 U/kg three times a week, or 40,000 U weekly SC. Dose modification should follow FDA recommendations. Discontinue ESA treatment when chemotherapy concludes.
- **Discontinuing Therapy for No Response:** Continuing erythropoietin treatment beyond 6 to 8 weeks in the absence of response (e.g. a < 1 to 2 g/dL increase in Hb or no diminution of transfusion requirements) does not seem to be beneficial, assuming an appropriate dose increase has been attempted in non-responders as per the FDA-approved label, and ESA therapy should be discontinued. Patients who do not respond should be

investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia.

- **HB target:** Current recommended Hb target is 12 g/dl. FDA warned that using ESAs to achieve a target Hb of ≥ 12 g/dl would shorten patient OS. Modification to reduce the ESA dose is appropriate when Hb reaches a level sufficient to avoid transfusion or the increase exceeds 1 g/dL in any 2-week period, and to avoid excessive ESA exposure, considering the risks of ESAs.
- **Anemia in Patients Not Receiving Concurrent Chemotherapy:** It is recommended that ESAs not be used in treatment of anemia associated with malignancy in patients who are not receiving concurrent myelosuppressive chemotherapy. Use of ESAs in lower-risk MDS to avoid transfusions is an exception to this recommendation.
- **Treatment of Anemia in Patients with Nonmyeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy:** Physicians caring for patients with MM, NHL, or CLL are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering erythropoietin. Particular caution should be exercised in the use of erythropoietin concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased. Blood transfusion is also a therapeutic option.
- **Treatment intent:** Limit the indication for ESA administration to patients receiving chemotherapy for palliative intent. ESAs are not indicated for patients receiving chemotherapy for curative intent.

12.4. Treatment of high-risk febrile neutropenia in hematologic malignancies

Prophylaxis: levofloxacin PO and fluconazole PO

TREATMENT OF FEBRILE NEUTROPENIA

Treatment should be started in patients with febrile neutropenia with *combination therapy* within the first 2 hrs at maximum.

Start with: depending on local resistance pattern

- Cefepime 2 gm / 8h or
- *Imipenem/Cilastatin or meropenem 1 gm / 8h or*
- *Cephoperazone sulbactam 3 gm/8 hr daily*
- Piperacillin tazobactam: 4.5 gm/6 h daily

Plus

A: Amikacin: 500 mg/12hr (adult), or 7.5 mg/ kg /12 hr (children)

At the 3rd-5thday of antibiotics, if the fever persists add:

- ***Amphotericin-B:*** 1 mg/kg/day given IV over 6-8 h daily or ***voriconazole*** or **Caspofungin** or **Liposomal Amphotericin-B** or ***posaconazole.***

- Vancomycin 1 gm / 12 hr (or **Linezolid**): can be added according to clinical (e.g. CVL infection) and lab (culture) criteria

WHEN TO STOP ANTIBIOTICS

1-Antibiotics should be stopped completely in case of:

*Neutrophil recovery (>1000 for 72 hr)

& *No fever for 72 hr. (in case of absence of documented infection)

2- In case of documented infection:

Continue antibiotics and /or antifungals for a total of at least 10-14 days.

3- Minimal duration of Amphotericin-B:

Non-documented infections: 7 days.

Documented infections: 14 days.

12.5. Treatment of osteoporosis and avascular necrosis (e.g. steroid induced)

- Calcium
- Vitamin D
- Risedronate 35 mg [or Alendronate 70 mg] PO weekly or Zoledronic acid 4 mg IV every 3 months
- Surgical (arthroplasty)

13. OTHER HEMATOLOGIC DISORDERS TREATED BY HEMATOLOGISTS

Diseases

13.1 Immune thrombocytopenia (ITP)
13.2 Autoimmune hemolytic anemia (AIHA)
13.3 Severe aplastic anemia (SAA), Fanconi's anemia (FA) and PNH
13.4. Hemophagocytic lymphohistocytosis (HLH) syndrome

13.1 Immune thrombocytopenia (ITP)

Definition: Immune-mediated disorder characterized by isolated thrombocytopenia (PLT <100 x 10^9/L) with absence of any obvious underlying cause of the thrombocytopenia.

Investigations at diagnosis

- **CBC:** Isolated thrombocytopenia (PLT <100 x 10^9/L); anemia only if due to significant bleeding, Normal WBC count and differential.
- **PB smear:** Identified platelets should be normal to large in size. Red and white blood cell morphology should be normal.
- **BM Evaluation:** in selected patients only: in patients > 60 years of age, in those with systemic symptoms or abnormal signs, in presence of abnormalities in the CBC or Pb smear, and in cases in which splenectomy is considered.
- Testing for HIV and HCV.

THRESHOLD FOR THERAPY

Consider treatment only for patients with a PLT count <30 X 10^9/L.

FIRST-LINE THERAPY IN ADULTS:

- Prednisone 1 mg/kg/day PO for 3-4 weeks then taper off. If there is no response, then the therapy should be stopped.
- IV Ig: If C.S. are contraindicated (DM): 1g/kg/day for 1-2 days or 0.4 gm/kg for 5 days
- **Emergency treatment:** IVIg 1g/kg/day for 1-2 days or 0.4 gm/kg for 5 days and /or high dose methylprednisone (1000 mg/day for 3-5 days); platelet transfusions, recombinant factor VIIa, Antifibrinolytics (aminocaproic acid and tranexamic acid); platelet transfusions, recombinant factor VIIa, Antifibrinolytics (aminocaproic acid and tranexamic acid)

SECOND-LINE THERAPY IN ADULTS:

Any of the followings as per local institutional Guidelines

- **Splenectomy:** A waiting period of ≥6 months following diagnosis before performing a splenectomy is recommended due to potential for spontaneous improvement or late remission
- **More potent immunosuppression:** Azathioprine, Cyclophosphamide, Cyclosporine-A; Mycophenolate mofetil
- **Thrombopoietin receptor agonists:**
  - **Romiplostim:** 1 mcg/kg SC weekly. If PLT <50 x 10^9/L after ≥ 2 weeks of therapy: successive dose increment of 1 mcg/kg (Max 10 mcg/kg)

- **Eltrombopag:** 50 mg PO once daily. If PLT <50 x 10^9/L after ≥ 2 weeks of therapy: increase dose to 75 mg/d

- **Other second line therapies:** Danazol (200 mg 2-4 times daily); Vincristine:1-2 mg per infusion weekly (total dose 6 mg)

THIRD-LINE THERAPY IN ADULTS:

- **Rituximab:** 375 mg/m^2 weekly for 4 weeks, **according to local institutional guidelines only**

13.2 Autoimmune hemolytic anemia (AIHA)

INITIAL INVESTIGATIONS

- CBC and differential counts
- Hemolytic profile: LFTs, Coombs' test (direct and indirect), reticulocytic count, and serum haptoglobin, LDH.
- Rule out TTP/HUS: fragmented RBCs in PB film, PT, PC, PTT, serum fibrinogen, FDPs, D-dimers.

MANAGEMENT

- **First-line:** prednisone 1 mg/kg PO daily for 1-2 months
- **Second-line:** splenectomy

13.3 Severe aplastic anemia (SAA) and Fanconi's anemia (FA)and PNH

INITIAL INVESTIGATIONS

- CBC and differential counts
- BM aspiration and BM biopsy
- Immunophenotyping for CD 55 and CD 59 to exclude PNH
- Cytogenetic studies (including DEB breakage stimulation test to exclude FA)
- Auto-immune screen: ANA, Anti-ds DNA, RF, ANCA, ASMA
- For FA: US/CT abdomen (to exclude absent or ptosed kidneys); skeletal survey (to exclude skeletal anomalies)

MANAGEMENT

HLA identical donor available + Age <50 y: **allogeneic HSCT**

No HLA identical donor available or Age >50 y:

- **Supportive treatment:** blood and platelet transfusions, antimicrobial therapies
- **Immune suppression (IS):**
  1. Cyclosporine (CSA) (3-6 mg/d PO daily) for 5-12 m ± steroids
  2. Triple IS therapy: CSA (as before) + ATG + CS
     a. **ATG-F**:10-15 mg/kg/d for 5 days [50-75 mg/kg]
     b. Thymoglobulin: 3.5 mg/kg/d for 5 days [17.5 mg/kg]

FA complicated by MDS or AL: manage accordingly (as mentioned before)

13.4. Hemophagocytic lymphohistocytosis (HLH) syndrome

DIAGNOSTIC CRITERIA

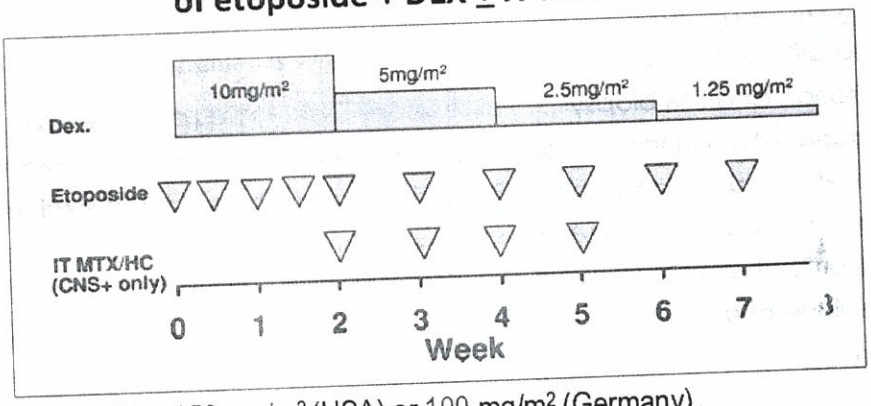
- **Diagnosis of a specific gene defect (in PB) (familial HLH) (FHL):**
  - **X-linked:** SH2D1A, BIRC4
  - **Autosomal recessive:** PRF1, MUNC13-4, STX11, STXBP2, RAB27A.

  And/or:
- **The presence of ≥5 of the following 8 criteria:**
  1. Low or absent NK cell function.
  2. Prolonged fever (> 38° C).
  3. Cytopenias affecting ≥2 of the 3 lineages in PB: Hb <9 g, PLT <100 x 10^9/L, Neutrophils < 1 x 10^9/L.
  4. Enlarged spleen.
  5. Increased triglycerides (≥ 265 mg) or decreased fibrinogen (< 150 mg).
  6. Increased ferritin (≥ 500 ng).
  7. Hemophagocytosis in BM, spleen, or LNs with no evidence of malignancy.
  8. Abnormally high CD25 (> 2400 U/ml).

MANAGEMENT

Standard of Care in Adult HLH

Induction: 8-week decrescendo course of etoposide + DEX ± IT MTX



Etoposide: 150 mg/m² (USA) or 100 mg/m² (Germany).
twice-weekly for the first 2 weeks and weekly dosing thereafter.

- **Intravenous immunoglobulins (IVIG):** 1-1.6 g/kg over 2-3 days in:
  1. Malignancy-associated HLH
  2. Chemotherapy-associated HLH
  3. EBV-triggered HLH.
  4. HLH after HSCT
- **Rituximab** (375 mg/m² once weekly) may added for EBV-associated
- **SCT in patients with persistent or recurring HLH or those with FHL**

NATIONAL BONE MARROW TRANSPLANTATION (BMT) PROTOCOLS

1 **Indications of allogeneic BMT:**
   1.1. Indications of allogeneic BMT in adults
   1.2. Indications of allogeneic BMT in children
   1.3. Indications of haploidentical BMT
2 **Indications of autologous BMT:**
   2.1. Indications of autologous BMT in adults
   2.2. Indications of autologous BMT in children
3 **Principles of BMT:**
   3.1. Pre-transplant WORK-UP
   3.2. Procedures of BMT:
   - Central venous line insertion
   - Isolation
   - Hydration
   - GIT Decontamination (sterile food)
   - Allopurinol
   - Antimicrobial Prophylaxis
   - Conditioning regimens
   - PBSC harvesting
   - Analysis of CD34+ cell count
   - PBSC infusion (D0)
   - Graft versus host disease (GVHD) prophylaxis
   - Supportive therapy
   - Potential Complications of BMT and their management
4 **Follow-up after discharge from BMT Unit**
5 **RESULTS of BMT in Egypt**
   5.1. Allogeneic BMT
   5.2. Autologous BMT

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1.2. Indications of allogeneic BMT in Children

As in adults PLUS:

- ***Chronic myeloid*** leukemia (CML) ***adult*** type: in first chronic phase
- ***Juvenile*** CML/MDS
- ***Juvenile myelomonocytic leukemia*** *(JMML)*
- ***B-thalassemia major (BTM):*** transfusion-dependent.
- ***Sickle cell*** anemia: with one of the followings
  - One cerebral stroke
  - Two acute chest syndromes
  - Three vaso-occlusive crises
  - Transfusion dependent
- **Congenital *immunodeficiency diseases (CID):*** including:
  - Leucocyte adhesion deficiency (LAD),
  - Severe combined immunodeficiency disease (SCID),
  - *Adenosine deaminase (ADA) deficiency.*
  - *Congenital T-cell defects*
  - *Chediak–Higashi syndrome,*
  - *Common variable immunodeficiency (CVID),*
  - Chronic granulomatous disease (CGD),
  - Griscelli syndrome,
  - Wiskott–Aldrich syndrome
  - Kostmann syndrome (severe congenital neutropenia)
  - Other CIDs
- **Inherited *metabolic* disorders (IMD):** including:
  - Niemann–Pick disease,
  - Adrenoleukodystrophy (ALD),
  - Mucopolysaccharidosis (MPS).
  - Gaucher disease
- ***Pure red cell aplasia (PRCA)*** *including Blackfan-Diamond* anemia: if steroid resistant
- ***Osteopetrosis:*** with hematological failure and imminent loss of vision (e.g. nystagmus and/or narrowed foramina of optical nerves in MRI/CT scans)

1.3. Indications of haploidentical BMT

Protocol for Haplo-identical Bone Marrow Transplantation

بروتوكول زرع النخاع من متبرع متوافق نصفيا في الانسجة

Indications for Haplo-identical Marrow Transplantation:

دواعي اجراء زرع النخاع من متبرع متوافق نصفيا في الانسجة:

Patients indicated for allogeneic BMT, lacking an HLA-identical donor, for treatment of the following diseases:

يمكن اجراؤه في المرضي الذي يستدعي مرضهم اجراء زرع نخاع عظمي من متبرع ولم يتوافر لديهم متبرع متوافق كليا في الانسجة وذلك في الامراض التالية:

Indications: Up to the age of 60 years

الامراض: حتى عمر ٦٠ عاما

- ***Acute myeloid*** leukemia (AML): — اللوكيميا الميلودية الحادة
  - High and intermediate risk in first complete remission (CR1)
  - All in second or subsequent CR.
- ***Acute lymphoblastic leukemia (ALL):*** — اللوكيميا الليمفاوية الحادة
  - High-risk ALL in CR1
  - ALL in second or subsequent CR
- ***Lymphoblastic lymphoma (LBL)*** in first or subsequent CRs. — سرطان الغدد اللمفاوية الليمفوبلاستية
- ***Myelodysplastic syndromes (MDS):*** *with intermediate or high-risk IPSS score* — اضطراب (خلل) *النخاع العظمي*
- ***Chronic myeloid leukemia (CML) in adults:*** — اللوكيميا الميلودية المزمنة في الكبار
  - **Patients in chronic phase (CP)** resistant and/or intolerant to at least one of the tyrosine kinase inhibitors (imatinib, nilotinib, dasatinib).
  - **Patients in accelerated phase (AP):** who do not achieve optimal response with TKIs
  - **Patients in blastic phase (BP):** should receive intensive chemotherapy + a TKI, and if they achieve a second CP, the can proceed forward for allo-SCT.
- ***Chronic myeloid leukemia (CML) in Children:*** — اللوكيميا الميلودية المزمنة في الأطفال
  - Adult type: in first chronic phase.
- ***Chronic lymphocytic leukemia (CLL):*** *high risk (e.g. del 17p) in CR2* — اللوكيميا الليمفاوية المزمنة
- ***Severe aplastic anemia (SAA)*** *including paroxysmal nocturnal hemoglobinuria* ***(PNH)****, and congenital BM failure syndromes including* ***Fanconi's anemia*** — أنيميا فشل النخاع والأنيميا الوراثية (فانكوني)

تليف النخاع العظمي

- ***Primary myelofibrosis (PMF):*** *high-risk, transfusion-dependent*

داء البلعمة الليمفاوية

- ***Hemophagocytic lymphohistiocytosis (HLH) syndrome:*** *patients with persistent or recurring HLH or those with familial HLH (FHL).*

اللوكيميا الليمفاوية المزمنة /اضطراب النخاع الصبياني

- ***Juvenile CML/MDS*** in children

سرطان الدم الميلومونوسي الصبياني

- ***Juvenile myelomonocytic leukemia (JMML)***

أنيميا البحر المتوسط

- ***B-thalassemia major (BTM):*** *transfusion-dependent.*

أمراض نقص المناعة الوراثية

- ***Congenital immunodeficiency diseases (CID):*** *including Leucocyte adhesion deficiency (LAD), Severe combined immunodeficiency disease (SCID), Adenosine deaminase (ADA) deficiency, Congenital T-cell defects, Chediak–Higashi syndrome, Common variable immunodeficiency (CVID), Chronic granulomatous disease (CGD), Griscelli syndrome, Wiskott–Aldrich syndrome, Kostmann syndrome (severe congenital neutropenia), Other CIDs*

أمراض الأيض (التمثيل الغذائي) الوراثية

- ***Inherited metabolic disorders*** *including: Niemann–Pick disease, Adrenoleukodystrophy, Mucopolysaccharidosis, Gaucher disease.*

نقص الخلايا الحمراء و الصفائح اللاتخليقي

- ***Pure red cell aplasia*** *(PRCA) and amegakaryocytic thrombocytopenia*

مرض *تصخر العظام*

- ***Osteopetrosis***

سرطان الغدد الليمفاوية (هودجكن و غير هودجكن)

- ***Lymphoma (NHL & HD):*** *patients with chemosensitive relapse unsuitable for autologous transplantation.*

2. INDICATIONS OF AUTOLOGOUS BMT

2.1. Indications of Autologous BMT in adults

Up to the age of 70 years:

1. ***Aggressive non-Hodgkin Lymphomas*:**
   - **Diffuse large B-cell lymphoma (DLBCL) and aggressive follicular lymphoma (FL)** (grade 3b or transformed):
     - Patients in in **second** or subsequent CRs (PET-CT and/or CT).
     - Primary refractory patients who require more than one induction regimen to achieve CR1
   - **Mantle cell lymphoma (MCL) and ALK-negative peripheral T-cell lymphomas (PTCL):**
     - Patients in in **first** or subsequent CRs (PET-CT and/or CT).
     - Primary refractory patients who require more than one induction regimen to achieve CR1.
2. ***Hodgkin Lymphomas:***
   - Patients in in second or subsequent CR (PET-CT and/or CT).
   - Primary refractory patients who require more than one induction regimen to achieve CR1
3. ***Multiple myeloma:***

   In ≥ very good partial response (VGPR): i.e.
   - ≥90% reduction in serum M-protein; and
   - Plasma cells in BM ≤ 5%;
   - Serum immune fixation: negative (CR) or positive
4. ***AML:*** Acute promyelocytic leukemia (APL) in second molecular remission (PCR-negative) lacking HLA-identical donor.

2.2. Indications of Autologous BMT in Children

As in adults PLUS:

- ***Neuroblastoma***: in CR or very good partial remission
  - High-risk in CR1
  - >CR1.
- ***Retinoblastoma*** stage IV in CR1 or CR2
- ***Medulloblastoma*** high-risk (<3 YEARS) in CR1
- ***Germ cell tumors*** in CR2
- ***Ewing sarcoma:*** high risk or >CR1
- ***Medulloblastoma***

3. PRINCIPLES OF BMT

3.1. Pre-transplant WORK-UP

3.1.1. SELECTION AND EVALUATION OF DONOR (IN CASE OF ALLOGENEIC BMT ONLY):

(1) ***HLA typing:*** is performed by serological typing or PCR of class I and class II MHC ***(not included in the BMT financial package).***

(2) ***Pre-transplant evaluation of the donor (included in the BMT financial package):*** including CBC, BM aspiration, liver and kidney function tests, blood group, coagulation profile, variable number tandem repeat (VNTR), serological tests for ***toxoplasmosis*** and the following ***viruses:*** HBV, HCV, CMV, HIV, EBV, HSV, and HZV. Serum Hb electrophoresis, serum iron and ferritin (for donors of thalassemia patients).

3.1.2. PRE-TRANSPLANT EVALUATION OF RECIPIENT (ALLOGENEIC AND AUTOLOGOUS TRANSPLANT): *(INCLUDED IN THE BMT FINANCIAL PACKAGE)*

Laboratory:

- CBC, BM aspiration and biopsy, cytogenetics.
- FISH and PCR for Ph chromosome (for ALL)
- Liver and kidney function tests,
- Blood group,
- Creatinine clearance,
- Variable number tandem repeat (VNTR): in allogeneic transplant only
- Serum protein electrophoresis, serum immune fixation (for multiple myeloma)
- CSF examination (for ALL)
- Serum Hb electrophoresis, serum iron and ferritin (for thalassemia patients)
- Serological tests for ***toxoplasmosis*** and the following ***viruses:*** HBV, HCV, CMV, HIV, EBV, HSV, and HZV.

Radiological:

- Chest X-ray + CT chest with contrast,
- Abdominal ultrasonography,
- Echocardiography, ECG,
- PET-CT (for lymphomas),
- Skeletal survey and MRI spine (for multiple myeloma)

Dental, ENT and gynecological examinations are done for all patients to exclude septic foci.

Written informed consent.

3.2. PROCEDURES of BMT (included in the BMT financial package)

3.2.1. CENTRAL VENOUS LINE INSERTION: prior to isolation, a Hickman right atrial catheter is inserted.

3.2.2. ISOLATION: all patients are nursed under strict protective isolation in either horizontal or vertical laminar airflow units.

3.2.3. HYDRATION: 3 Liters /m² [D 5 %: NS (3:1)] starting 2 days before conditioning

3.2.4. GIT DECONTAMINATION: sterile food (from isolation till engraftment)

3.2.5. ALLOPURINOL: 300 mg /d P.O. from isolation till D -1.

3.2.6. ANTIMICROBIAL PROPHYLAXIS

- *PCP Prophylaxis:* by trimethoprim–sulfamethoxazole (T1:S5)

  Total daily dose = T150 mg: S750 mg/m²/day
  - From isolation till D -2
  - From engraftment throughout the period of immunosuppression.

- *Bacterial prophylaxis:* levofloxacin 500 mg PO daily from isolation (hold during IV antibiotics for febrile neutropenia).

- *H.S. Prophylaxis:* by Acyclovir
  - Dose: 1600 mg/day PO in 3-5 divided doses or 750 mg/m²/day (15 mg/kg/ day) IV in 3 divided doses
  - From isolation till 5 weeks post-engraftment.

- *Fungal infection Prophylaxis:*
  - *Fluconazole 450 mg /day PO till day + 80.*
  - *Voriconazole or Posaconazole (in case of documented previous fungal infection)*

3.2.7. CONDITIONING REGIMENS

***Conditioning regimens used in BMT** (Do = day of transplant)*

Regimen (Alphabetical)	Dosage	Type of Transplant	Indications
ALK	**Melphalan** 100 mg/ m² IV for 2 days (D-3 and D-2)	Autologous	MM
BEAM	▪ BCNU (carmustine) 300 mg/m² D-7 ▪ **Etoposide:** 200 mg/m²/day (D−6 to D−4) ▪ **Ara-C (cytarabine):** 400 mg/m²/day (D−6 to D−3) ▪ **Melphalan:** 140 mg/m² D −2	Autologous	▪ NHL ▪ HD

Regimen (Alphabetical)	Dosage	Type of Transplants	Indications
BeEAM	▪ **Bendamustine:** 200 mg/m²/day (D −8 and −7) ▪ **Etoposide:** 200 mg/m²/day (D−6 to D−3) ▪ **Ara-C (cytarabine):** 400 mg/m²/day (D−6 to D−3) ▪ **Melphalan:** 140 mg/m² D −2	Autologous	▪ NHL ▪ HD
Bu/ALK	▪ **Bu**sulphan**: 4-5 mg/kg/day PO for 4 days (D-8 → D-5) ▪ **Melphalan** 70 mg /m²/d for 2 days (D-3, D-2)	Autologous	Neuroblastoma
Bu/Cy (≤8y)	▪ **Bu**sulphan**: 5 mg/kg/day PO for (D-7 → D-4) ▪ **Cy**clophosphamide* (Cy): 60 mg/kg/day for 2 days (D-3 & D-2)	▪ MAC-Allo*** ▪ Autologous	▪ AML, ALL, MDS ▪ CML ▪ NHL, HD ▪ JMML ▪ IMD, OP
Bu/Cy (>8y)	▪ **Bu**sulphan**: 4 mg/kg/day PO (D-7 → D-4) ▪ **Cyclophosphamide***: 60 mg/kg/day (D-3 & D-2)	▪ MAC-Allo*** ▪ Autologous	▪ AML, ALL, MDS <40y ▪ CML <40y ▪ NHL, HD
Bu/Cy/ATG	▪ **Bu**sulphan**: 4-5 mg/kg/day PO (D -7 → D -4) ▪ **Cy**clophosphamide*: 60 mg/kg/day (D -3 & D -2) ▪ **ATG:** ATG-F 11 mg/kg/d (or Thymoglobin 2.5 mg/kg/day) for 5 days before and 5 days after the day of transplant.	Allogeneic	BTM
CMV	▪ **Cy**clophosphamide* (Cy): 3g/m² /d (days -6 & -5) ▪ **Melphalan:** 100 mg/m² IV (day -2) ▪ **VP16:** 150 mg/m²/d (days -6 to -2)	Autologous	NHL, HD
Cy/ATG	• **Cy**clophosphamide*: 50 mg/kg/day (D-5→ D-2) • **ATG** 10 mg/kg/d (D-5→ D-3)	Allogeneic	SAA
Flu/Alk	▪ **Fludarabine:** 30 mg /m²/d IV (D-8 → D-4) ▪ **Melphalan** 70 mg /m²/d IV for 2 days (D-3, D-2)	RIC-Allo****	▪ MDS >40y ▪ AML, ALL, CML with comorbidities ▪ CID
Flu/Alk + PT-CY* (Haplo-allo)	▪ **Fludarabine:** 25 mg/m²/d IV (D-6 → D-2) ▪ **Melphalan** 75 mg /m²/d IV for 2 days (D-3, D-2)	Haplo-allo	Of haplo-allo***** SCT

Regimen (Alphabetical)	Dosage	Type of Transplants	Indications
Flu/Bu/VP16+ PT-CY* (Haplo-allo)	▪ **Fludarabine:** 30 mg/m²/d IV (D-6→D-2) ▪ **Busulphan**:** 4 mg/kg/day (D-4 to D-2) ▪ **Etoposide:** 150 mg/m² (D-6 to D-2)	Haplo-allo	Of haplo-allo***** SCT
Flu/Bu/ATG	▪ **Fludarabine:** 30 mg/ m²/d (d- 8 to d -4) ▪ **Busulphan**:** 4 mg/kg/d (d-5 to d-4), 2 mg/kg/d (d-3) ▪ **ATG-F:** 10 mg/kg/d (d-3 to d-1)	MAC-Allo***	PMF
Flu/Bu/Cy	▪ **Fludarabine:** 30 mg/m²/d (d- 9 to d -4) ▪ **Busulphan**:** 4-5 mg/kg/d (d-7 to d-4) ▪ **Cyclophosphamide*:** 30 mg/kg/d X 4d (d-5 to d-2)	MAC-Allo***	LAD
Flu/Cy	▪ **Fludarabine** 40 mg/m²/d (D-3 → D-1) ▪ **Cy**clophosphamide*: 50 mg/kg/day X 4 days (D-5→ D-2)	Allogeneic	▪ SAA ▪ CID ▪ Dyskeratosis congenita
Flu/Cy/ATG	▪ **Fludarabine:** 25 mg/m² for 5 days (d-10 to d-6) ▪ **Cyclophosphamide*:** 5 mg/kg/day (d-5 to d-2) ▪ **ATG-F:** 5mg/kg/d (d-4 to d-1), 2.5mg/kg (D+1, D+3, d+6, d+11)	RIC-Allo****	FA
Flu/Cy/Bu/TBI + PT-CY* (Haplo-allo)	▪ **Fludarabine:** 30 mg/m²/day on days -6 to -2 ▪ **Cyclophosphamide*:** 14.5 mg/kg/day on days -6 and -5 ▪ **Busulphan**:** 3.2 mg/kg/day on days -3 and -2 ▪ **Total body irradiation (TBI):** 2 Gy on day -1 ▪ **Post-transplant Cyclophosphamide* (PT-Cy):** 50 mg/kg/day on days +3 and +4	Haplo-allo	Of haplo-allo***** SCT
TBI/Cy	▪ **Total body irradiation (TBI):** 250 cGy/day for 5 days (D-8 → D-4) ▪ **Cyclophosphamide*:** 60 mg/kg/day (D-3 & D-2)	▪ MAC-Allo*** ▪ Autologous	▪ ALL <40y ▪ CML <40y ▪ NHL, HD

*HD cyclophosphamide should be given I.V. with I.V. Mesna; PT-Cy: Post-transplant Cyclophosphamide: 50 mg/kg/day on days +3 and +4

**Bu should be given with anticonvulsant prophylaxis (Epanutin or Levetiracetam)

***MAC-Allo= Myeloablative conditioning allo-transplant

****RIC-Allo= reduced intensity conditioning (non-myeloablative) allo-transplant

*****Haplo-allo: Haplo-identical allo-transplant

One locus mismatch allogenic BMT can be performed in rare cases (2-3 cases per year) with the addition of ATG to the suitable conditioning regimen (separate financial package).

List of drugs/therapies used in conditioning regimens in allogeneic and autologous transplantation: in alphabetical order

All included in BMT package EXCEPT ATG: ***All IV except otherwise specified:***
1. Ara-C (cytarabine) 2. ATG (Grafalon, Thymoglobin) 3. BCNU (carmustine) 4. Bendamustine 5. Busulphan PO (Myeleran), or IV (Buselvex) 6. Cyclophosphamide 7. Etoposide 8. Fludarabine 9. Melphalan 10. Mesna 11. Total body irradiation (TBI) 12. Thiotepa

3.2.8. STRONG ANTIEMETICS should be given throughout **ALL THE DAYS OF ALL CONDITIONING REGIMENS** mentioned in table (1):

- Ondansetron, or granisetron ***Plus***
- Fosaprepitant ***Plus***
- Dexamethasone

3.2.9. PBSC HARVESTING

- *Autologous:* For autografting, the patient must first undergo stem cell collection from the peripheral blood (PB) or central vein by leukapheresis using a continuous or non-continuous flow cell separator. This is followed by cryopreservation of the marrow using a controlled rate biofreezer and 10% dimethylsulfoxide (DMSO) as cyroprotectant. The stem cells are then stored in vapor phase liquid nitrogen.
- *Allogeneic:* the donor receives granulocyte-colony stimulating factor (G-CSF) (filgrastim) 10 µgm/kg S.C. from day –4 to the last day of pheresis. After mobilization, PBSCs are collected from PB using ***cell separator*** as in the autologous setting. BM can be collected from posterior superior iliac spine in the ***operation theatre under general anesthesia*** in case of small donors (<30 kg body weight)

3.2.10. ANALYSIS OF CD34+ CELL COUNT

Fresh PBSC harvest aliquots are immunostained and analyzed by flow cytometer for CD34+ cells within 24 hours of each leukapheresis aiming to collect at least a total of 3 X 10^6/kg BW CD34+ cells.

3.2.11. PBSC INFUSION (D0)

Two to four days after completion of conditioning regimen stem cells are infused to the patient:

- ***Autologous:*** PBSCs are thawed in water bath (37^0 C) at the patient's bedside and rapidly infused through the central venous line. Prior to infusion, the patient must be prepared by I.V. hydration, alkalinization of urine, steroids, diuretics, anti-emetics and antihistaminics.
- ***Allogeneic:*** after leukapheresis, the PBSCs are immediately infused to the recipient through the central venous line in less than 1 hour. Vital signs should be monitored during and after infusion.

3.2.12. GRAFT VERSUS HOST DISEASE (GVHD) PROPHYLAXIS (in case of allogeneic BMT only)

a) MAC SCT:

- ***Cyclosporine-A:*** 1.5 mg / kg IV every 12 hours from day –1 till oral intake is tolerable then 3-5 mg/kg/day PO (to keep trough level <200 ng/ml) or ***Tacrolimus*** (TAC) (Prograf) 0.75-1 mg/kg daily (to keep trough level 5-15 ng/ml) for 9-12 months. ***Tacrolimus (Prograf)*** can be used in case of intolerance to cyclosporine
- ***Methotrexate:*** 15 mg/m^2 IV day 1; then 10 mg/m^2 IV days +3, +6, +11 (except in any ATG-based regimen).
- ***Methylprednisolone:*** 2 mg/kg from D-7 to D+4 then tapered 50% every week so long there is no GVHD (in BTM only).

b) RIC SCT: CSA/TAC (as before) + Mycophenolate mofetil (MMF) (CellCept or Myfortic) 1gm/12hr or 30 mg/kg/d in children

c) One locus mismatch SCT (2-3 case per year): as before + ATG-F 10 mg/kg for 3 days (D-3 to D-1)

d) Post-transplant cyclophosphamide in haplo and identical settings (Johns-Hopkins protocol): Cyclophosphamide 50 mg/kg daily for 2 successive days (D +3 and +4) with MESNA Uroprotection.

3.2.13. SUPPORTIVE THERAPY: (INCLUDED IN THE BMT FINANCIAL PACKAGE)

- **Leukocyte depleted (# CMV) red blood cell transfusions** are given from random donors to maintain HB level >8 gm/dl.
- **Single donor platelet transfusions** are given to maintain the platelet count > 10,000/cmm.
- **All blood products are irradiated** with 15 Gy prior to transfusion in:
    - **Allogeneic SCT recipients:**
        - From the time of initiation of conditioning.

- Continued as long as the patient receives GVHD prophylaxis, i.e. usually for 6-9 ms post-transplant.
- If cGVHD is present or if continued IS treatment is required, irradiated blood components should be given indefinitely.

- **Allogeneic SCT donors:**
  - Allogeneic blood transfused to BM and PBSC donors 7 d prior to or during the harvest should also be irradiated.
- **Autologous SCT patients:** should receive irradiated cellular blood components:
  - 7 days before and during BM/PBSC harvest to prevent the collection of viable allogeneic T lymphocytes, which can potentially withstand cryopreservation.
  - From initiation of conditioning until 3 months post-transplant (6 months if TBI was used in conditioning).

- **Post-transplant IV IG** for CID
- **Post-Transplant G-CSF:** for all auto-BMT patients starting from D +6 till neutrophilic recovery, and for patients of allo-BMT in case of delayed neutrophilic recovery (>21 days post-BMT) till neutrophilic recovery.

Treatment of febrile neutropenia (FN)

Treatment should be started in patients with febrile neutropenia with *combination therapy* within the first 2 hrs at maximum.

Start with: depending on local resistance pattern

- Cefepime 2 gm / 8h or
- Imipenem/Cilastatin or meropenem 1 gm / 8h or
- Cephoperazone sulbactam 3 gm/8 hr daily
- Piperacillin tazobactam: 4.5 gm/6 h daily

Plus

- Amikacin: 500 mg/12hr (adult), or 7.5 mg/ kg /12 hr (children)

At the 3rd-5thday of antibiotics, if the fever persists add:

- ***Amphotericin-B:*** 1 mg/kg/day given IV over 6-8 h daily or ***voriconazole*** or **Caspofungin** or **Liposomal Amphotericin-B** or ***posaconazole.***
- Vancomycin 1 gm / 12 hr (or **Linezolid**): can be added according to clinical (e.g. CVL infection) and lab (culture) criteria

WHEN TO STOP ANTIBIOTICS:

1- Antibiotics should be stopped completely in case of:

*Neutrophil recovery (>1000 for 72 hr) and

*No fever for 72 hr (in case of absence of documented infection).

2- In case of documented infection:

Continue antibiotics and /or antifungals for a total of at least 10-14 days.

3- Minimal duration of Amphotericin-B (OR VORICONAZOLE):

Non-documented infections: 7 days.

Documented infections: 14 days.

Sino-pulmonary aspergillosis: 2-3 months.

3.2.14. Potential Complications of BMT and their management (Included in the BMT financial package)

Graft versus host disease (GVHD)

- **Acute CVHD (aGVHD):** presumably triggered by disparity between donor and recipient for polymorphic non–HLA determinants occurs in about 40% of allografts. The reaction manifests itself by skin rash, cholestatic jaundice and diarrhea of different severity grades.

- **Chronic GVHD (cGVHD):** a distinct clinical syndrome affecting approximately 30% of transplant recipient who survive more than 3 months. Two- third of affected patients have preceding acute GVHD but in one-third it develops de novo. The incidence of cGVHD increases with recipient age (more than 40 years). Clinical and pathological features are similar to those seen in several hematologic and autoimmune disorders involving skin, muscles, fascia, joints, mouth, eyes, nails, lungs, GIT and liver.

TREATMENT OF GVHD

Treatment of aGVHD

- **First-line:** Methylprednisone (IV or PO): 2-5 mg/kg/day + CSA/TAC
- **Second-line drugs:**
  - ***Tacrolimus***: 0.75-1 mg/kg daily (to keep trough level 5-15 ng/ml),
  - ***Mycophenolate mofetil (MMF):*** 1gm/12hr
  - ***ATG***
  - ***MTX***
  - ***Extracorporeal photopheresis (ECP)***

Treatment of extensive cGVHD

- **First-line: Prednisone** and **Cyclosporine-A** (CSA).
- **Second-line drugs: MMF** (mycophenolate mofetil or mycophenolic acid): 1gm/12hr or 30 mg/kg/d in children, ***Azathioprine*** 100-150 mg daily PO, ***Tacrolimus***, ***ATG***, ***Chloroquine***, **methotrexate, Extracorporeal photopheresis (ECP).**

Response to cGVHD therapy:

Re-evaluation should be done on weeks **8, 20 and 40.**

Response	Definition	What to do?
No response:	*Progressive* cGVHD after 2 months of treatment.	***Stop*** therapy and consult BMT Committee
Fair response:	The patient is clinically stable or improved but chronic GVHD is still active in ***some involved*** organs.	If fair response is seen after 9-12 months of therapy, **give *another* 9 *months*** of treatment without change.
		If still only a fair response after ***18*** months of treatment, the patients is declared a treatment ***failure.***
Good response	The patient is well and has ***clinically inactive*** disease. Biopsy reveals no active cGVHD.	Taper the prednisone by 5 mg per week until discontinued entirely. Observe closely for a flare of cGVHD. If stable for one month then discontinue cyclosporine over one month.
Flare	Defined when treatment is reduced or stopped after achieving a good response but active cGVHD returns	Patients will be retreated on the same treatment regimen for 9 more months after a flare

Opportunistic Infections

The early post-transplant phase is characterized by infection with gm +ve and gm –ve bacteria, viral infection and fungal infection especially *Candida albicans* and *Aspergillus fumigatus*. Most troublesome are the interstitial pneumonias that typically occur between 30 and 100 days after BMT. Formerly, approximately 10% of these pneumonias were related to Pneumocystis carinii, but prophylaxis with trimethoprim–sulfamethoxazole has largely eliminated this problem. Approximately 60% of the pneumonias are associated with the finding of CMV, and more than one-half of these are fatal.

CMV infection management

- ***Ganciclovir*** (Cymevene): 5 mg/kg IV BID until quantitative PCRs are negative × 2 weeks, then 5 mg/kg IV daily × 14 days
- ***Valganciclovir*** *(Valcyte)*: 900 mg po BID until quantitative PCRs are negative × 2 weeks, then 900 mg po daily × 14 days

HBV infection: Lamivudine PO for at least 1-year post BMT

Pneumocystis jiroveci pneumonia (PCP):

First-line treatment is trimethoprim-sulfamethoxazole 15–20 mg/kg/day divided into 3–4 daily doses for 21 days. If patient is sulfa-allergic, alternative therapies include

pentamidine 4 mg/kg/day IV for 21 days (for severe disease) or clindamycin 450 mg po 6 h with primaquine 30 mg po daily (for mild to moderate disease) for 21 days. Corticosteroids at a dose of 40 mg po BID days 1–5, then 40 mg po daily for days 6–10 and 20 mg po daily for days 11–21 can be considered in combination with antimicrobic therapy if patient not already receiving steroids in comparable dosages in the setting o moderate to severe disease.

Sinusoidal obstruction syndrome or veno-occlusive disease of the live (SOS/VOD): 5%

- Maintaining careful fluid (water and sodium) balance
- Aggressive diuresis
- Discontinuing/avoiding agents that may exacerbate hepatotoxicity
- Preserving renal blood flow (renal dose dopamine 2–5 mcg/kg/min)

Other complications of BMT and their management

- **Diffuse alveolar hemorrhage (DAH):** managed in ICU by mechanical ventilatio immunosuppressive therapy with high-dose corticosteroids; correction of underlying coagulopathy by maintaining platelet count above 50,000/mm3 and INR <2; examine for concomitant infectious pathogen using bronchoalveolar lavage; Recombinant factor VIIa; aminocaproic acid.
- **Idiopathic pneumonia syndrome (IPS):** managed by Corticosteroids: starting dose is 2 mg/kg daily of prednisolone for the first week, followed by a slow taper ov the course of 2–3 months; PCP and fungal prophylaxis; Etanercept (Enbrel) 25 mg S twice weekly for 8 weeks
- **Graft failure:** Hematopoietic growth factors (e.g., GM-CSF); stem cell boost (±additional conditioning agents), i.e., back- up stem cell/marrow infusion, second transplant, etc.; immunosuppression particularly in this setting of failing donor chimerism; pharmocologic review to remove myelotoxins (ganciclovir, bactrim, vancomycin, linezolid, H2 blockers, etc.); eliminate infections.
- **Relapse after Allo-SCT:** Donor lymphocyte infusion **(DLI)** can be considered
- **Osteoporosis and avascular necrosis of hip:** Ca, vitamin D, Risedronate 35 mg [or Alendronate 70 mg] PO weekly or Zoledronic acid 4 mg IV every 3 months, surgical (arthroplasty, joint replacement)

Cost of BMT (allogeneic and autologous) includes a max hospital stay of 2 months and **does not include the followings** (should have a separate budget):

1. HLA-typing.
2. Use of anti-thymocyte globulin (ATG).
3. Stay in the hospital beyond 2 months.
4. Follow up after discharge from the BMT unit.

4. FOLLOW-UP AFTER DISCHARGE FROM BMT UNIT
(SEPARATE FINANCIAL PACKAGE)

4.1. Follow up intervals

- ALLOGENEIC TRANSPLANT patients may be seen twice weekly through day +50–60, then weekly through day +100. Visits will occur more often for patients with complications. Allogeneic transplant patients after day +100 may be seen at least every 1–2 weeks for 6 months after transplant, then monthly. Visits should occur more often for patients with GVHD or those individuals with other post-transplant complications. All allogeneic transplant patients should be checked thoroughly for signs and symptoms of GVHD at every follow-up visit.

- AUTOLOGOUS TRANSPLANT patients may be seen in clinic twice weekly until patient is clinically stable, then weekly until day +25–30. Patients may then be seen at 2-week intervals until day +90, monthly for 3 months, every 2 months until 1 year, every 3–6 months for 2–5 years, then annually.

- ANTIBIOTICS THAT MAY BE USED FOR INFECTION AFTER DISCHARGE:
as before + phenoxymethylpenicillin, Amoxicillin/Clavulanate, Ampicillin/Sulbactam, Ciprofloxacin, levofloxacin, azithromycin, itraconazole, voriconazole, or IV BS antibiotics (if indicated).

4.2. Follow-up investigations

The following routine investigation at regular intervals after discharge:

- Complete blood count, reticulocyte count
- Liver function tests, coagulation profile.
- Kidney function tests, electrolytes (Mg, Ca, Na, K), FBS
- ***In allo-SCT only:*** Cyclosporine-A trough level in the blood, CMV by PCR weekly in seropositive recipients, or if donor is seropositive until day +100; VNTR after 1 and 2 months posttransplant and when indicated thereafter.

4.3. Long-term follow up of recipients includes:

- **Post-transplant vaccination against:** Pneumococci, H. influenza, MMR, Diphtheria-tetanus, Pertussis (<7y), Meningococcal, seasonal Influenza, Hepatitis A and B, and IM Polio vaccines.
- **Detection of chimerism** by either sex mismatch or VNTR.
- Follow-up of the **original disease.**
- **Detection of associated disease markers** e.g. Ph chromosome cytogenetically or by PCR in CML and Ph+ ALL.

5. CURRENT RESULTS OF BMT IN EGYPT

5.1. Allogeneic SCT

Disease	Overall survival
B-thalassemia major	82% (12y)
Severe aplastic anemia	74% (8y)
AML	57% (9y)
ALL	58% (9y)
MDS	54% (9y)
CML (in chronic phase)	67% (9y)
CML (beyond chronic phase)	50% (9y)
FA	65% (5y)
CID	62% (5y)
IMD	46% (5y)
All allo-patients	**60%**

5.2. Autologous SCT

Disease	5-year Overall survival
HL	76%
NHL	65%
MM	58%