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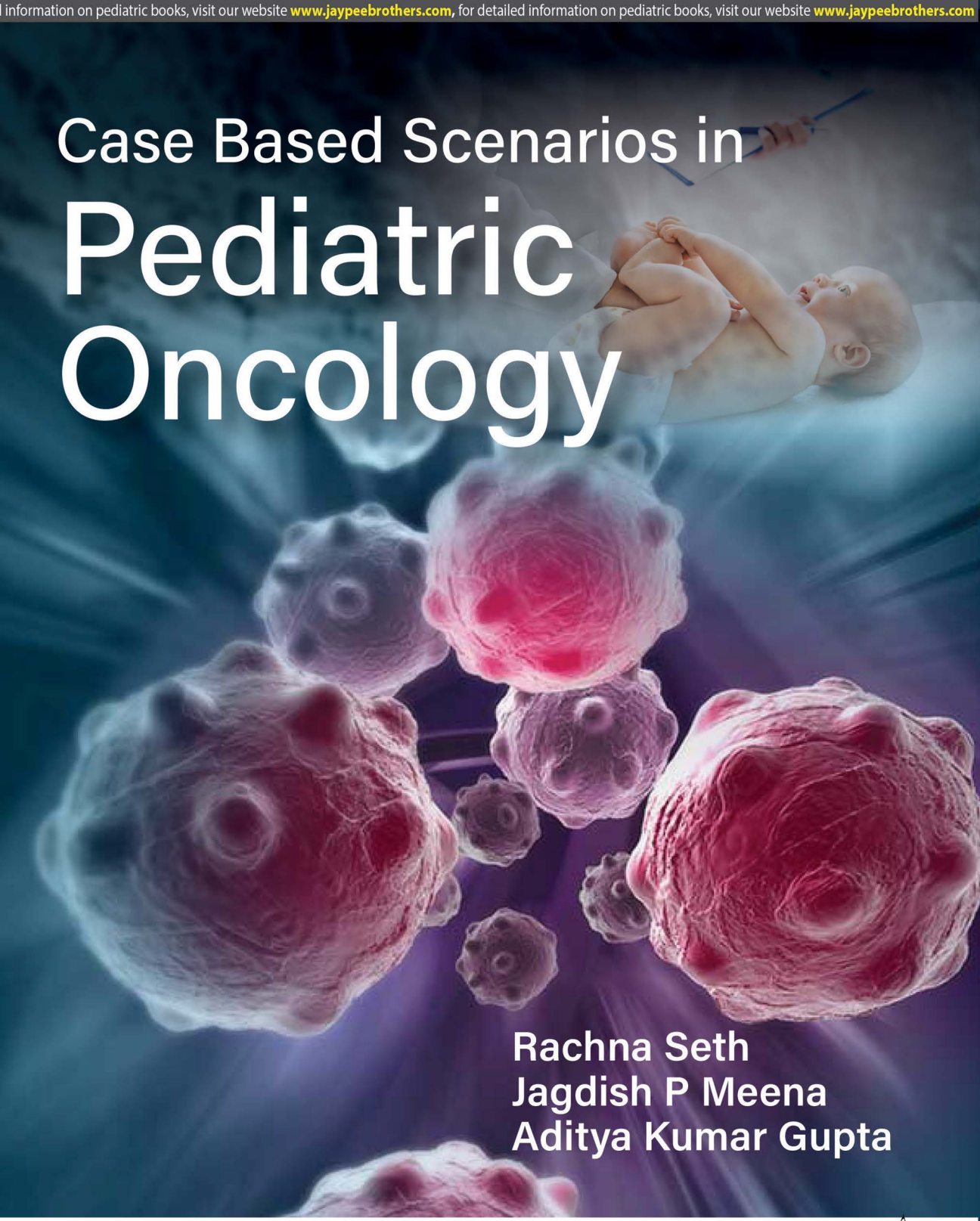
Case Based Scenarios in Pediatric Oncology



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CHAPTER 3

Acute Myeloid Leukemia

Kritika Setlur, Jagdish P Meena

CASE VIGNETTE

Patient L presented at 6 years of age with a 1-month history of progressive pallor, fever, and gum bleeding. His peripheral smear was suggestive of myeloid blasts, and bone marrow examination and flow cytometry confirmed a diagnosis of acute myeloid leukemia (AML). Further work-up revealed an 8:21 translocation on karyotyping.

1. How do we diagnose AML?

The international consensus classification of myeloid neoplasms and acute leukemia lays down diagnostic criteria for AML as 20% or more myeloid blasts in blood or bone marrow, *or* a blast count of 10% or more in the presence of certain recurrent genetic abnormalities, as listed below.

- Acute promyelocytic leukemia (APML) with t(15;17)(q24.1;q21.2)/PML::RARA
- APML with other RARA rearrangements
- t(8;21)(q22;q22.1)/RUNX1::RUNX1T1
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11
- t(9;11)(p21.3;q23.3)/MLLT3::KMT2A
- Other KMT2A rearrangements [e.g., t(10:11), t(4:11)]
- t(6;9)(p22.3;q34.1)/DEK::NUP214
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2; MECOM(EVI1)
- Other MECOM rearrangements [e.g., t(2:3), t(3:8)]
- Mutated NPM1
- In frame bZIP, CEBPA mutations ≥10%.

As well as certain other rarer recurrent abnormalities such as AML with t(16;21)(q24.3;q22.1)/RUNX1::CBFA2T3, AML (megakaryoblastic) with t(1;22)(p13.3;q13.1)/RBM15::MRTF1, etc.[1]

ELN 2017 recommendations for the morphological diagnosis of AML states that for morphological diagnosis, we must count at least 200 leukocytes on blood smears and 500 nucleated cells on spiculated marrow smears. The blast count also includes so-called "blast equivalents," which in AML with monocytic or myelomonocytic differentiation include monoblasts and promonoblasts.[2]

Immunophenotyping is required for the diagnosis of AML M0 and AMKL, and plays a supportive role in the diagnosis of other subtypes as well. It is also useful for differentiating AML from mixed phenotypic acute leukemia (MPAL).

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Useful markers for immunophenotyping are given in **Table 1**.

TABLE 1: Immunophenotyping markers.

AML diagnosis	
Precursors	CD34, CD117, CD133, HLA DR
Myelomonocytic	CD4, CD11b, CD11c, CD13, CD14, CD15, CD33, CD64, CD65, CD184, iMPO or lysozyme
Megakaryocytic	CD41, CD42, CD61
Erythroid	CD235a
Lineage aberrant	CD2, CD7, CD19, CD56
Pan leucocyte markers	CD11a, CD45
MPAL diagnosis	
Myeloid	MPO, monocytic differentiation (2 of lysozyme, CD11c, CD14, CD64)
B lineage	CD19 strong with one of OR CD19 weak with two of: CD79a, CD22, CD10
T lineage	cCD3 or sCD3

(AML: acute myeloid leukemia; cCD: cytoplasmic clusters of differentiation; CD: clusters of differentiation; iMPO: intracellular myeloperoxidase; MPAL: mixed-phenotype acute leukemia; sCD: surface clusters of differentiation)

Source: Creutzig U, van den Heuvel-Eibrink MM, Gibson B, Dworzak MN, Adachi S, de Bont E, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood. 2012;120(16):3187-205.

The minimum panel recommended to use for diagnosis of AML to fulfil World Health Organization (WHO) and European Group for the Immunological Characterization of Leukemias (EGIL) criteria include: CD34, CD117, CD11b, CD11c, CD13, CD14, CD15, CD33, CD64, CD65, iMPO, lysozyme, CD41, and CD61.[3]

2. Are all AMLs the same? How do we risk stratify a new case of AML?

The treatment of AML has long remained a challenge to pediatric hematoncologists.

Retrospective analysis of the AML Berlin-Frankfurt-Munster (BFM) trials found that the 5 years probability of overall survival (OS) has increased from 49 (years 1987–1992) to 76% (years 2010–2012) without much change in the rate of relapse and nonresponse. On further analysis, three main factors were identified by this group as contributing to improved outcomes, the first being *intensification of first-line therapy*, the second being *better supportive care*, and the third *salvage therapies in nonresponders and relapsed AML*. Of the three, the last factor was found to have contributed most significantly and consistently to improved outcomes.[4] This observation emphasizes the importance of early identification of patients that are likely to be at high risk for nonresponse/relapse in order to institute salvage therapies early.

3. How do we identify these so-called "high-risk AMLs"?

Risk stratification of pediatric acute myeloid leukemia (pAML) at baseline is guided by the identification of certain known "favorable risk" and "adverse risk" genetic alterations. Since these have a prognostic and therapeutic significance, the International BFM Study Group

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AML Committee recommends cytogenetics and molecular studies as a part of the baseline diagnostic workup in AML.

At the time of initial bone marrow studies, the following are recommended:[3]

- Cytogenetics/FISH (fluorescence in situ hybridization) with AT LEAST the following:
  - t(8;21)(q22;q22)/RUNX1-RUNX1T1
  - inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB-MYH11
  - t(15;17)(q22;q21)/PML-RARA
  - MLL
- Molecular genetics reverse transcription-polymerase chain reaction/next-generation sequencing (RT-PCR/NGS) to identify AT LEAST the following:
  - FLT3-ITD
  - WT1
  - C-KIT
  - CEBPA (double mutation)
  - NPM1
  - Specific MLL-abnormalities with favorable or very poor prognosis (e.g., MLL-AF1Q, AF6, AF10)

On the basis of the above, AML may be classified at baseline into standard risk (i.e., presence of a favorable risk genetic alteration), high risk (i.e., presence of an adverse risk genetic alteration), and intermediate risk (i.e., presence of neither known favorable nor known adverse risk genetics).

4. What is the role of NGS in initial workup of a case of AML?

The role of NGS in the initial workup of a case of AML lies in the following four areas:

1. *Risk stratification:* Genetic alterations form an important part of initial risk stratification for AML. The latest ELN 2022 risk categorization includes a variety of molecular abnormalities, including NPM, FLT3 ITD, CEBPA, TP53, ASXL 1, BCOR, RUNX1, SF3B1, and others. While a targeted NGS panel may be useful to detect known genetic abnormalities for risk stratification, some important genes such as CEBPA (a GC-rich area which is difficult to amplify by PCR) and FLT3 ITD (variably sized due to internal tandem duplications) may require more specialized NGS-based approaches.[5]
2. *Response assessment by NGS-based minimal residual disease (MRD):* The approaches to MRD measurement in AML are enumerated below. NGS-based MRD holds an advantage especially at the time of subsequent relapse, when small subclones present at diagnosis may be picked up as the dominant clone subsequently at relapse.[6]
3. *Identification of novel fusion partners:* RNA-based NGS targeted at the known clinically relevant genes to identify novel fusion partners, expanding our understanding of the molecular drivers of AML.[6]
4. *Identification of potentially targetable lesions:* Potentially targetable lesions are being increasingly explored in adult as well as pAML, examples of these being FLT3–ITD mutations and IDH1/IDH2 mutations. In fact, the modifying effect of FLT3–ITD inhibitor midostaurin in AML therapy has been a factor in moving FLT3 ITD from adverse risk to intermediate risk (regardless of allelic ratio) in the ELN 2022 risk stratification.[5]

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5. What are the implications of risk stratification in AML at therapy onset?

The first important implication is on treatment. While induction courses remain uniform regardless of risk stratification, the choice of method of consolidation may vary. There is consensus that standard risk AMLs will not benefit from hematopoietic stem cell transplantation (HSCT), however, guidelines are less clear in higher-risk cases. Though there has been evidence to suggest that there is a significantly lower relapse risk in patients undergoing allo-HSCT, this may or may not imply an improvement in survival.[4,7-9] Therefore, the International BFM Study Group AML Committee recommends consideration of benefit versus toxicity of allogeneic HSCT at first remission for high-risk and certain intermediate-risk cases who have MRD positive.[3]

The second important implication of risk stratification is on prognostication. Treatment of any pAML is often an arduous journey, and families of children with pAML require careful counseling with due consideration given to treatment-related morbidity and mortality, possibility and costs of an HSCT, and expected survival as well as long-term toxicities. A baseline high-risk stratification [with current event-free survival (EFS) rates of just 28%][10] would require prior preparation of the family with regards to the possibility of relapse and options thereafter.

CASE *(Continued)*

L was started on chemotherapy in February 2018. He received induction containing 3 + 7 regime of daunorubicin and cytarabine. Postinduction marrow was in remission.

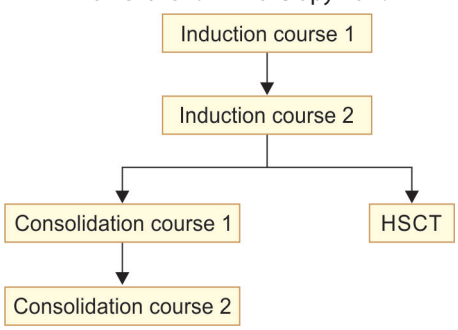
6. What is the structure of treatment of a case of AML? When do we assess response?

The current consensus on treatment involves two phases, induction and consolidation. Induction consists of two courses and usually is composed of a backbone of cytarabine with an anthracycline, while consolidation (also called "intensification") consists of two to three courses of high-dose cytarabine with or without mitoxantrone. In higher-risk patients, this consolidation is carried out with HSCT rather than chemotherapy.[11]

The AML committee of the BFM study group recommends response assessment at the end of the first and second course of induction, with complete remission (CR) being defined as <5% blasts in bone marrow, absence of any blasts with Auer rods, and absence of extramedullary disease, having achieved the independence of red cell transfusions, absolute neutrophil counts (ANC) of >1,000/μL and platelet count exceeding 80,000/μL. An additional provision for CR with incomplete recovery (CRi) is allowed in which remaining criteria for remission are met in the absence of ANC or platelet thresholds. CRi is currently a definition used predominantly for trial purposes, however, rather than in routine clinical management.

Apart from molecular genetics and cytogenetics, response to the first course of therapy is the most important indicator of outcome in AML.[3]

Flowchart 1: AML therapy flow.



(HSCT: stem cell transplantation)

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Various studies, including those by the Medical Research Council (MRC) 10 study group and the Nordic group, have found that outcomes varied significantly between those who achieve CR and those who achieve an intermediate response at the end of the first induction, with the British group finding that 5-year survival fell from 53 to 44% and the Nordic group found that EFS fell from 61 to 35%.[9,12] Both these groups, however, used only morphological CR criteria for assessment, which leaves us with the question, what is the role of MRD in AML.

7. What is the role of MRD in AML?

Minimal residual disease, simply put, refers to low levels of residual leukemia that cannot be detected by morphologic assessment alone. The role of MRD has been long well established in the management of pediatric acute lymphoblastic leukemia (ALL), its role in AML is gaining prominence as well. A systematic review and meta-analysis of 81 trials published in 2020 found that the estimated OS and estimated 5-year disease-free survival (DFS) for patients without MRD were 68 and 64%, respectively, which fell to 34 and 25% respectively in those with MRD.[13]

The challenges faced by the widespread adoption of MRD assessment in AML are the lack of standardization and comparability among the various available assays.[8] To address this issue, in 2021, the European Leukemia Net MRD working party published recommendations for technical standards of flow and molecular-based MRD, as well as MRD thresholds and definitions for MRD response. While the full details of this document are beyond the scope of this chapter, briefly; PCR-based MRD monitoring is recommended in patients with mutant NPM1, RUNX1-RUNX1T1, and CBFB–MYH11, and remaining patients should be monitored using multiparametric flow cytometry-based MRD.[8]

Recommended thresholds for MRD negativity are <0.1% of CD45 cells expressing target phenotype in flow-based MRD and a cycling threshold of at least 40 in 2 of 3 replicates (with at least 10,000 copies of the selected housekeeping gene). Optimal thresholds for NGS-based MRD are yet to be defined for various genes and time points.[8]

8. What are the treatment implications if MRD is positive?

Various study groups, including the Nordic group, Children's Oncology Group (COG), and the Italian group, have since explored the implication of MRD on therapy, many finding that a positive MRD (>0.1%) at the end of induction-2 is a poor prognostic feature and has suggested intensification of therapy in such patients including using of HSCT as consolidation therapy. Based on these findings, MRD positivity has been used in addition to molecular genetics to risk stratify AML, especially those patients in intermediate risk categories as per genetics.[14-16] The AML02 multicenter trial used response to treatment as an additional risk stratification factor. Apart from baseline molecular and cytogenetics group, patients with ≥25% blasts post first induction or positive MRD after first-three courses were assigned to the "high risk" strata, in whom HSCT would be done in all cases where feasible. Their findings were that there was no difference in OS between high-risk patients undergoing HSCT (n = 48) or receiving chemotherapy; however, when they analyzed only high-risk patients with MRD >1% after induction 1, OS was better among those who underwent HSCT compared with those who did not: 43.5% (12.4) versus 23.1% (10.1; p = 0·14), findings that are likely to justify the consideration of HSCT in these patients when logistics and donor availability allow for it.[17]

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9. What are the current treatment regimens being used by major study groups?

The most recently concluded AML upfront treatment trial protocols by the MRC and BFM groups, along with the outcomes of both, are given in **Table 2**.

TABLE 2: Summary of recently concluded trials by MRC and BFM groups.

Study	*MRC AML 15*[18]	*BFM AML 2004*[19,20]
Stratification	Based on cytogenetics *Favorable:* • t(8;21) • t(15;17) • inv(16) (alone or with other abnormalities) *Intermediate:* • Abnormalities not classified as favorable or adverse, *or*, lack of identifiable cytogenetic abnormalities *Adverse:* • –5 • –7 • del(5q) abnormal 3q complex karyotype	*SR*: • M1/M2 with Auer rods • *M4eo or favorable cytogenetics*: – t(8:21) – t(16:16) or inv(16) • BM blasts <5% on day 15 • All FAB M3 patients *HR*: • Those not meeting the criteria for SR • SR patients found to be positive for FLT3 ITD
Induction	Ara C + DA versus Ara C + DA + Etoposide (ADE) versus Fludarabine + Cytarabine + Idarubicin + G-CSF (FLAG IDA) In induction course 1, all three groups were also randomly assigned to receive/not receive a single dose of GO	Cytarabine + Idarubicin + Etoposide (AIE) versus Cytarabine + L-DNR + Etoposide (ADxE) *Induction 2 for SR patients*: Cytarabine + Idarubicin (AI) *Induction 2 for HR patients*: High-dose cytarabine 3 g/m^2 + High-dose cytarabine and mitoxantrone
Reassessment	18–21 days from the end of course 1 → 15% or more blasts → HR irrespective of the initial risk	• On day 15, patients were stratified into SR or HR • Postinduction 1: Response to induction therapy • Postinduction 2: Decision for HSCT (after 2006)
Consolidation	• Amsacrine + Cytarabine + Etoposide followed by Mitoxantrone + Cytarabine 1 g/m^2 (MACE-MiDAC) versus high-dose ARAC (HiDAC) 3 g/m^2 versus HidAC 1.5 g/m^2 • All three groups were randomly assigned to receive/not receive a single dose of GO in the first course of consolidation • Further all patients were randomized to either receive a third consolidation or stop after two courses (i.e., a total of four vs. five courses)	All SR patients received HAM • *HR patients randomized*: Cytarabine 0.5 g/m^2 + Idarubicin + Cladribine (AI/2-CDA) versus Cytarabine 0.5 g/m^2 + Idarubicin (AI) • *Intensification*: High-dose cytarabine and etoposide in SR, HAM followed by HSCT in HR, 1-year maintenance with IT cytarabine, and randomization between 12 and 18 Gy CRT (stopped in 2009)
HSCT	Permitted for intermediate or HR disease	Pre-2006 HSCT to all HR patients at CR1 when feasible; after 2006 HR patients with BM blasts >5% after second induction

Contd...

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Study	*MRC AML 15*[18]	*BFM AML 2004*[19,20]
Outcomes	*Induction*: • No benefit in rate or durability of response with the addition of Etoposide • FLAG IDA significantly better relapse-free survival but greater hematologic toxicity • The benefit of FLAG IDA in all groups, including poor-risk patients. Idarubicin lower dose of 8 mg/m^2 also shows benefits • Patients who received only two courses of FLAG IDA (no consolidation) had similar outcomes to DA/ADE with consolidation *Consolidation*: • MACE/MidAC is equivalent to HiDAC in favorable and intermediate risk but superior in adverse risk. (Finding in adult subjects as a proportion of pediatric adverse risk patients was very low) • MACE/MidAC had more hematologic toxicity • No significant difference between HidAC 3 g/m^2 and 1.5 g/m^2 • No benefit of a fifth course GO • The benefit of addition of 3 mg/m^2 single dose in induction in favorable and intermediate groups, not adverse groups • No benefit of the addition of GO in consolidation (*Note:* These conclusions were from a mixed population, not from a pediatric population)	*Induction*: • Benefits seen in patients with t(8:21) with L-DNR • Overall patient population, the initial blast count on day 15 was better with Idarubicin, but two cohorts no longer different on day 28 → reflects prolonged action of L-DNR *Consolidation*: • Similar overall survival with and without the addition of Cladribine • Tolerable toxicity profile of Cladribine
Further studies	*MyeChild 01* is planned to build on findings of previous studies in regard to four main areas: 1. *Randomization 1*: (To find optimum anthracycline to use during induction) Mitoxantrone and Cytarabine versus L-DA and Cytarabine 2. *Randomization 2*: (Dose finding study for GO) single dose 3 mg/m^2 versus two doses of 3 mg/m^2 each in induction (further planned to increase to three doses based on safety data) 3. *Randomization 3*: (Addition of Fludarabine to consolidation) Fludarabine and Cytarabine versus high-dose Cytarabine 4. *Randomization 4*: (To check outcomes of reduced intensity conditioning in AML HSCT) RIC versus MAC prior to allogeneic HSCT	*BFM AML 2012* was planned to study the difference in outcomes in pediatric AML patients when cytarabine, liposomal daunorubicin and clofarabine *(ADxC)* were randomized against the standard induction course of cytarabine, etoposide, and L-DNR (*ADxE*). Unfortunately, enrolment was terminated early due to the cessation of availability of L-DNR[21]

(AML: acute myeloid leukemia; ADE: ara-C, daunorubicin, and etoposide; BFM: Berlin-Frankfurt-Munster; BM: bone marrow; CRT: crania radiotherapy; DNR: daunorubicin; FLAG: fludrabine cytarabine G-CSF; GO: gemtuzumab ozogamicin; G-CSF: granulocyte colony-stimulating factor; HiDAC: high dose cytarabine; HSCT: hematopoietic stem cell transplantation; HR: high risk; IDA: idarubicin; L-DA: liposomal daunorubicin; MACE: amsacrine cytarabine etoposide; MRC: Medical Research Council; MiDAC: mitoxantrone and intermediate dose cytarabine; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; SR: standard risk)

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10. Apart from chemotherapy, what is the role of targeted therapies in first-time AML?

In 2018, Bolouri et al. published the findings of the COG TARGET initiative, which aimed to describe the molecular landscape of pAML. This data was collected from 1,023 patients who had been enrolled in previous COG AML studies. Some of the key findings were:[22]

- *Most common mutated genes*: *RAS*, *KIT*, *FLT3*
- IDH1 and 2 mutations are exceedingly rare in pAML.
- Epigenetic regulators like KMT2A and WT1 showed a higher mutation rate than in adults.
- Some novel focal deletions (IL9R, MBNL1, ZEB2) and fusion genes (*CBFA2T3-GLIS2*, *NUP98-NSD1*) seem to be almost exclusively associated with pAML.

Data emerging from this and related studies suggest that there will be an increasing role for targeted therapies in pAML in the years to come. As described in a review by Yu et al. targeted therapies in AML can be broadly classified into three categories:[23]

1. Therapies targeting oncogenic mutations (e.g., FLT3 inhibitors).
2. Therapies targeting metabolic or maintenance pathways (e.g., epigenetic modifiers like hypomethylating agents).
3. Targeted delivery of cytotoxic agents [e.g., antibody drug conjugates (ADC) like gemtuzumab ozogamicin].

Current ongoing studies for some of the important agents in upfront pediatric AML are presented in **Table 3**. The role of targeted therapies in relapsed/refractory pAML will be summarized later in the chapter.

TABLE 3: Studies for targeted therapy in upfront pediatric AML.

Target/Mechanism	*Drug*	*Evidence/Ongoing studies*
FLT3 inhibitors	Midostaurin	*NCT03591510:* Ongoing phase II study, in children with FLT ITD allelic ration of 0.5 or greater, previously untreated—phase 1 is a dose-finding study, followed by phase 2 to evaluate efficacy (EFS at 24 months) tolerability and safety[24]
	Gilteritinib	*COG AAML 1831:* Phase III trial ongoing to compare standard chemotherapy with liposomal cytarabine + daunorubicin (CPX 351) with or without Gilteritinib (ongoing)
	Sorafenib	*COG AAML 1031:* Sorafenib + chemotherapy, post-HSCT maintenance sorafenib in high allelic ratio FLT3 ITD + AML improved CR rates and EFS[25]
ADC, CD33 antibody	GO	• *MRC AML 15:* Survival benefit good and intermediate risk cytogenetics[18] • *COG AAML 0531:* One dose each of GO added to ADE induction and MA (MiDAC) consolidation—significant improvement in EFS, no improvement in OS, increased toxicity and neutropenia[26] • *NOPHO AML 2004:* AML patients not undergoing HSCT were randomly assigned to receive two doses of GO postconsolidation, with no improvement in survival compared to no further treatment[27] • *MYECHILD 01:* Ongoing, dose-finding for GO, one dose during induction versus two doses (to increase to three depending on safety data)

(ADC: antibody drug conjugates; AML: acute myelogenous leukemia; CR: complete remission; COG: Children's Oncology Group; EFS: event-free survival; GO: gemtuzumab ozogamicin; HSCT: hematopoietic stem cell transplantation; MRC: Medical Research Council; MA: mitoxantrone and cytarabine; MiDAC: mitoxantrone and intermediate dose cytarabine)

Source: Lonetti A, Pession A, Masetti R. Targeted therapies for pediatric AML: gaps and perspective. Front Pediatr. 2019 Nov 15;7:463.

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CASE *(Continued)*

L received induction-2 (one more cycle of daunorubicin and cytarabine). During the course, he had one episode of invasive aspergillosis, which was successfully treated.

11. Children with AML have a high incidence of infections; what can be done to prevent the same? What is the role of antifungal and antibacterial prophylaxis?

While infectious complications are seen in almost all patients undergoing treatment for cancer, children with leukemia, especially AML, are especially susceptible. Various studies have shown that patients with AML experience, on average, three infectious episodes during therapy, with <3% of all patients remaining free from infections.

Indian studies on AML have shown that infectious complications occur in up to 64% of all patients.[28] One study found that 100% of their AML patients had an episode of febrile neutropenia (FN) during induction chemotherapy, with 65% having positive blood cultures.[29] Patients with AML also have a high incidence of invasive fungal infections with Indian data revealing incidence ranging anywhere between 3 and 55%, with the highest numbers found during induction.[30,31]

The Infectious Diseases Society of America (IDSA) constituted a clinical practice guideline for the use of antibacterial prophylaxis in pediatric cancer and HSCT in which they recommend that one may consider systemic antibacterial prophylaxis administration in children with AML and relapsed ALL receiving intensive chemotherapy expected to result in severe neutropenia (ANC < 500 µL for at least 7 days).[32] The basis of this recommendation is a large study published in 2018 by Alexander et al. that compared levofloxacin versus no prophylaxis in children with acute leukemia and those undergoing HSCT. Of the 200 patients with acute leukemia, they found that the likelihood of bacteremia was significantly lower in the levofloxacin prophylaxis group than in the control group (21.9 vs. 43.4%). FN was also less common in the levofloxacin group (71.2 vs. 82.1%), and there was no significant increase in the risk of invasive fungal disease (IFD), Clostridium difficile-associated diarrhea, or musculoskeletal toxicity in the group receiving levofloxacin.[33] This recommendation has, however, been termed as a weak one by the expert panel due to reservations regarding the emergence of resistant strains as demonstrated in two studies[34,35] also the uncertain implications of widespread use of fluoroquinolones (FQ) prophylaxis over longer treatment periods and the possible emergence of cross-resistant species. At this time, the use of antibacterial prophylaxis in patients with first time AML remains an institutional decision, to be taken after carefully weighing possible risks and benefits.

With regards to antifungal prophylaxis, evidence is clearer, with IDSA making a strong recommendation toward the use of antifungal prophylaxis in children and adolescents with AML receiving treatment expected to cause prolonged or profound neutropenia. The basis for the recommendation is a systematic review that found that compared with no systemic prophylaxis, systemic antifungal prophylaxis significantly reduced proven or probable IFD, proven or probable yeast, and fungal infection-related mortality, with the reduction in probable and proven IFD being the greatest in those at greatest risk for the same. Antifungal prophylaxis is hence widely used in AML. Further, they recommend using a mold-active antifungal, as compared with fluconazole would significantly reduce proven or probable IFD, mold infections, and invasive aspergillosis as well as fungal infection-related mortality.[36]

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A systematic review and meta-analysis published in 2020 of five randomized controlled trials (RCTs) with 1,617 participants found that posaconazole prophylaxis significantly reduces the risk of invasive fungal infections as compared to other antifungal agents, however, the fact that the drug is currently only approved in children 13 years of age and above precludes its widespread use in pAML.[37]

12. Is the use of granulocyte colony-stimulating factor (G-CSF) safe in children with AML?

Granulocyte colony-stimulating factor has been used during the therapy of many solid tumors, both as primary prophylaxis to reduce the duration and depth of neutropenia postmyelosuppressive chemotherapy. Its use in AML is less well established. Earlier concerns of G-CSF increasing the risk of relapse have now been largely disproved, with various studies showing no increase in relapse rates and no difference in remission and OS in those patients who receive G-CSF during therapy.[38] The effectiveness of G-CSF in preventing infection in AML is yet to be established. In the AML BFM 98 trial, 538 patients with AML were randomized to receive or not receive prophylactic G-CSF at the end of induction chemotherapy. It was found that there was no significant effect on the incidence of FN, documented infections, infection-associated mortality, or EFS; only the time of neutropenia was significantly reduced.[39]

In contrast, a study from the Korean University AML registry found that prophylactic G-CSF in AML reduced infection-related deaths without affecting remission relapse or OS. The American Society of Clinical Oncology (ASCO), in their clinical practice guidelines on growth factor usage, *do not* recommend the use of prophylactic G-CSF in nonrelapsed AML and recommend its use in the presence of infections only in case of presence of risk factors for poor outcomes, for example, hemodynamic instability. A retrospective study by Relling et al. found an increased risk of therapy-related acute myeloid leukemia (tAML) in patients who received G-CSF along with topoisomerase inhibitors would further caution us in the use of G-CSF in etoposide-containing protocols.[40]

CASE *(Continued)*

L received two cycles of high-dose ARAC and completed treatment in July of 2018. End of treatment marrow was in remission. Echocardiography done post-treatment revealed diastolic cardiac dysfunction, for which he was started on cardioprotection (enalapril).

13. In addition to infections, drug toxicity contributes to treatment-related mortality. What are the current protocols used, and how effective are they in reducing toxicity?

With gradually improving outcomes in pAML, efforts have been made in recent years to optimize treatment schedules to achieve these outcomes with the least possible toxicity.

As mentioned earlier, the treatment of pAML in most protocols involves a total four or five courses of chemotherapy, of which the latter two or three courses are often consolidation blocks centered around high-dose cytarabine. In an effort to reduce the exposure to cytarabine, the COG group compared the results of the AAML1031 trial using four courses (a cumulative cytarabine dose of 21.6 g/m^2) with those of the AAML0531 trial using five courses (a cumulative cytarabine dose of 45.6 g/m^2), they found that in the subset of low-risk

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(LR) patients who had no favorable or unfavorable cytogenetics with the end of induction MRD negative, DFS was significantly less with four courses, OS was also less, but this was not statistically significant. On the other hand, children with favorable risk cytogenetics were not found to have any statistically significant differences in outcomes.[41] The MRC 15 study group, on the other hand, found no benefit in the addition of a fifth course in any of their patients.[18]

The MRC 15 study also had significant findings in the area of cytarabine doses in adults. Compared to 3 g/m^2, 1.5 g/m^2 cytarabine had a trend toward higher relapse risk but no difference in OS. However, it was noted that the 3 g/m^2 arm had a significantly higher requirement of supportive care and hematological toxicity, suggesting that 1.5 g/m^2 may be a sufficient dose in consolidation to achieve remission with reduced toxicity however this remains to be studied in the pediatric age group.[18]

Etoposide, an important drug used as a part of induction in many AML protocols, is known to cause therapy-related leukemia. Various studies have looked into the dose of etoposide at which this risk increases, with one study finding a 3.3% risk of secondary leukemia in 6 years in doses as low as <1.5 g/m^2.[42] Many trials used etoposide as a part of their induction chemotherapy, with some adding etoposide into later courses as well. The COG 0531 used 1.75 g/m^2 of etoposide, the COG 1031 between 1.5 and 2.2 g/m^2 depending on randomization, and the ADE arm of MRC 15 used 1 g/m^2 of etoposide.[26,43] The MRC 15 trial compared the traditional ADE with an etoposide free arm using only 12 hourly cytarabine with three doses of daunorubicin and found that they were equivalent with respect to relapse risk, deaths in remission, relapse-free survival, and OS, opening up the possibility of using etoposide-free protocols in the future with a corresponding decrease in secondary leukemia.[18]

14. Which patients may require dosage modification during treatment?

Though comorbidities at treatment initiation are a concern encountered more frequently in the elderly, it is important to take into account any possible requirements of dosage modification prior to initiation of therapy. As a part of baseline workup, the BFM AML study group recommends the following:[3]

Assessment of WHO performance status:

1. Physical examination for syndromes and comorbidities
2. Biochemistry (liver and renal functions)
3. Coagulation tests
4. Chest X-ray, 12 lead electrocardiogram (ECG), and echocardiography
5. Hepatitis A, B, C, and cytomegalovirus (CMV).

In addition, each individual centers have various protocols for screening for infections at baseline prior to treatment induction; for example, at our center we screen with a tuberculin skin test, computed tomography (CT) of the chest and paranasal sinuses, and a serum galactomannan, while some other centers also include a rectal screening swab for extended-spectrum beta-lactamase resistant organisms.

The following situations may warrant dosage modification:

- *Cardiac dysfunction:* A left ventricular ejection fraction of 45% is the most commonly used threshold while deciding on the use of anthracyclines in therapy. This cutoff is largely based on adult studies, especially in patients with breast cancer. In patients with cardiac dysfunction detected at baseline, an option of HidAC-based therapy instead of

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anthracycline-based may be considered; however therapy must be decided based on the risk–benefit of the individual case.

- *Liver dysfunction:*
  - Anthracyclines are metabolized primarily by the liver, and administration of anthracyclines in the context of liver dysfunction may worsen doxorubicin-related toxicity, especially myelosuppression. A study done over 40 years ago by Benjamin et al. exploring bilirubin adjusted dosage of doxorubicin recommended the following modifications **(Table 4)**:[44]

TABLE 4: Anthracycline dose modification in liver dysfunction.[44]

Bilirubin mg/dL	*Transaminases*	*Dose*
3.0–5.0	Any	50%
5.0–7.0	Any	25%
>7.0	Any	With hold
<3.0	Any	No adjustment

Adapted from: Benjamin RS, Wiernik PH, Bachur NR. Adriamycin chemotherapy-efficacy, safety and pharmacologic basis of an intermittent single high-dosage schedule, Cancer 1974:33(1)19-27.

The above cutoffs have widely been incorporated into practice. It is important to bear in mind that these cutoffs are based on adult studies, and metabolism in the pediatric age group may vary.

Subsequently Donelli et al. 1998 suggested no dosage adjustment below 3.0 mg/dL and to withhold the drug above that cutoff.[45] Some isolated case reports have described unmodified doses even in bilirubin >5.0 mg/dL.

  - Cytarabine is metabolized in the liver, but a part of it is excreted unchanged by the kidney. Following rapid intravenous (IV) infusion of cytarabine, 90% of the dose is excreted as inactive metabolite uridine arabinoside while 10% is excreted unmetabolized. Though uniform recommendations are lacking, Floyd et al. suggest a 50% reduction of cytarabine dose in the presence of elevated transaminases.[46] The Indian Collaborative Childhood Leukemia group (ICiCLe) suggests the following dose adjustments in their ALL protocols **(Table 5)**.

TABLE 5: Cytarabine dose modification in liver dysfunction.

Bilirubin mg/dL	*Transaminases*	*Dose reduction*
2.0–3.0	>3 × ULN	50%
3.0–5.0		25%
>5.0		Withhold

(ULN: upper limits of normal)

Adapted from: Indian Collaborative Childhood Leukemia group (ICiCLE) protocol for ALL treatment.

  - Etoposide toxicity depends on liver function in two different ways. It is metabolized by the liver and partially cleared in the bile; hence liver dysfunction causes delayed clearance. The other mechanism is due to reduced serum albumin, which results in a greater fraction of unbound etoposide. Studies have shown that mild to moderate liver

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