Pediatric acute myeloid leukemia: updates on biology, risk stratification, and therapy

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Purpose of review
Despite advances in therapy over the past decades, overall survival for children with acute myeloid leukemia (AML) has not exceeded 70%. In this review, we highlight recent insights into risk stratification for patients with pediatric AML and discuss data driving current and developing therapeutic approaches.

Recent findings
Advances in cytogenetics and molecular profiling, as well as improvements in detection of minimal residual disease after induction therapy, have informed risk stratification, which now relies heavily on these elements. The treatment of childhood AML continues to be based primarily on intensive, conventional chemotherapy. However, recent trials focus on limiting treatment-related toxicity through the identification of low-risk subsets who can safely receive fewer cycles of chemotherapy, allocation of hematopoietic stem-cell transplant to only high-risk patients and optimization of infectious and cardioprotective supportive care.

Summary
Further incorporation of genomic and molecular data in pediatric AML will allow for additional refinements in risk stratification to enable the tailoring of treatment intensity. These data will also dictate the incorporation of molecularly targeted therapeutics into frontline treatment in the hope of improving survival while decreasing treatment-related toxicity.

Keywords
acute myloid leukemia, molecularly targeted therapy, pediatric, risk-stratification, supportive care

INTRODUCTION

Acute myeloid leukemia (AML) is relatively rare in children but causes disproportionate mortality. Although outcomes for children with AML have improved over the last decades, overall survival remains near 70% [1–3]. Due in large part to collaborative international efforts, treatment approaches for pediatric AML have converged to a standard that includes four or five cycles of myelosuppressive chemotherapy with cytarabine and anthracyclines followed by hematopoietic stem-cell transplant (HSCT) for a subset of patients. Collaborative efforts have also enabled refinement of risk stratification on the basis of clinical characteristics and molecular profiling. In this review, we will discuss new insights into the risk stratification of pediatric AML and review the literature driving current therapies and upcoming clinical trials.

PROGNOSTIC FACTORS AND RISK STRATIFICATION

The identification and validation of prognostic factors enabling therapy to be tailored to individual patients has been the focus of many recent AML investigations. Advances in sequencing have identified molecular subsets with prognostic significance, which, in conjunction with clinical factors, drive current risk stratification.

Host factors

Unmodifiable patient characteristics such as age, race, weight at diagnosis, and germline predisposition impact outcomes for children with AML. With intensive chemotherapy and supportive care, infants fare similarly to children but adolescents and young-adults experience higher rates of treatment-related

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KEY POINTS

- Risk stratification in pediatric AML is now based on cytogenetic and molecular disease features, as well as response to induction therapy detected by MRD.
- Induction therapy for AML includes administration of anthracycline and cytarabine; consolidation therapy varies by risk stratification and includes high-dose cytarabine or HSCT.
- The incorporation of molecularly targeted agents for specific AML subtypes is a central focus for further investigation.
- Ongoing efforts to optimize supportive care, particularly improving infectious prophylaxis and minimizing cardiotoxicity, have enabled the dosing intensification required to improve survival in pediatric AML.

mortality (TRM) and relapse [4–10]. Compared with their white counterparts, black children have consistently had poorer outcomes on Children's Cancer Group (CCG)/Children's Oncology Group (COG) trials [10,11]. This difference has not been observed in smaller studies [12,13] but may be attributable to increased illness severity at presentation [14]. Finally, the CCG2961 study showed that patients who are underweight or overweight have worse overall survival compared with patients with normal weight because of increased TRM [15]. These results were validated in a subsequent meta-analysis [16].

Patients with AML or myelodysplastic predisposition syndromes, such as Fanconi Anemia or Kostmann syndrome, tend to present with AML characterized by adverse cytogenetic features and chemotherapy resistance. These patients often have compromised ability to recover normal hematopoiesis following treatment and increased sensitivity to chemotherapeutic agents with excess toxicity necessitating dose attenuation. As such, patients with bone marrow failure syndromes are usually excluded from standard AML clinical trials. Thus, the therapeutic approaches for these patients are outside the scope of this review. Similarly, myeloid leukemia of Down's syndrome is a unique disease entity defined by mutations of GATA1. Although children with trisomy 21 have a 150-fold risk of developing AML [17], those who are younger than four also have increased sensitivity to chemotherapy with resultant remission rates over 90% and overall survival above 80% [7,18–20]. Dose reduction has been the focus of treatment protocols for this subgroup.

Clinical characteristics

The peripheral white blood cell (WBC) count on presentation is predictive with WBCs above 100 000 cells/μl linked to unfavorable outcomes [4]. Genomic and functional studies have begun to provide the biological basis for these elevated presenting WBC counts. Studies of the prognostic significance of cerebrospinal fluid (CSF) involvement at diagnosis have been conflicting, which may be attributable to differences in the definition of CSF involvement, intrathecal chemotherapy selection, and the dose and timing of high-dose cytarabine [21,22]. Central nervous system and orbital chloromas are associated with improved outcomes, whereas cutaneous disease is linked to inferior outcomes, again likely because of the underlying biology of these lesions [23]. None of these presentations, however, is currently used to risk-stratify patients, although intensified intrathecal therapy is recommended for patients with CSF disease.

Cytogenetic and molecular abnormalities

Although AML is a heterogeneous disorder at the cytogenetic and molecular levels, many of these alterations have not been definitively associated with prognosis in the context of current treatment regimens. Alterations with potential prognostic significance are summarized in Table 1. Future refinements of risk stratification will likely be the result of additionally identified and validated karyotypic and molecular lesions.

Overall, the molecular landscape underlying pediatric AML remains quite distinct from adults [24▪▪]. For one, the consensus low-risk cytogenetic group consisting of core-binding factor, nucleophosmin 1 and CEBPA gene mutations comprise approximately one-third of pediatric AML, a larger proportion than seen in adults [25]. In addition, cryptic translocations are significant contributors to childhood AML with a high prevalence in young children that declines in adulthood. Finally, somatic mutations impacting DNA methylation are highly prevalent in adults, whereas structural alterations in methyltransferase genes are prevalent in young children, but rare or absent in adults. These differences between children and adults have important implications when considering potential therapeutic targets.

Minimal residual disease

Initial response to induction therapy is a critical predictor of outcome in AML. Failure to achieve a clinical remission is highly predictive of poor outcome, even if subsequent therapy results in a remission

Table 1. Cytogenetic and gene rearrangements and gene mutations in newly diagnosed childhood acute myeloid leukemia

Molecular lesion	Frequency in childhood AML	Prognosis	References
Alterations associated with a favorable prognosis			
t(8;21) RUNX1-RUNX1T1	10–12%	5-year overall survival 80–90%	[98,99]
Inv(16) CBFB-MYH11	10%	5-year overall survival 85%	[98,99]
NPM1 gene mutations	8–10% Very uncommon in young patients	5-year EFS 80% and OS 85% Abrogates adverse prognosis of FLT3 ITD mutations	[100–102]
CEBPA gene mutations	5–10%	5-year overall survival 80% for double mutants; prognostic significance of single allele mutations unknown	[103–106]
Alterations associated with a poor prognosis			
Monosomy 7 Monosomy 5, del(5q)	2–4%	5–10-year overall survival 30–40%	[50,98,107]
FLT3/ITD	10–20% Frequency increases with age	5-year overall survival 30–40% in patients with high allelic ratios[a] Important therapeutic target	[101,108–111]
11q23 (KMT2A) rearrangements	20% Occurs most frequently in infants Associated with secondary leukemias because of epipoophyllotoxin exposure	Prognostic significance dependent on fusion partner but ranges from 5-year EFS above 90% for t(1;11) to 10% for t(6;11)	[98,99,112,113]
t(6;9) (*DEK-NUP214*)	<1%	5-year overall survival 20%	[114,115]
t(7;12) (*MNX-ETV6*)	Up to 30% of children younger than 2 (and only found in this age group)	3-year EFS 10–24%	[116–119]
t(5;11) (*NUP98-NSD1*)	10% Highly associated with FLT3/ITD	4-year EFS 10%	[114,120–122]
inv(16)(p13.3q24.3) (*CBFA2T3-GLIS2*)	2% Occurs only in patients younger than 3	5-year EFS 27%	[123,124]
Alternations of uncertain significance			
t(1;22)	<1% Primarily in patients younger than 1	Conflicting outcomes in the literature	[125,126]
t(8;16)	10%	In infants diagnosed in the first month of life, spontaneous remission has been observed	[127–132]
FLT3/TKD mutations	7%	No prognostic significance in pediatric AML	[101,108–111]
KIT gene mutations	<5% overall but 25% of patients with favorable prognosis cytogenetics	May negatively impact response to therapy; potential therapeutic target for exploration	[133,134]

AML, Acute myeloid leukemia; EFS, event-free survival; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; TKD, tyrosine kinase domain.
[a]High mutant to normal allelic ratio, usually at least 0.3.

[6]. Multiparameter flow cytometry immunophenotyping has been progressively refined to be able to distinguish leukemic blasts from normal hematopoietic precursors, providing a far more sensitive methodology for stratification than morphologic response alone [26]. Results from cooperative group trials have clearly demonstrated that minimal residual disease (MRD) after induction is an independent prognostic marker in patients with uninformative molecular features [27–29]. However, the COG trials AAML03P1 and AAML0531 found that the presence of MRD in patients with low-risk cytogenetics was not associated with adverse outcome. These studies conversely demonstrated that high-risk patients had adverse outcomes despite negative MRD. These data have informed a two-tiered risk stratification schema, where patients with informative cytogenetic or molecular lesions are allocated to the appropriate risk class and those without informative risk biomarkers are stratified by disease response.

A newer approach to detecting MRD is based on polymerase chain reaction or deep nucleic acid sequencing, designed to detect specific gene mutations or chromosomal translocations. Although

such approaches offer the benefit of improved sensitivity for low-level disease, they are currently only applicable in half of AML patients because of molecular heterogeneity and instability genetic changes particularly when present at low allelic frequency [30]. The specific role for molecular MRD in determining response to therapy or guiding therapeutic decisions is an area of active research.

TREATMENT OF CHILDHOOD ACUTE MYELOID LEUKEMIA

Intensification of chemotherapy – both in induction and consolidation – has emerged as the fundamental AML treatment paradigm [25]. Currently, induction seeks to achieve an initial remission and is then followed by consolidative courses of therapy, including allogeneic HSCT for select patients. More recently, novel and molecularly targeted agents have been developed to enhance overall efficacy but maintain tolerability of current chemotherapy regimens. Table 2 summarizes key findings from recent clinical trials conducted by large consortia. In parallel, the development of evidence-based supportive care guidelines has been critical to supporting the intensification of AML chemotherapy.

Approaches to upfront therapy

Since the early 1980s, induction therapy is based on administration of daunorubicin and cytarabine [31,32]. Multiple trials have tested alternative anthracyclines, intensification of cytarabine dosing, and inclusion of additional agents. To date, substituting alternative anthracyclines into this regimen has not provided consistent improvements in remission rates [33–38]. However, the new formulation of liposomal daunorubcin and cytarabine (CPX-351) has recently been approved for the treatment of AML in adults and demonstrated promise in the pediatric relapsed/refractory setting [39▪] and is now being studied in frontline trials [25]. Simultaneously, multiple trials have sought to define the optimal dosing and timing of cytarabine, the other critical component of induction. Results of trials comparing low-dose cytarabine (100–200 mg/m^2) to high dose (1000–3000 mg/m^2 twice daily) are mixed [29,40,41]. Thus, pediatric cooperative groups remain divided on cytarabine dosing in induction.

Collaborative groups have tested the addition of a third agent to this backbone. The most recent Medical Research Council (MRC) trial evaluated the addition of etoposide to daunorubicin and cytarabine and reported no improvement in outcome for patients randomized to receive etoposide [42]. Based on these data, etoposide will be removed from standard therapy in the COG AAML1831 trial. Finally, clofarabine, a second-generation purine nucleoside analog has been incorporated into induction therapy in some trials. The St. Jude Children's Research Hospital AML08 (stood for acute myeloid leukemia)

Table 2. Characteristics and treatment results from selected clinical trials for childhood AML

Study group (trial acronym)[a]	Study period	No. of patients[b,c]	Early deaths (%)	Complete response rate (%)[d]	Time of complete response evaluation	EFS ± standard error	Overall survival ± standard error	Time of EFS/OS evaluation (years)	References
AIEOP (AAML2002/02)	2002–2001	482	3	87	2 courses	55% ± 2.6	68% ± 2.4	8	[135]
BFM (AML2004)	2004–2010	611	2–3	88–89	4 courses	55 ± 2	74 ± 2	5	[136]
COG (AAML0531)	2006–2010	1022[e]	1.8	86.7	2 courses	46.9 ± 4.4–53.1 ± 4.4	65.4 ± 4.4–69.4 ± 4.2	3	[10]
JPLSG (AML05)	2006–2010	443			2 courses	54 ± 2	73 ± 2	3	[137]
MRC (AML12)	1994–2002	455	4	92	4 courses	53	64	10	[37,50,52]
EORTC-CLG (58921)	1993–2000	177	1	84	2 courses	49 ± 4	62 ± 4	7	[138]
NOPHO (AML2004)	2004–2007	151	1.3	97.4	2 courses	57 ± 5	69 ± 5	3	[139,140]
SJCRH (AML08)	2008–2017	285	1.5	93	2 courses	52.9%	64.6%	3	[43▪]

COG AAML0531 numbers represent outcomes for patients not receiving gemtuzumab ozogamicin compared with those who did receive this antibody conjugate. This table was adapted from Pui *et al.* [1]. AIEOP, Italian Association for Pediatric Hematology and Oncology; BFM, Berlin–Frankfurt–Munster group; COG, Children's Oncology Group; EFS, event-free survival; EORTC-CLG, European Organization for Research and Treatment of Cancer-Children Leukemia Group; JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group; MRC, Medical Research Council; NOPHO, Nordic Society of Pediatric Hematology and Oncology; SJCRH, St. Jude Children's Research Hospital.

[a]Results are reported for only those trials that had at least 150 patients and information provided for each of the column headings.

[b]No. of patients excludes patients with Down Syndrome.

[c]Ages include patients from 0 to 15 years, inclusive.

[d]Complete response was determined by morphology of less than 5% leukemic blasts.

[e]Age for inclusion in trial was 0–29 years of age.

study randomized patients to receive clofarabine versus daunorubicin and etoposide with cytarabine in the first block of induction therapy. This trial reported a three-year overall survival and event-free survival (EFS) that was not significant between the two arms, although the point estimates for day 22 MRD and three-year overall survival suggest that the clofarabine arm may be inferior [43▪]. Further data are needed before widespread adoption of this approach. The Berlin–Frankfurt–Munster–acute myeloid leukemia group will perform a similar randomization in their current study.

Post-remission consolidation therapy consists of high-dose cytarabine for patients who do not proceed to HSCT [10,29,42,44–47]. Although the need for intensive consolidation is well established, the necessary number of consolidation cycles remains undefined. Most cooperative groups provide an additional two to three cycles of intensive chemotherapy to give a total of three to five cycles of chemotherapy. Although recent trials from the Japanese cooperative group and MRC both demonstrated no change in survival with an additional cycle of chemotherapy [37,48–50], the COG AAML1031 trial saw inferior outcomes for patients treated with four cycles when compared with five on the prior trial [51]. Subgroup analyses found that the fifth cycle could be eliminated in patients with favorable molecular features and negative MRD without impacting survival. As a result, the number of consolidation cycles will be based on molecular features and disease response in AAML1831, the upcoming COG phase III trial.

Hematopoietic stem-cell transplant

The efficacy of HSCT in AML is at least partially linked to a graft-versus-leukemia (GVL) effect resulting from immune surveillance by donor T-lymphocytes. Of course, HSCT also poses risk of additional TRM because of graft-versus-host-disease (GVHD), infection, and organ toxicity. Thus, application of HSCT must be carefully considered with potential benefit, especially in an era of improved outcomes using intensified chemotherapy regimens.

Patients with favorable-risk AML are currently only offered HSCT in second clinical remission [40,52,53–56]. In contrast, patients with high-risk AML are nearly always offered HSCT as consolidative therapy. This latter group includes patients with complex cytogenetics, monosomy 7, monosomy 5, del(5), high allelic ratio FMS-like tyrosine kinase 3 (FLT3)/internal tandem duplication (ITD) without good prognosis modifiers, and those with poor response to induction therapy [10,57,58]. Research is ongoing to further define which patients with intermediate-risk AML will benefit from HSCT. However, although short of definitive information, there is enough evidence demonstrating that allogeneic HSCT results in more effective leukemia eradication and overall patient survival that it a reasonable option to consider in this still undefined risk group subset.

As the field of transplantation evolves, the improved TRM for alternative donor transplants has provided the means to offer HSCT – and potential GVL – when no matched family donor is available [59]. Retrospective analyses in AML have demonstrated that matched unrelated donors [60], mismatched unrelated donors [61], and unrelated cord blood [62,63] are all reasonable donor sources no matched related donor is available [64,65]. In addition, the use of haploidentical donors has seen significant advances over the past several decades in terms of feasibility, successful engraftment, and reduction in GVHD and TRMs [66–73]. Haploidentical HSCT after αβ T-cell/B-cell depletion holds promise for retaining the antileukemic capacity of the graft while minimizing infection and GVHD [74▪]. Identification of which patients will benefit from consolidative HSCT will be refined in the coming years, but will likely not be based, as historically, on availability of a matched related donor.

Molecularly targeted therapies

Further therapy intensification of traditional cytotoxic chemotherapy is impractical given the risks of both short-term and long-term organ dysfunction. As a result, emphasis has been placed upon the development of complementary, molecularly targeted therapeutic approaches. Two agents have thus far been incorporated into frontline phase III trials for childhood AML. Several additional agents are under investigation in early phase trials or used in the relapsed setting. Table 3 describes some of these approaches.

Gemetuzumab ozogamicin, a humanized anti-CD33 monoclonal antibody conjugate, has sound rationale for use in AML as the majority of cases express CD33 [2]. The randomized Phase III trial AAML0531 performed definitive efficacy testing of gemetuzumab ozogamicin in children. Although the addition of gemetuzumab ozogamicin did not improve remission rates or overall survival, EFS was improved compared with chemotherapy alone [10]. Based on the higher EFS and adult trials showing benefit to this agent [75], gemetuzumab ozogamicin will be included in the therapeutic backbone for the next COG phase III trial.

Due to the adverse prognosis associated with FLT3 mutations, and the demonstrated signaling

Table 3. Novel drugs and treatment modalities in childhood AML

Drugs by modality	Comments
Immunotherapy	
Monoclonal antibodies (e.g., gemtuzumab ozogamicin)	Anti-CD33 monoclonal antibody conjugated to cytotoxic calicheamicin. Based on data from adults [75], and demonstrated activity in pediatric studies [9,10], gemtuzumab will be incorporated into upfront therapy in the next COG phase III trial
CAR T cells	T cells with genetically engineered CARs to target tumor antigens are in development for AML. The paucity of well characterized, leukemia-specific surface antigens in AML have complicated their development; however, several antigens have been identified for investigation including CD33, CD38, CD123, and Lewis-Y [141]. Early phase trials are planned including a phase I/II trial of CD33 CAR in children and young adults (NCT03971799)
Tyrosine kinase inhibitors	
FLT3 inhibitors (e.g., sorafenib, midostaurin, giltiritinib)	There is biologic rationale for the use of FLT3 inhibitors based on the increased signaling dependence in FLT3/ITD blasts. First generation multikinase inhibitors midostaurin and sorafenib have shown promising efficacy when used with standard chemotherapy and as postconsolidation maintenance [76▪▪,77]. The latter has been studied in children specifically [78,79]. Second generation FLT3 inhibitors, including giltiritinib, have increased potency and selectivity for FLT3. These agents have been evaluated in early phase clinical trials in adults and will be incorporated into upcoming pediatric studies [141,142▪▪,143]
KIT inhibitor (e.g., dasatinib)	Because of the frequency of KIT mutations in AML with favorable prognosis cytogenetics, KIT is an appealing target for drug development
Proteasome/ubiquitin pathway inhibitors	
Proteosome inhibitor (e.g., bortezomib)	Proteosome inhibitors have been investigated in the treatment of multiple malignancies. Although early phase studies in relapsed/refractory AML suggested efficacy and tolerability of bortezomib, the most recently completed COG trial did not show a benefit to the addition of bortezomib to upfront therapy
NEDD8 inhibitor (e.g., pevonedistat)	The small molecule has the potential for significant antitumor effect through triggering apoptosis and autophagy. Early phase clinical trials to assess dosing and safety in conjunction with fludarabine, cytarabine, and azacytidine are underway in relapsed/refractory AML (NCT03813147) [144▪]
Epigenetic targetting	
Methyltransferase inhibitors (e.g., azacytidine, decitabine)	These agents are incorporated into DNA resulting in a variety of mechanisms with antileukemic potential, including but not limited to induction of global hypomethylation, downregulation of oncogenes, reactivation of tumor suppressors, and increasing sensitivity to cytotoxic agents. Studies are ongoing to evaluate these agents alone, as priming for conventional chemotherapy, or in combination with other epigenetic strategies including inhibition of histone deacetylase, NEDD8 or BCL2 [141]
Histone deacetylase inhibitors (e.g., vorinostat, panobinostat)	HDAC inhibitors induce cell cycle arrest and apoptosis. Early phase trials are evaluating the feasibility of dosing with conventional chemotherapy in the relapsed/refractory setting (NCT03263936)
Other novel agents	
BCL-2 inhibitors (e.g., venetoclax)	BCL2 is an oncogenic protein that blocks apoptosis and is therefore a promising target in many hematologic malignancies. Current studies are testing the combination of venetoclax with cytarabine and an anthracycline for relapsed/refractory AML (NCT03826992, NCT03194932) [144▪]

The majority of the medications listed in this table are not labeled specifically for pediatric AML or are still under investigation. BCL2, B-cell lymphoma 2; CAR, chimeric antigen receptor; COG, Children's Oncology Group; FLT3, FMS-like tyrosine kinase 3; HDAC, histone deacetylase; ITD, internal tandem duplication.

dependence on FLT3/ITD blasts, small molecule inhibition of FLT3 kinase has also been pursued as a therapeutic strategy. Midostaurin, a first-generation kinase inhibitor, was recently approved by the Food and drug administration (FDA) for treatment of FLT3 mutated AML in adults on the basis of promising efficacy data for its use in conjunction with conventional chemotherapy, as well as use a postconsolidation maintenance therapy [76▪▪,77]. This agent is not currently FDA approved in children. Similarly, phase I studies of the multikinase inhibitor sorafenib provided an early efficacy signal for FLT3 inhibition in children [78,79]. The AAML1031 trial nonrandomly stratified children with high allelic ratio FLT3 ITD to receive sorafenib; efficacy analyses are currently ongoing.

Supportive care

Although the intensification of AML therapy has improved outcomes for children with AML, this approach also causes substantial morbidity and mortality. The effectiveness of this therapy, therefore, depends on judicious and timely application of supportive care.

More than half of pediatric patients with AML will experience a severe bacterial infection while on therapy and approximately 10% will experience invasive fungal infections [80–82]. Thus, effective prophylaxis has been a longstanding area of interest. Recently, Alexander *et al.* [83▪▪] reported the first prospective, randomized trial of antimicrobial prophylaxis in pediatric AML demonstrating that levofloxacin prophylaxis significantly reduces the risk of bacteremia and neutropenic fever. Bacterial prophylaxis has therefore become standard at many institutions. In addition, based on compelling retrospective data that antifungal prophylaxis decreases invasive fungal infection and TRM, antifungal prophylaxis is recommended in pediatric AML [84–91]. A prospective randomized trial comparing antifungal agents in children (NCT01307579) was recently completed and those results are pending.

Recent work identifying worse overall survival in patients experiencing on-protocol cardiac dysfunction has spurred new efforts to mitigate anthracycline-associated cardiac toxicity, particularly dexrazoxane, and liposomal anthracycline formulations [92▪]. Although an early study reported an increased risk of secondary malignancy in Hodgkin's lymphoma [93], subsequent reports in leukemia patients have not identified the same risk [94–96]. With recent data demonstrating a cardioprotective benefit of dexrazoxane in pediatric AML without a signal for increased relapse or toxicity [97], dexrazoxane will be incorporated as the standard of care in the next phase III COG clinical trial.

CONCLUSION

Most currently used prognostic classification systems for childhood AML now consider cytogenetic and molecular factors and disease response by MRD with host factors and clinical characteristics for determining risk. Titrating therapeutic intensity – including the role of HSCT – to balance baseline risk and TRM may provide the best likelihood of improving survival. Future risk stratification is likely to include additional molecular/genomic factors as well as epigenetic factors and drug sensitivity testing. In addition, new molecularly based therapies may alter the implications of some of these lesions. Future prospective, clinical trials will be designed to therapeutically leverage such prognostic factors, as well as further optimizing supportive care to minimize therapy-related toxicity.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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