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CLINICAL PRACTICE GUIDELINE

Guideline for treating relapsed or refractory myeloid leukemia in children with Down syndrome

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Abstract

Treatment of relapsed and refractory myeloid leukemia in Down syndrome (r/r ML-DS) poses significant challenges, as prognosis is dire and there is no established standard treatment. This guideline provides treatment recommendations based on a literature review and collection of expert opinions, aiming to improve overall and event-free survival of patients. Treatment options include fludarabine and cytarabine (FLA) ± gemtuzumab ozogamicin (GO), azacytidine (AZA) ± panobinostat, and hematopoietic stem cell transplantation (HSCT). Preferred approaches are AZA ± panobinostat for cases with low blast count or FLA ± GO for cases with high blast count, followed by HSCT after remission. Further research is crucial for the investigation of targeted therapies (e.g., BH3 mimetics, LSD1, JAK inhibitors).

KEYWORDS
acute myeloid leukemia, Down syndrome, guideline, trisomy 21

1 | BACKGROUND

ML-DS represents a distinct subtype of leukemia associated with somatic mutations in exon 2 or 3 of *GATA1* that occurs in children with DS.[1] Children with DS face a 150-fold increased risk for developing myeloid leukemia within the first 4 years of life.[2–4] ML-DS exhibits several distinctive characteristics compared to non-DS acute myeloid leukemia (AML), including a younger age diagnosis (younger than 4 years) in addition to characteristic genetic alterations in the *GATA1* gene.[2,5–9] ML-DS often manifests through decreased

Abbreviations: AML, acute myeloid leukemia; AZA, azacytidine; BCL, B-cell lymphoma; BCL-2, B-cell lymphoma 2; BCL-XL, B-cell lymphoma-extra large; CNS, central nervous system; CR, complete remission; DNA, deoxyribonucleic acid; DS, Down syndrome; EFS, event-free survival; FLA, fludarabine, cytarabine; G-CSF, granulocyte colony-stimulating factor; GO, gemtuzumab ozogamicin; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HD, high dose; HDAC, histone deacetylase; HSCT, hematopoietic stem cell transplantation; i.th., intrathecal; i.v., intravenous; Ida, idarubicin; LSD1, lysine-specific demethylase 1; MDS, myelodysplastic syndromes; ML-DS, myeloid leukemia associated with Down syndrome; OS, overall survival; r/r, relapsed and refractory; RIC, reduced intensity conditioning; SC, subcutaneous; TAM, transient abnormal myelopoiesis; TRM, treatment-related mortality.

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platelet counts, megakaryocytic dysplasia, and frequently evolves from a subclone of neonatal transient abnormal myelopoiesis (TAM). The pathogenesis of both TAM and ML-DS is initiated by mutations, resulting in the N-terminal truncation of the mutant protein (termed GATA1s) and propelled to ML-DS by additional co-operating mutations.[6,10–12]

Treatment and prognosis of ML-DS significantly differ from non-DS AML. Remarkable outcomes for primary ML-DS have been achieved with reduced intensity therapy, and 5-year overall survival (OS) and event-free survival (EFS) are now 89% and 87%, respectively.[2,4,13–15] The favorable outcome of primary ML-DS can at least in part be attributed to a high sensitivity of ML-DS blasts to cytarabine and anthracyclines.[13,16,17] In contrast to the highly favorable prognosis of children with primary ML-DS, the probability of survival after a relapse of ML-DS is very low (3-year OS of 22% ± 5% and an EFS of 21% ± 5%).[2,4,13,18,19] In the ML-DS 2006 study, seven out of nine patients with relapse died, and in the AAML1531 study, patients with relapse had a 1-year OS of only 16%.[2,13] Relapses typically occur early—after a mean of 6.8 months (range: 1.1–45.5).[2,4,13,18,19] Risk factors for relapse have not yet been well defined, but include complex cytogenetics and poor early treatment response.[13,19]

There is no established treatment recommendation for children with r/r ML-DS. Therapeutic approaches vary widely and are largely left to the discretion of individual physicians. This clinical guideline aims to define treatment options for patients with r/r ML-DS and provide practical recommendations. Its objective is to equip clinicians with insights that enable informed decision-making based on current evidence. Suggested treatment encompasses epigenetic therapy with AZA ± panobinostat,[18,20–23] intensive chemotherapy with fludarabine and cytarabine (FLA) ± gemtuzumab ozogamicin (GO) (Figures 1 and 2), and hematopoietic stem cell transplantation (HSCT).

2 | METHODS AND PANEL

Systematic reviews of the existing literature, clinical trial data, experts' insights, and the latest research findings were integrated into the guideline to develop recommendations to improve treatment for children with r/r ML-DS. The panel comprised ML-DS specialists from North America, Europe, and Japan, who used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method to develop a consensus regarding the evaluation of the quality of the evidence and the design of recommendations.[24–26] This guideline incorporates current literature and research findings, and serves as a guide for clinicians. Recommendations are categorized as strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…").[24] The panel plans to update these recommendations according to future advances in the treatment of r/r ML-DS.

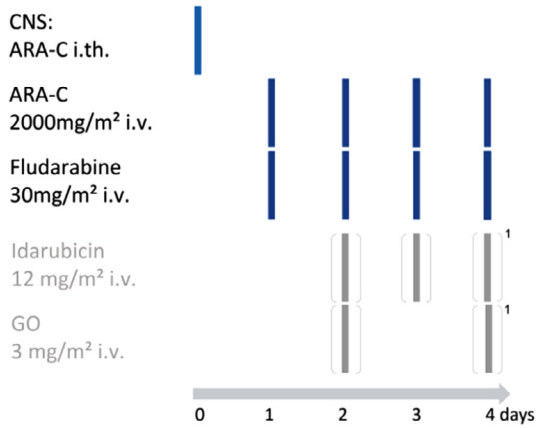

FIGURE 1 FLA therapy protocol: CNS therapy with ARA-C intrathecal (age-adjusted dosing; Day 1); as an alternative or for CNS-positive patients, triple intrathecal therapy (methotrexate, prednisolone, and ARA-C) and/or repeated doses can be administered on Day 4 and Day 7. ARA-C 2000 mg/m^2 intravenously (IV) (Days 1–5), fludarabine 30 mg/m^2 IV (Days 1–5). Optional: G-CSF subcutaneously (SC) or IV (Days 1–5).[2] The addition of idarubicin 12 mg/m^2 IV [Days 1, 3, 5]; Ida-FLA) or gemtuzumab ozogamicin (3 mg/m^2/dose [Day 6]; FLA + GO) may be considered as an additional treatment option. ARA-C, cytarabine; CNS, central nervous system; FLA, fludarabine and cytarabine; GO, gemtuzumab ozogamicin.

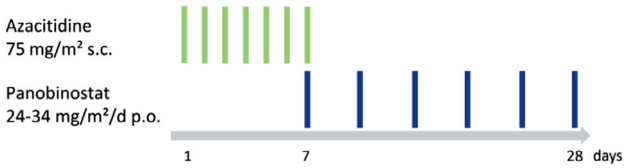

FIGURE 2 Therapy protocol of AZA and panobinostat: AZA 75 mg/m^2 subcutaneously (SC) (Days 1–7) and oral panobinostat (starting on Day 7, thrice weekly for seven doses) in 28-day cycles. Panobinostat starting dose of 24 mg/m^2/day, with gradual escalation to 30 and 34 mg/m^2/day, if well tolerated. The capsules can be dissolved in water.

2.1 | Formulation of specific clinical questions

Q1. How efficacious is FLA ± anthracycline therapy in achieving remission and improving OS rates in children with r/r ML-DS?

Q2. What are the outcomes of patients with r/r ML-DS treated with AZA ± panobinostat in terms of remission and survival rates, and what is the most appropriate patient population?

Q3. What is the impact of adding GO to chemotherapy for patients with r/r ML-DS on EFS and relapse rate?

Q4. What are the survival rates and outcomes for patients with ML-DS undergoing HSCT compared to those receiving chemotherapy alone?

Q5. What are the potential benefits and side effects of BH3 mimetics (e.g., venetoclax, navitoclax) in treatment, and what is the recommended dosage?

3 | RECOMMENDATIONS OF MANAGEMENT STRATEGIES FOR R/R ML-DS

3.1 | Recommendation 1

The guideline panel suggests that based on risk stratification of patients (see below), the initial course of relapse treatment should consist of either azacytidine (AZA) ± panobinostat or FLA ± GO (Figures 1 and 2).

Comments:

- Treatment choice depends on a patient's blast percentage in the bone marrow, clinical condition, and prior first-line therapy. The guideline panel suggests that
  - patients with fewer than 20% blasts in bone marrow at relapse receive AZA ± panobinostat (Figure 2).
  - patients with 20% or more blasts in the bone marrow receive FLA ± GO -(Figure 1).
- Efficacy of AZA ± panobinostat requires prolonged exposure, and multiple cycles may be required before response is observed. Therefore, a minimum of two to three cycles is recommended before response to AZA ± panobinostat is assessed.

3.1.1 | Specific background

Chemotherapy regimen

The treatment of r/r ML-DS in children presents a clinical challenge due to the absence of standardized treatment recommendations. The JPLSG study enrolled 26 patients with r/r ML-DS. Fifty percent achieved CR, with a 3-year OS rate of 26% ± 9%. Patients were treated with various chemotherapy courses and without central nervous system (CNS) prophylaxis. Most patients received a combination of mitoxantrone, intermediate-dose cytarabine, and etoposide, but other therapeutic regimens such as FLA were also used. Eight out of 13 patients, who achieved CR, underwent HSCT. Among the remaining five patients in CR who received chemotherapy only, four (80%) survived, underscoring the efficacy of chemotherapy in some contexts of r/r ML-DS with a favorable response.[19] In contrast, other study groups did not observe survival of patients with r/r ML-DS treated with chemotherapy only.[2,13,27,28]

FLA with or without anthracyclines is widely used as standard therapy for r/r (non-DS) AML in Europe and North America (Figure 1).[29] Fludarabine, a purine analog, inhibits various enzymes involved in deoxyribonucleic acid (DNA) and RNA synthesis.[30] When combined with cytarabine, it increases the synthesis of active cytarabine metabolite. The synergy between both drugs increases the efficacy of the salvage therapy.[30–32] Figure 1 illustrates the FLA treatment protocol. Inclusion of granulocyte colony-stimulating factor (G-CSF) is used by some but not others, and therefore is optional in this guideline. Similar to non-DS patients, FLA ± anthracycline was also found to be the most commonly used chemotherapy regimen for patients with r/r ML-DS. The use of anthracyclines should be carefully determined based on the cumulative anthracycline dosage from prior treatments and pre-existing conditions, particularly cardiac comorbidities.[27,33] While dexrazoxane has been shown to reduce cardiotoxicity, there have been concerns about an increased risk of secondary malignant neoplasms. Given that the balance of benefits and risks associated with dexrazoxane treatment remains uncertain, treatment with dexrazoxane should be carefully considered for each individual patient.[34–36] Similarly, other common health problems in children with DS, such as abnormal development of the gastrointestinal system, should also be taken into account when choosing the specific r/r ML-DS treatment plan.

As CNS involvement is rare in ML-DS, CNS prophylaxis has been significantly reduced in frontline therapy in Europe and North America to avoid toxicity and long-term side effects, such as cognitive impairment. It is not standard of care in Japan.[2,28,37] Nevertheless, CNS involvement can occur in rare cases, so patients with r/r ML-DS should receive intrathecal chemotherapy with cytarabine. The addition of prednisolone and methotrexate can be considered (triple intrathecal therapy). Regular monitoring for CNS involvement during treatment is also crucial.

In a retrospective analysis of international trials from 2000 to 2021 encompassing 62 patients with r/r ML-DS, treated with curative intent, 45% achieved CR. Notably, 45% received chemotherapy consisting of high-dose (HD) cytarabine either alone or combined with fludarabine, anthracycline, or both. FLA was also the most frequent choice for treatment of a second relapse of ML-DS.[27] While dose-reduced regimens are common for ML-DS, the FLA regimen is administered at standard doses and should not be reduced.

Gemtuzumab ozogamicin (GO) is an antibody–drug conjugate targeting CD33. The randomized phase III trial AAML0531 conducted by the Children's Oncology Group (COG) evaluated the efficacy of one dose of GO (3 mg/m^2/dose) added to two courses of chemotherapy in patients with non-DS AML. Addition of GO resulted in improved 3-year EFS but not OS, and decreased relapse rate in the low-risk group. However, this benefit was accompanied by an increased treatment-related mortality (TRM).[38] The benefit of GO extended to high-risk patients with FLT3/ITD at a high allelic ratio. Those who received GO during the induction phase exhibited markedly reduced relapse frequencies post hematopoietic stem cell transplantation (HSCT).[39] However, data regarding the use of GO to treat r/r ML-DS in which blasts usually express CD33 are lacking.[40,41]

Epigenetic therapy

Genomic profiling of patients with ML-DS has revealed a plethora of somatic mutations in epigenetic regulators, including factors that influence histone modifications and DNA methylation, and likely are pivotal in gene regulation of leukemic cells.[11,42–44] Prompted by the pioneering work of Scheer et al., who achieved CR utilizing the histone deacetylase (HDAC) inhibitor vorinostat in a pediatric patient with a second ML-DS relapse after HSCT, there has been

an increased interest in the development and application of targeted therapeutic HDAC inhibitors and DNA methyltransferase inhibitors, namely AZA and decitabine.[22,23,45,46] Case reports highlight the therapeutic potential of AZA in patients with r/r ML-DS even following a second ML-DS relapse post HSCT, and suggest a heightened sensitivity of specific ML-DS clones to this treatment modality.[23]

Panobinostat is an HDAC inhibitor that is significantly more potent than vorinostat. It inhibits 11 HDACs and shows 10–100-fold increased activity compared to vorinostat with lower IC_{50} values indicating higher efficacy.[47,48] A phase I trial enrolled children with r/r hematologic malignancies focusing on the safety, tolerability, and appropriate dosing of panobinostat.[45] Pediatric patients with leukemia administered panobinostat orally on 3 non-consecutive days weekly at doses of 24, 30, and 34 mg/m^2/day tolerated the treatment well. However, disease progression or electrolyte imbalances limited a comprehensive evaluation of toxicity. Adverse events were predominantly gastrointestinal.[45]

HDAC inhibitors, known to modulate DNA accessibility and influence gene expression, manifest augmented therapeutic effects when combined with DNA methyltransferase inhibitors. A phase Ib/II study in adult patients with AML and high-risk myelodysplastic syndromes (MDS), which aimed to rectify epigenetic dysregulation, employed a combination of panobinostat and AZA, and reported promising outcomes. Partial remission was achieved in 31% of patients with AML, while patients with MDS showed an overall response rate of 50%. The median OS was 8 months for AML and 16 months for patients with MDS. The most common adverse events were febrile neutropenia, nausea, infections, and hematologic toxicities.[49] No data are available for pediatric AML.

Another approach is the combination of HDAC inhibitors and DNA methyltransferase inhibitors (e.g., vorinostat and decitabine) with intense chemotherapy to improve response of leukemic blasts to chemotherapy.[22] Case reports have shown that vorinostat is well tolerated and enhances the efficacy of chemotherapy.[46] In adult trials, panobinostat increased the remission rate (55% vs. 64%) and prolonged time until disease progression (9 vs. 14 months).[50] Predominant side effects were nausea, fatigue, and thrombocytopenia.[51] Studies involving children are still pending at this time.

3.1.2 | Benefits and harms

The guideline panel agreed that the advantages of treatment include achievement of morphological remission, and ultimately higher OS rates. The potential risks depend on the patient's clinical status, the blasts count in the bone marrow, and the response to prior therapy. The consideration of coexisting congenital anomalies, autoimmune diseases, or persistent gastrointestinal issues in children with DS is also crucial when selecting treatment with its range of side effects and evaluating its impact on outcomes.

FLA therapy is considered safe and widely used in children with r/r leukemias. However, FLA is an intense therapy with substantial adverse effects (mucositis, infections, and hematologic toxicity). At the same time, FLA often exhibits suboptimal therapeutic outcomes. In contrast, AZA ± panobinostat therapy seems well tolerated, and may achieve responses even in heavily pretreated patients. The panel is aware that large studies on epigenetic approaches to determine optimal dosing and efficacy are currently lacking. After treatment, patients typically present in a good clinical condition, an essential consideration in the context of subsequent HSCT. Therefore, the guideline panel suggests that this treatment modality be prioritized as the initial course of treatment for r/r ML-DS. If this regimen does not result in a response, subsequent use of FLA ± GO remains a viable alternative. In addition, in children with rapidly progressing disease, that is, with high blast percentage or rapid increase of blasts in the bone marrow, the use of epigenetic therapies might not be optimal, as response of AZA ± panobinostat might require prolonged exposure and multiple cycles.[49] These children should immediately receive FLA ± GO. The guideline panel favors the addition of GO to FLA over the addition of an anthracycline, considering the potential cardiac toxicity in children with DS.[33] Moreover, GO adds an immunotherapeutic approach to which children were not exposed during first-line therapy. A potential harm is introduced by the increased risk of veno-occlusive disease if busulfan-based conditioning regimen is used for HSCT.[52–54] The panel is aware that large studies on epigenetic approaches to determine optimal dosing are currently lacking.

3.1.3 | Rationale for this recommendation and conclusion

Attaining morphologic remission is essential for successful HSCT and survival in patients with r/r ML-DS. A specific treatment protocol for children with r/r ML-DS is currently not available. Conventional therapy for r/r ML-DS includes FLA with an anthracycline or GO (Figure 1). Based on available evidence, the panel concluded that children with r/r ML-DS who are in good clinical condition and have a low blast count in the bone marrow (less than 20%) should receive epigenetic therapy with AZA ± panobinostat as the first course of relapse therapy (Figure 2). In case blast percentage cannot be assessed due to a dry tap during bone marrow aspiration, a repeat aspiration, trephine biopsy, or additional examinations such as immunohistochemistry or flow cytometry can be performed. Clinical correlation is crucial. The number of peripheral blood blasts can be useful for monitoring disease progression and response to treatment. However, while the percentage of peripheral blood blasts sometimes correlates with the bone marrow blast percentage, discrepancies may also occur.

The panel is aware that evidence supporting this approach is limited by small datasets and short follow-up. The guideline panel noted the urgency for further investigations to refine risk stratification and guide patients toward the most appropriate therapeutic course (FLA ± GO vs. AZA ± panobinostat; Figures 1 and 2). The initiation of a global registry study for children with r/r ML-DS is necessary to establish a standardized therapy regimen and collect data on safety and efficacy of the treatment.

3.2 | Recommendation 2

The guideline panel recommends that only patients who achieve at least a morphological remission proceed to HSCT.

Comments:

- CR is defined by less than 5% blasts in the bone marrow (assessed by morphology), regenerating hematopoiesis, and absence of blasts in the cerebrospinal fluid.
- An optimized chemotherapy regimen is important to achieve CR.
- Securing morphologic remission is crucial, regardless of the selected treatment strategy.

3.2.1 | Specific background

Optimizing the chemotherapy regimen plays an important role in achieving remission, which is crucial for the success of subsequent HSCT. Regardless of the therapeutic approach chosen for remission induction, achieving a morphological remission is important. Patients who underwent transplantation without achieving remission had a survival rate of only 15%–20%.[19] In particular, in cases where the disease remains uncontrolled, the outcome is poor. None of the six patients survived who underwent HSCT without having first achieved remission. A recent review highlights the importance of achieving remission before HSCT, and shows that OS and EFS were 56% and 50% for patients who achieved remission prior to SCT compared to 10% for those who did not. The main cause of treatment failure after HSCT was a subsequent relapse (68%) and not TRM (10%).[27] In addition, post-transplant therapy strategies may need to be explored to improve leukemia control after HSCT.[18]

In addition to achievement of morphological remission prior to HSCT, a longer duration of first remission (longer than 6 months) was associated with improved 3-year OS. Early relapse was correlated with reduced probability of achieving a second remission with relapse chemotherapy. Patient sex, initial white blood cell count, and chromosomal abnormalities were not prognostic.[18,19]

3.2.2 | Benefits and harms

The guideline panel agrees that ensuring patients are in at least morphologic remission prior to HSCT is of significant benefit, leading to improved OS and EFS. At the same time the harm of HSCT without first achieving remission appears substantial, as evidenced by the high risk of disease relapse and TRM.

3.2.3 | Rationale for this recommendation and conclusion

The recommendation to only proceed to HSCT if a morphologic remission is achieved is based on compelling evidence demonstrating significant impact on survival and treatment success. The underlying goal is to reduce the risks associated with HSCT. Further research is needed to determine whether achieving a morphologic remission is sufficient or whether minimal residual disease (MRD)-negative remission further improves prognosis in r/r ML-DS.

3.3 | Recommendation 3

The guideline panel recommends that patients who achieve a morphological remission undergo HSCT as soon as possible.

Comment:

- According to the most recent literature, patients who achieve a morphological remission and then undergo HSCT have the highest probability of survival.

3.3.1 | Specific background

While HSCT is well established for non-DS AML, outcomes for patients with r/r ML-DS appear less satisfactory.[20,55] The OS after transplantation for r/r ML-DS (21%) is significantly lower than that for patients with non-DS AML (51%).[18] In addition, in a recent registry study, transplant-related mortality (24%) was higher compared to non-DS patients (15%).[18] The main reason for treatment failure after HSCT was not treatment-related toxicity, but post-transplant relapse (61%).[18]

A recent retrospective analysis of a cohort of 62 patients treated for r/r ML-DS between 2000 and 2021 underscored the shortcomings of chemotherapy alone as therapeutic intervention for r/r ML-DS, and revealed a significant benefit of HSCT. Overall, 45% (28/62) of patients achieved a second remission, resulting in a 3-year OS of 22% ± 5% and 3-year EFS of 21% ± 5%. Of the 33 patients who received chemotherapy only, 27 did not remain in remission and experienced disease progression within 4.1 months after diagnosis. Only three patients (9%) survived after receiving chemotherapy alone.[27] Conversely, patients who received HSCT had a markedly superior prognosis, with an OS of 56% and an EFS of 51%. These data support the efficacy of HSCT as a treatment strategy for appropriately selected subpopulations of patients with r/r ML-DS.

The advent of reduced intensity conditioning (RIC) transplantation has emerged as a promising therapeutic strategy for fragile patient subgroups, for example, elderly patients and those with pre-existing

comorbidities.[56] Preliminary findings indicate that this approach is yielding encouraging outcomes even in pediatric ML-DS cohorts. Muramatsu et al. reported a pronounced improvement in 3-year survival rates for patients undergoing RIC transplantation (80% OS), in stark contrast to the 10% they observed otherwise.[57] Given that subsequent relapse, and not TRM, is the predominant cause of treatment failure after HSCT, further study is required to determine the optimal preparative regimen for HSCT for r/r ML-DS.[18,57]

3.3.2 | Benefits and harms

The panel agreed that HSCT is beneficial for patients with r/r ML-DS assuring the best long-term prognosis. The health-related risks of HSCT, including TRM, vary among individuals and depend on the patient's clinical condition and therapeutic response to prior chemotherapy. Patient-specific factors such as comorbidities and achievement of a second remission therefore should be considered.

3.3.3 | Rationale for this recommendation and conclusion

The rationale in favor of considering HSCT for r/r ML-DS is based on the observed benefits of HSCT and the limitations of chemotherapy as a single treatment. The potential benefits and risks of HSCT should be carefully weighed for each patient with r/r ML-DS, including consideration of patient and family preferences. Further research including long-term studies are needed to determine the benefits and risks of an HSCT and determine the optimal HSCT procedure for patients with DS.

4 | SUMMARY OF RECOMMENDATIONS

Children with Down syndrome (DS) are at higher risk of developing myeloid leukemia (ML-DS).[2–4,58] While front-line therapy is associated with an excellent prognosis, outcomes for patients with relapsed and refractory (r/r) ML-DS are extremely poor, and there is no standardized treatment recommendation for these patients.[2,4,13,18,19,58] This guideline incorporates current literature and research findings, and serves as a guide for clinicians. Recommendations were made by a panel of experts from North America, Europe, as well as Japan, and categorized as strong ("*the guideline panel recommends…*") or conditional ("*the guideline panel suggests…*").[24]

4.1 | Recommendation 1

The guideline panel suggests that based on risk stratification of patients, the initial course of relapse treatment should consist of either epigenetic therapy with azacytidine (AZA) ± panobinostat or intensive chemotherapy with fludarabine and cytarabine (FLA) ± gemtuzumab ozogamicin (GO).

Comments:

- Treatment choice depends on a patient's blast percentage in the bone marrow, clinical condition and prior first-line therapy. The guideline panel suggests that
  - patients with fewer than 20% blasts in bone marrow at relapse receive AZA ± panobinostat.
  - patients with 20% or more blasts in the bone marrow receive FLA ± GO.
- Efficacy of AZA ± panobinostat requires prolonged exposure, and multiple cycles may be required before response is observed. Therefore, a minimum of two to three cycles is recommended before response to AZA ± panobinostat is assessed.

4.2 | Recommendation 2

The guideline panel recommends that only patients who achieve at least a morphological remission proceed to HSCT.

Comments:

- Complete remission (CR) is defined by less than 5% blasts in bone marrow (assessed by morphology), regenerating hematopoiesis, and absence of blasts in the cerebrospinal fluid.
- An optimized chemotherapy regimen is important to achieve CR.
- Achieving a second, at least morphologic, remission is crucial regardless of the selected strategy for remission induction.

4.3 | Recommendation 3

The guideline panel recommends that patients who achieve a morphological remission undergo HSCT as soon as possible.

Comment:

- According to the most recent literature, patients who achieve at least a morphological second remission and then undergo HSCT have the highest probability of survival.

5 | LIMITATIONS OF THE GUIDELINE

Currently, there is no established therapy for children with r/r ML-DS. Existing guidelines for relapsed myeloid leukemia do not address special considerations for patients with DS. For patients with r/r ML-DS, the number of reports, cohort size, and duration of follow-up are limited due to a low incidence of r/r ML-DS. The lack of consistent international studies and uniform standards also presents challenges for the review of evidence and the evaluation of safety and efficacy of treatment approaches. As a result, this guideline is limited to a low level of evidence due to the rarity of this condition, limited data, and lack of long-term studies.

6 | OUTLOOK AND PERSPECTIVE

If a patient does not respond to remission induction therapy with AZA ± panobinostat or FLA ± GO, additional treatment attempts with experimental agents may be considered. However, in the absence of sufficient data, such treatment attempts are considered to have a palliative intent.

6.1 | BCL-2 and BCL-XL inhibitors

Venetoclax is a small-molecule inhibitor (BCL-2 [B-cell lymphoma 2] inhibitor) used in adults with chronic lymphocytic leukemia (CLL) and AML.[59] Venetoclax was shown to be effective when used in combination with other agents (azacitidine or decitabine) or low-dose chemotherapy, and emerged as the standard of care for elderly or unfit patients with AML.[60] It also showed efficacy in patients with r/r AML.[61] In r/r ML-DS, only a limited number of patients are reported who received treatment with venetoclax. In a recent survey, none of the three patients treated achieved a remission.[27] Therefore, the use of venetoclax in this setting should be approached cautiously and primarily in a palliative setting. Further studies are essential to confirm efficacy and safety in the treatment of r/r ML-DS. Recent studies demonstrate that AML cells with erythroid or megakaryocytic differentiation, as seen in ML-DS, depend on the antiapoptotic protein B-cell lymphoma-extra large (BCL-XL), rather than BCL-2. The BCL-XL antagonist navitoclax showed efficacy against acute megakaryoblastic leukemia models in vitro and in vivo. These cells were resistant to pharmacological inhibition by venetoclax, but proved sensitive to navitoclax. In addition, the combination of navitoclax with low-dose cytarabine reduced leukemia burden in mice. Further studies in this area are needed.[62,63]

6.2 | New preclinical strategies

The genomic landscape of ML-DS is characterized by a combination of mutations in signaling pathway genes and epigenetic modifiers, while aberrant lysine-specific demethylase 1 (LSD1) and JAK-STAT activation have both been implicated in leukemogenesis.[64] This suggested that LSD1 and JAK-STAT inhibition would be a vital therapeutic strategy to target important steps in ML-DS leukemogenesis. Interestingly, preclinical studies demonstrated that the combination of LSD1 inhibitors with a JAK1/JAK2 inhibitor (ruxolitinib) resulted in synergistic growth inhibition in ML-DS cells. A combination of induced apoptosis and blocked cell cycle progression may provide an effective therapeutic strategy for patients with JAK mutations. In mouse models, this combination therapy resulted in a significant reduction of leukemic blasts in the bone marrow. However, efficacy was not linear with dosage, suggesting it might induce differentiation and growth arrest rather than direct cytotoxicity. Further clinical trials are needed to investigate the efficacy of a combination of LSD1 and JAK inhibitors as potential treatment of r/r ML-DS.[64]

7 | FUTURE DIRECTIONS

Due to the rarity of r/r ML-DS, improvement of survival outcomes requires the mobilization of an international clinical and mechanistic research initiative. Two objectives appear most urgent: (i) establishment of an international registry study for children with r/r ML-DS to apply a standardized treatment approach and collect data on its safety and efficiency; and (ii) support for laboratory-based research in r/r ML-DS to identify new targets, biomarkers, and drugs that are efficacious for this form of leukemic relapse that to date has proved largely resistant to available treatment.

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CONFLICT OF INTEREST STATEMENT

Jan-Henning Klusmann has advisory roles for Boehringer, Novartis, Roche, and Jazz Pharmaceuticals. Dirk Reinhardt has advisory roles for Celgene Corporation, Novartis, Bluebird Bio, Janssen, and receives research funding from CLS Behring and Roche.

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