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Prognosis and management of acute myeloid leukemia in patients with Down syndrome

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Abstract

Children with Down syndrome (DS) are at a substantially increased risk to develop acute myeloid leukemia (AML). This increase in incidence is tempered, however, by favorable overall survival rates of approximately 80%, whereas survival for non-DS children with similar leukemic subtypes is <35%. In this review, the clinical studies that have contributed to this overall high survival will be presented and their individual successes will be discussed. Important issues including intensity of treatment regimens, the role of bone marrow transplants and prognostic indicators will be reviewed. In particular, the roles of high- vs low- vs very low-dose cytarabine will be discussed, as well as potential therapeutic options in the future and the direction of the field over the next 5 years. In summary, children with DS and AML should be treated with a moderate-intensity cytarabine-based regimen with curative intent.

Keywords

acute myeloid leukemia; Down syndrome; GATA1; prognosis; treatment

Children with Down syndrome (DS), in which the underlying genetic abnormality is due to the presence of trisomy 21, are at a greatly increased risk for the development of a set of

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myeloid neoplasms known collectively as the myeloid leukemias of Down syndrome (ML-DS). Interestingly, this increase in incidence is countered by superior outcome rates: DS acute myeloid leukemia (AML) patients have overall survival (OS) rates that approach 80%, whereas OS in non-DS children with similar AML subtypes is only approximately 35% or less (in contrast, survival in non-DS AML as a whole has improved dramatically to approximately 75% [1,2]). In this review, an overview of the effective therapeutic strategies for the treatment of ML-DS, as well as the biological processes that contribute to the relatively excellent OS in this population, will be discussed.

Epidemiology & subtype distribution of ML-DS

In the USA, the incidence of DS is approximately 1 in every 1000 live births [3]. Despite this, DS patients account for approximately 14% of all pediatric AML cases, indicating that children with DS are at a substantially elevated risk for the development of AML [4]. In comparison to non-DS children who develop AML, ML-DS patients are significantly younger, with the vast majority presenting before 4 years of age [4–10]. Further differentiating DS from non-DS AML is the unusually high prevalence of the megakaryocytic (FAB M7) AML (AMKL) subtype. In fact, as many as 100% of ML-DS patients in some studies [9] were found to have AMKL, and it has been estimated that DS children are at a 500-fold greater risk [10] to develop AMKL than non-DS children [4–8]. Importantly, AML in the DS population is often considered to be a different entity than AML in non-DS patients. This is in part due to the high prevalence of AMKL, the unique biology of DS-AMKL, the presence of what is known as both transient myeloproliferative disorder, or more officially, transient abnormal myelopoiesis (TAM), in many DS infants and the high incidence of a myelodysplastic phase prior to the onset of AML, which will all be discussed below. As a result, DS-AML and its associated precursors are often referred collectively as ML-DS.

Importantly, the leukemic blasts from patients with ML-DS display unique features that allow them to be distinguished from those of other seemingly similar diseases such as non-DS AMKL. On a structural level, blasts from ML-DS patients may have features of both megakaryoblastic and erythroblastic lineages [11–13] and are largely indistinguishable from blasts from other diseases. Despite this, blasts from both TAM and ML-DS may be identified using a unique immunophenotype that was well described in the 2005 paper by Langebrake *et al.* [12]. Briefly, they found that blasts reliably could be characterized by $CD33^{+}/CD13^{+/-}/CD38^{+}/CD117^{+}/CD34^{+/-}/CD7^{+}/CD56^{+/-}/CD36^{+}/CD71^{+}/CD42b^{+}/CD4dim^{+}/TPO\text{-}R^{+}/EPO\text{-}R^{-}/IL\text{-}3\text{-}R\alpha^{+}/IL\text{-}6\text{-}R\alpha^{-}$, with CD34 expression being especially variable.

Biology of ML-DS

As mentioned above, ML-DS is largely considered to be a disease that is unique from non-DS AML. Importantly, ML-DS offers a unique disease model in which the biological underpinnings of leukemogenesis and favorable chemotherapy response are fairly well understood. While an in-depth discussion of these issues is beyond the scope of this study,

there are two important points worth noting (for those more interested in these topics, see other paper in this issue or the recent reviews by Xavier *et al*. [14] and Khan *et al*. [15]).

The first is that the process of leukemogenesis in ML-DS begins *in utero*, where the presence of trisomy 21 leads to aberrant hematopoiesis [16,17] and the subsequent acquisition of mutations in the *GATA1* transcription factor gene [18]. These first- and second-hits set the stage for the development of TAM, and with additional mutations, eventually ML-DS [19,20]. GATA1 functions as a master regulator of several hematopoietic pathways under normal conditions. However, in TAM and ML-DS, mutations result in the translation of a short-form protein (GATA1s) with altered transactivation potential that, in the context of fetal development and constitutional trisomy 21, contributes to both hyperproliferation of megakaryocytic precursors and the pathobiology of the disease [21–25].

The second main point is that the unique combination of trisomy 21 and mutation of the *GATA1* gene contribute to chemotherapy sensitivity. These two genetic alterations cooperate to increase the amount of active cytarabine (araC) metabolites present in ML-DS cells, thereby enhancing cytotoxicity [26–30]. Furthermore, DS-AMKL has a unique gene-expression profile compared to non-DS AMKL, including differential expression of genes like MYC and BST2 that further contribute to chemotherapy sensitivity and leukemogenesis [25,31,32]. Further review of this topic may be found in [33]. Unfortunately, chemotherapy sensitivity in these patients is not necessarily limited to the leukemic cells. Patients with DS have long been known to be at an increased risk for toxicity after treatment with chemotherapy. Additionally, DS children have a high incidence of congenital cardiac malformations, and are thus more sensitive to anthracycline-based chemotherapy [34–36]. Highlighting this risk were results from the Pediatric Oncology Group 9421 trial, in which all three DS patients who died of cardiomyopathy after receiving anthracyclines had a congenital heart defect [35].

History of outcomes in ML-DS

Historically, being a DS individual was considered an unfavorable prognostic indicator for an AML patient. This was thought to be due to the poorer tolerance of DS patients to chemotherapy, which has been well known for many years and is especially well characterized in the case of acute lymphoblastic leukemia in DS patients. As such, ML-DS patients were frequently treated using individualized chemotherapy regimens that were largely ineffective. However, in the late 1980s and early 1990s, ML-DS patients began to be regularly treated on protocols that were used for non-DS AML patients, and outcomes improved dramatically (Table 1).

The first major study to identify that ML-DS patients represented a group with excellent outcomes was the Pediatric Oncology Group 8498 study, originally published in 1992 [9]. The 12 DS patients (of 248 total) treated on this study had 3-year event-free survival (EFS) of 100%, compared to only 28% for the non-DS patients in the same study ($p = 0.003$). The ML-DS patients were significantly younger, with 83% of DS patients presenting at less than 2 years of age, compared to only 15% of non-DS patients. Furthermore, ML-DS patients

were more likely to have blasts with the AMKL phenotype. One of the proposed explanations for the improved survival in this study was the early incorporation of high-dose cytarabine (HiDAC, 3 g/m^2 q12 h × 4 or 6 doses) into consolidation and induction therapy [37]. This sentiment was echoed in a retrospective review of DS patients treated as part of the Berlin–Frankfurt–Münster (BFM) studies [6], published in 1996. In that study, the authors found that patients with longer survival were more likely to have been administered HiDAC. The authors concluded that intensive chemotherapy should be considered for ML-DS patients, and that these patients may be better served by being treated on protocols similar to those used in standard-risk non-DS AML patients. Similar conclusions were made in a study published in 1996 by the Nordic Society of Paediatric Haematology and Oncology (NOPHO) [38].

In 1998, the results from two Children's Cancer Group (CCG) studies, CCG-2861 and CCG-2891 were evaluated to determine the success of ML-DS patients on those trials [8]. Of particular interest, the authors compared survival after either intensively-timed (treatment given on days 0–3 and 10–13) or standard-timed induction therapy, which allowed more time for marrow recovery (treatment on days 0–3 and 14–17 if >5% blasts, otherwise after marrow recovery). Importantly, it was demonstrated that survival was much worse with the intensively-timed induction regimen, with a 32% treatment-related mortality in that group. This was in stark contrast to the standard-timed group, with only a 2% treatment-related mortality rate. Furthermore, after consolidation therapy with HiDAC, disease-free survival at 4 years among DS patients was 88%, compared to only 42% in the non-DS group. This study also investigated the role of bone marrow transplant (BMT) in first remission, although like the intensively-timed induction, it was found to be associated with unacceptable toxicity and was thus not recommended. Similar conclusions regarding toxicity of high-intensity regimens were drawn from the UK Medical Research Council AML 10 and AML 12 studies [39], in which 11% of DS patients died during induction. The authors speculated that the high cumulative anthracycline doses (which were not adjusted for DS patients) may have played an important role in the high treatment-related mortality seen in those studies.

The report detailing the outcomes of DS patients on the AML-BFM 93 and AML-BFM 98 studies, published in 2005, was largely in agreement with these findings [40]. For the AML-BFM 93 study, OS for treated patients was 70%, and OS (3 years) for the AML-BFM 98 study was 91%. The treatment protocols were similar in both studies, both including HiDAC during consolidation. It was proposed by the authors that one contributing factor to the difference in survival was the inclusion of explicit instructions to treat ML-DS patients like those without DS to ensure that protocol adherence was maintained, while emphasizing the prevention of severe toxicity. This was expected to be of help because at the time, physicians were still largely reluctant to treat DS patients with intensive-dose chemotherapy regimens. Similar results were found by analyzing the results of the NOPHO-AML88 and NOPHO-AML93 protocols [41]. As in the BFM studies, survival improved from the earlier to the later study, with EFS (median 8-year follow-up) being 47 and 85% on the NOPHO-AML88 and NOPHO-AML93 protocols, respectively. Both protocols utilized HiDAC in the intensification phase of the treatment plan. The main reason for improvement between the studies was suggested to be that the NOPHO-AML93 protocol called for allowing full bone

marrow recovery prior to the beginning of induction II. In this way, both the AML-BFM 98 and the NOPHO-AML93 reflected the findings of the CCG studies above, namely that DS patients require longer intervals between treatment cycles and that aggressively-timed treatment protocols likely contribute to poorer outcomes in this patient group.

The most recent study for which data are available is the COG-A2971 study, in which 132 patients with ML-DS were enrolled [42]. The goal of this study was to confirm the results from the CCG-2891 in a study directed specifically at describing the outcomes of ML-DS patients. The dose regimen used in COG-A2971 was similar to that in the standard-timing arm of CCG-2891 (same araC and anthracycline doses), but without etoposide or dexamethasone. Additionally, maintenance therapy was removed. Reflecting the results from the above CCG studies, the induction timing was such that marrow recovery was required before the initiation of the next cycle of chemotherapy, unless the marrow showed >30% blasts after day 14. Consolidation included the use of HiDAC. Outcomes in COG-A2971 were equivalent to CCG-2891, with 5-year OS and EFS rates of 84 and 79, and 79 and 77%, respectively.

Prognostic markers in ML-DS

In contrast to non-DS AML, which includes a heterogeneous group of leukemia subtypes and presenting characteristics, ML-DS is generally considered fairly homogenous. Still, there are some characteristics of ML-DS to which prognostic significance has been attributed. The first and likely the most important prognostic factor at presentation is age; ML-DS patients over 4 years of age have been shown to have significantly poorer outcomes [40,43]. Similar results were found in a recent study that identified age >3 to be associated with a worse prognosis [44]. In fact, it has been suggested that DS children older than 4 years develop an AML that is more similar to AML seen in non-DS patients as they have a lower prevalence of *GATA1* mutations [45]. In general, we consider DS patients with AML over 4 years of age to be a high-risk AML subgroup.

In ML-DS, the role of cytogenetic changes in determination of prognosis is less clear than in non-DS AML. Monosomy 7, a well-known indicator of poor prognosis in non-DS AML [46,47], has been shown to be a predictor of a relatively poor outcome in ML-DS as well [48,49]. However, a recent, larger study did not replicate this finding, instead suggesting that normal karyotype (only constitutional trisomy 21) was in fact an indicator of poorer prognosis [44]. Similarly, the impact of preceding TAM on prognosis of ML-DS is somewhat unclear. A report by Klusmann *et al.* published in 2008 found that antecedent TAM significantly improved EFS rates (91 vs 70%; 29 TAM, 142 *de novo* ML-DS; $p = 0.039$) [50]. In contrast, patients on COGA2971 with and without antecedent TAM had similar outcomes (57 TAM, 75 *de novo* ML-DS; $p = 0.814$) [42]. As such, it is difficult to assign any prognostic value to the role of antecedent TAM.

Despite the overall comparatively excellent outcomes seen in ML-DS patients, outcomes for those patients who suffer from either refractory or relapsed disease have been shown to be dismal. In the Pediatric Oncology Group 9421 and CCG-2891 trials, patients with relapsed ML-DS had OS rates of only 11%, while those who did not achieve remission had OS rates

of only 8% [51,52]. Slightly more favorable results were found in a Japanese study by Taga *et al.*, in which relapsed and refractory ML-DS patients had OS rates of approximately 26% [53]. As such, relapsed and refractory cases of ML-DS should be considered to be very high risk.

Role of transplant in ML-DS

Though BMTs are frequently utilized in the treatment of non-DS AML, the results in the DS population have been very discouraging. Early studies utilized BMT in ML-DS patients, often resulting in poor outcomes [8,54], and the largest series to specifically investigate its use in ML-DS by comparing with non-DS AML (that by Hitzler *et al.* [55]) echoed these findings. In their study, the authors report that 3-year OS rates after transplant in 21 ML-DS patients was only 19%. In addition to being unacceptably toxic (24% transplant-related mortality), BMT was largely ineffective, with 62% of patients experiencing relapses post-transplant. Of note, all but one patient in this study received myeloablative conditioning.

Contrasting findings were reported in a recent Japanese study by Muramatsu *et al.*, which investigated the use of a lower-intensity conditioning regimens preceding BMT for ML-DS [56]. In this patient cohort, the 3-year EFS rates were approximately 80%, which were significantly better than in the group that received a more standard conditioning regimen (EFS approximately 10%). However, five patients received transplants in first remission who conceivably were already cured by frontline chemotherapy, which would skew their favorable results. Importantly, a common cause of treatment failure after transplant was relapse, as opposed to treatment-related mortality (5/11 vs 2/11 patients, respectively). Therefore, if ways of more effectively reducing leukemic burden prior to transplant can be found, it is possible that this transplant regimen may be more applicable.

The role of low-dose araC in the treatment of ML-DS

The historically poor survival of ML-DS patients was first overcome by treating ML-DS patients using more aggressive treatment protocols that were similar to those for non-DS-AML patients. Unfortunately, individualized, conservative treatment for ML-DS patients continued for many years, often with poor results. However, in 1993 Kojima *et al.* reported that seven ML-DS patients were successfully treated with a protocol that used low-dose araC [57]. In their study, six patients received seven 1-week courses of araC 100 mg/m^2/day × 7 days, daunorubicin 25 mg/m^2/day on days 1 and 2 and etoposide 150 mg/m^2/day on days 3, 4 and 5. All six patients achieved a complete remission (CR) at the time of reporting. This study was subsequently expanded, and the results were reported in 2000 [58]. The authors reported excellent outcomes, with estimated 8-year EFS of 80% in 33 patients who all achieved a CR after 1 or 2 rounds of induction, and only 3 patients relapsed. Two of these patients died from their disease and one was successfully re-induced with HiDAC. Furthermore, the toxicity of this regimen was fairly well tolerated, with two patients dying from cardiac toxicity and one dying from infectious complications. Finally, similar results were obtained in a more recent study from the same group that looked at data from 72 patients treated using a protocol that substituted pirarubicin for daunorubicin to potentially reduce cardiac toxicity [7,49]. Using this protocol, consisting of five courses of

chemotherapy, the estimated 4-year EFS rate was 83%, with only one treatment-related death. Unfortunately, all nine patients who suffered a relapse, died, indicating that there were patients for whom this treatment strategy was insufficient. Similar results were found in AMKL patients with DS mosaicisim [59]. The favorable outcomes from these studies have led other groups to attempt treatments without HiDAC.

First proposed by Tchernia *et al.* in their 1995 paper was the long-term treatment with very low-dose araC [60]. The authors reported treating seven children with ML-DS of either megakaryoblastic or erythrocytic phenotype with araC 10 mg/m^2 twice a day subcutaneous injection for a 21-day induction phase. Following that, patients were treated with the same dose for 7–15 days every 4–6 weeks, for 24 months. In contrast to other treatment protocols, no severe adverse drug effects were noted, other than a short window of pancytopenia during induction. Interestingly, all seven patients experienced a CR; however four of these subsequently relapsed and succumbed to their disease. Of those patients who survived, none experienced a relapse so no conclusions can be drawn from this study about the potential for salvage/reinduction after relapse. As the authors noted, the important finding from this study was that some patients could be effectively treated with very low-dose araC with minimal toxicity. At the time, there were no reliable methods of determining who those patients with susceptible disease were, so the authors suggested that their regimen should be considered in patients in whom there may be contraindications to use high-dose chemotherapy, such as patients with significant congenital heart defects.

In their paper published in 2006, Al-Ahmari *et al.* reported comparable survivals between a very low-dose, long-term araC regimen and standard HiDAC regimens from contemporary protocols [5]. The low-dose regimen, used in 18 patients, consisted of araC 10 mg/m^2 twice-a-day subcutaneous injection for 7 days, with vincristine 1 mg/m^2 and retinylpalmitate 25,000 units/m^2/day. There were 16 patients in the standard-dose arm. This regimen was repeated every 2 weeks for 2 years. Using intent-to-treat analysis, 5-year EFS between the low- and high-dose regimens was not significantly different (67 and 75%, respectively) and neither was the OS (77 and 80%, respectively). In the very low-dose regimen, three patients did not achieve remission, with one patient being successfully reinduced with standard-dose araC. Comparatively, only one patient in the standard-dose arm had refractory disease, but they achieved a remission after treatment with more intensive therapy. Three patients relapsed from each group, all of whom eventually died, including one patient who died of pulmonary hypertension after achieving a second remission after undergoing an allogeneic BMT. Importantly, the rates of febrile neutropenia in patients treated at the home institution of the authors were lower in the low-dose regimen; however, the study was not powered to detect significant differences. These results suggested that significant dose reduction may be beneficial from a toxicity standpoint without compromising outcomes.

In contrast to that finding, a 2010 report found that treatment with very low-dose araC (20 patients) was significantly inferior to standard treatment (22 patients) [61]. Using a regimen based on the Tchernia *et al.* report above that consisted of araC alone, this group performed induction therapy using araC 10 mg/m^2 twice daily for 21 days, followed by 2 years of maintenance with a 5- to 10-day course each month. While 5-year OS rates were not significantly different in the two groups by intent-to-treat analysis (65 and 85% for low-dose

and standard-dose, respectively, p = 0.08), the EFS rate was significantly poorer in the low-dose group (45 vs 80%). Only 80% of the very low-dose araC-treated patients achieved a CR, and half of those who did eventually relapsed. The difference in outcome between this study and the one above (Al-Ahmari *et al.*) was attributed partially to the differences in regimen of the very low-dose treatment (araC alone vs araC with vincristine and retinylpalmitate, dose timing) as well as a potential lack of statistical power to identify differences in the first study, although OS in this study only trended toward being significantly different.

Expert commentary

Low-dose araC

One of the more looming questions regarding the treatment of ML-DS relates to the use of low-dose araC. However, making sense of the variable results reported for the effectiveness of low-dose araC treatment for ML-DS is somewhat difficult. The studies from Japan consistently report success with their lower dose therapies [7,49,57–59], while studies out of North American and Europe have been less consistent [5,60,61]. Possibly contributing to this disparity is a potential, as of yet uncharacterized, difference in biology between Japanese AML patients compared to Caucasian, Hispanic and African American patients, who comprise the vast majority of patients in North American and European studies. It has been shown that in Japanese patients, non-DS patients with AMKL have similar outcomes to those with DS-AMKL [62], whereas studies from both North America and Europe have consistently demonstrated that non-DS AMKL patients have very poor outcomes with EFS rates <35% [63–67]. Further complicating matters are the low number of patients in each study, and the different drug regimens used. Due to these inconsistencies, treatment for all ML-DS patients with low- or very-low-dose araC alone is inappropriate. However, there is a clear benefit in some patients, so in patients for whom more standard dosing of araC is contraindicated, there may be a role for low-dose araC.

Recommended treatment for ML-DS

In the pediatric DS population, AML is typically a very treatable disease with excellent survival rates, especially when compared with AML in children without DS. To achieve excellent treatment efficacy, it is important to not undertreat, as this is likely to result in unnecessarily high rates of relapse and places an undue burden on the patient. However, the heightened sensitivity to chemotherapy seen in DS patients must be kept in mind, as treatment-related mortality has historically been high in this patient group [8,35]. Further complicating matters is the lack of reliable prognostic markers to readily identify low-risk ML-DS patients who may be adequately treated by lower-intensity regimens.

For the majority of ML-DS patients, we recommend beginning treatment using a moderate-intensity regimen that utilizes minimal residual disease (MRD) analysis based on patient-specific markers to guide therapy. Induction should consist of three to four courses of moderate-intensity araC and anthracycline-based chemotherapy, preferably utilizing at least one more intense course of higher-dose araC. Importantly, cumulative anthracycline dose should be minimized to prevent toxicity. Consolidation therapy should be performed in

accordance with previous reports, and maintenance chemotherapy is unnecessary. It is important in this population to allow time for the marrow to recover after each course of chemotherapy, as more intensive timings have repeatedly been associated with unacceptable treatment-related mortality. BMT should only be utilized if absolutely necessary, and should not be administered in first remission. Most important, however, is that DS children with AML should be treated with curative intent, preferably using an established protocol. If there is a good reason that such treatments are contraindicated, (e.g., severe cardiac disease, patients are clinically unstable and not thought to be able to tolerate associated toxicities), very low-dose araC regimens may be considered, however, a high index of suspicion for relapse must be maintained.

In the event of relapse, therapy should continue with curative intent. Higher-intensity araC-based regimens should likely be used, ideally in combination with a novel agent to which the disease is naïve. Disease should be monitored using MRD, with MRD negativity being the proximal goal. If transplant is thought to be appropriate, a reduced-intensity conditioning regimen should at least be considered. Unfortunately, there are not enough data on the successful treatment of relapsed ML-DS to make any specific recommendations at this time.

Five-year view

Moving forward, questions about the treatment of ML-DS still remain unanswered. One of the most significant of these is how to identify patients with low-risk disease who could potentially be treated by less intensive therapy. Recently, the ability of MRD detection by either multi-parameter flow cytometry or PCR has been shown to be effective for stratification of treatment in pediatric AML [67]. If these techniques were able to be refined such that low-risk ML-DS patients could be identified, they could be placed on lower-intensity chemotherapy regimens without compromising efficacy. The results of the Children's Oncology Group Phase III trial 'The Treatment of Down Syndrome Children with Acute Myeloid Leukemia and Myelodysplastic Syndrome Under the Age of 4 Years', which performed MRD analysis, may answer these questions.

Most of the work that demonstrated the biological bases for chemotherapy sensitivity was in DS cases of AMKL with *GATA1* mutations, and was found to be due at least in part to the reduced transactivation potential of the GATA1s protein [29,30]. Another question that remains unanswered is why ML-DS patients without AMKL have such good outcomes. However, the proportion of ML-DS patients with the AMKL phenotype have varied among different studies and it is likely that AMKL may have been underdiagnosed. Recent advances in sequencing technologies and molecular diagnostics have allowed for higher sensitivity in detecting *GATA1* mutations, which is only associated with the AMKL phenotype. In their 2013 study, Roberts *et al.* were able to identify *GATA1* mutations in up to 20% of newborns, which was approximately double what had been seen previously [68]. As such, better characterization of a patient's disease may not only help with treatment stratification, but with identification of biological features that affect outcomes. Expanding upon this, by better characterizing the biology of ML-DS, much can be learned about leukemogenesis and chemotherapy response. Two studies in 2013 were able to use sequencing to track the evolution of transient myeloproliferative disorder to AMKL in

individual patients [19,20]. These results were encouraging because in addition to confirming previous hypotheses, they demonstrated that there is still much to be learned about the biology of cancer from this unique patient group, which has a clearly defined precursor or preleukemia condition. Furthermore, it is very likely that next-generation sequencing will continue to play ever-larger roles in the diagnosis and management of ML-DS in the coming years. As the cost-per-genome continues to decrease, it is possible that patient-specific mutation profiles will eventually be used to identify druggable mutations and disease-specific mutations that can be used to more sensitively detect residual disease, thereby guiding prognosis and treatment.

While better prognostication and treatment stratification will definitely be of use for future ML-DSL patients, if outcomes for those with relapsed and refractory disease are to be improved, it is likely that new therapies will be needed. Fortunately, two cell-cycle regulatory kinases, wee1 and aurora A kinase, have recently been identified as favorable targets for the treatment of ML-DS.

The wee1 kinase is responsible for the addition of inhibitory phosphorylation to CDK1 and CDK2 that allows for the activation of DNA damage checkpoints, and can be inhibited by the first-in-class wee1 inhibitor MK-1775 [69]. In a 2014 paper from this group, a potential role for MK-1775 in the treatment of ML-DS was identified [70]. It was shown that the addition of MK-1775 was able to synergistically enhance the cytotoxic effects of araC in ML-DS cell lines and *ex vivo* patient samples by abrogation of an intra-S-phase DNA damage checkpoint and enhancement of araC-induced DNA damage. As MK-1775 has been identified as an attractive option for the treatment of several malignancies, including AML [71–73], and is currently in several Phase I and II clinical trials (clinicaltrials.gov), it is expected to be of increasing importance in the coming years.

Aurora A kinase is primarily thought to be important for the regulation of the complicated processes required for successful mitosis (reviewed in [74]). Early-stage clinical studies of the Aurora A kinase-specific inhibitor MLN8237 have demonstrated promising efficacy in lymphomas and other solid tumors [75,76]. Importantly, Wen *et al.* demonstrated a specific role for this agent in the treatment of AMKL [77]. They were able to demonstrate that inhibition of aurora A kinase with MLN9237 was able to induce polyploidization and differentiation of non-DS AMKL cells and an ML-DS cell line.

With the movement into the ‘post-genomic era’, epigenetic mechanisms are being recognized as having great importance to cellular function. It has been recently shown that sequential changes in DNA methylation play an important role in the development of ML-DS [78]. Targeting histone deacetylases (HDACs) has been one of the most promising approaches to epigenetic-targeted therapy and a role for HDAC inhibitors in the treatment of ML-DS has recently been described [79]. In their work, Stankov *et al.* have demonstrated that treatment of ML-DS cells with HDAC inhibitors blocks autophagy, thereby contributing to cell death. These results are especially encouraging, as some HDAC inhibitors are already US FDA approved (e.g., vorinostat) and more are currently in late-stage clinical trials/under review by the FDA (e.g., panobinostat). Similarly, it has been shown that BRD4 inhibition with JQ1 can decrease MYC expression and decrease GATA1s-induced hyperproliferation

[80]. As more therapeutic options for targeting epigenetic processes emerge, they will likely present exciting new options for the treatment of ML-DS.

Although outcomes for ML-DS are generally favorable compared to those for patients without DS, there are still patients who are unable to be treated effectively. Improvement in the outcome for these patients will likely be the result of a combination of better treatment stratification, improved supportive care measures and new therapeutic options. The advances in the treatment of patients with ML-DS in the last two decades have been encouraging, but there is still much work to be performed to continue to improve survival rates for these patients.

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Key issues

- Children with Down syndrome (DS) are at substantially increased risk to develop acute myeloid leukemia, especially of the megakaryocytic subtype.
- Myeloid leukemias of Down syndrome (ML-DS) is a unique disease that has relatively excellent survival rates.
- Historic treatment failures were largely the result of undertreatment.
- As more ML-DS patients were treated on protocol, survival increased.
- Survival rates after relapse or in the context of refractory disease are dismal, even after bone marrow transplant.
- The efficacy of low-dose amount of active cytarabine is unclear; however, low-dose protocols may be useful in those for whom higher-dose therapy is contraindicated.
- Children with ML-DS should be treated on moderate-intensity protocols, preferably designed for ML-DS patients, with curative intent.

Table 1

Outcomes of ML-DS patients.

Study (year)	Numbers	Complete remission %	Overall survival %	Event-free survival %	Years	High- or low-dose amount of active cytarabine	Ref.
POG 8498	12	100	100	100	3	High	[9]
CCG 2861/CCG 2891	110	88	88 (DFS)	68	4	High	[8]
AML 10/AML 12	46	89	74	74	5	High	[39]
NOPHO-84/NOPHO-88	23	74	79 (DFS)	–	≥6	High	[38]
AML-BFM 93	44	82	79 (DFS)	68	3	High	[40]
AML-BFM 98	66	100	98 (DFS)	89	–	High	[40]
COG-A2971	132	84	84	79	5	High	[42]
Kojima *et al.* (1993)	9	89	78	78	≥5 mo	Low	[57]
Kojima *et al.* (2000)	33	100	–	80	8	Low	[58]
Kudo *et al.* (2007)	72	97	84	83	4	Low	[49]
Tchernia *et al.* (1996)	7	100	43	–	≥5	Very low	[60]
Al-Ahmari *et al.* (2006)	18	83	77	67	5	Very low	[5]
Tandonnet *et al.* (2010)	20	80	65	45	5	Very low	[61]

DFS: Disease-free survival.