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Acute Leukemia in Down Syndrome Children, A Morroccan Retrospective Review

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Abstract

Children with Down syndrome (DS) are at higher risk of developing acute leukemia and has been recognized to have unique clinical features and significant differences in treatment response and toxicity profiles compared to patients without Down syndrome. One of the challenges faced in treating children with Down syndrome and leukemia is balancing curative therapy against potential toxicities.

A retrospective review of the clinical features, treatment outcomes of DS children with acute leukemia was conducted in the Center for Pediatric Hematology and Oncology in rabat child hospital.(CHOP) from 2006 to 2016. This review included a total of 30 patients with DS. Ten were diagnosed with acute lymphoblastic leukemia and 20 had acute myeloid leukemia (AML). This study points out that investigators will have to carefully assess the balance between the antileukemic efficacy and treatment-related mortality of current chemotherapy regimens. Several studies are currently in progress that will answer some of the many questions raised in this field .

Keywords: Leukemia; Down syndrome; Chemotherapy; Toxicity

Introduction

Down syndrome (DS) is the commonest type of trisomy in live born infants, characterized by dysmorphic features and congenital abnormalities, such as heartdefects and cognitive impairment. It occurs in approximately 1 in 691 live births Patients with DS have a unique pattern of malignancy predisposition, with a higher incidence of developing leukemia than solid tumors Compared with the general population [1]. Children with DS are estimated to have 10 to 20 folds increased risk of developing leukemia, particularly acute myeloid leukemia (AML) Children with DS account for 8% to 14% of all pediatric AML cases, with up to 500- folds increased risk of developing acute megakaryoblastic leukemia compared with the general population [2]. Transient myeloproliferative disease (TMD), characterized by spontaneous regression of abnormal blasts, occurs in approximately 10% of neonates with DS. As for acute lymphoblastic leukemia (ALL), children with DS exhibit specific patterns ofimmunophenotype and cytogenetics, and they account for about 3% of all childhood ALL. Treatment of acute leukemia in children with DS is particularly challenging due to their high susceptibility to treatment-related toxicities Reducing treatment intensity seems to be beneficial for patients with DS. This study reviews the current knowledge and research questions regarding DS-associated acute leukemias.

Patients and Methods

We conducted a retrospective review on acute leukemia(ALL and AML) in children with DS in Rabat from 2006 to 2016. 30 Patients with DS were identified from the leukemia registry of the Center for Pediatric Hematology and Oncology in rabat child hospital (CHOP).

The center coordinates treatment protocols for all pediatric oncology patients below 18 years of age. Data on demographic, clinical features, important prognostic factors, treatment complications, and outcomes were collected retrospectively and additional information was supplemented from review of medical records using a uniform study sheet. The inclusion criteria were:

- DS phenotype and clinical feature of constitutional trisomy 21.
- Acute leukemia (lymphoblastic and myeloblastic), diagnosed on Bone morrow aspiration with cytochemistry and immunophenotyping (the karyotype was mostly Is performed in patients with acute myeloblastic leukemia).

The mean follow-up duration of this cohort of patients was 2.3 years .Children with ALL were treated according to MARALL 2006 protocol (Figure1) And were given the standard risk treatment with lower dosage of most of the chemotherapy drugs espicially methotrexate during the consolidation phase by 25 to 30% Children with AML were treated according to the AML-MA 2011 protocol except for one patient who received the AML-MAROC 2006 protocol (Figures 2 and 3). They all had dose reduction of all chemotherapy agents by 25% to 50% ,

2 patients received only Ara-C during induction 1.

Results

Patient characteristics: All patients were born in morrocco and majority were from urban areas (27/30, 81%). For the remaining 3 Patients , they were all from the rural areas of the north of the country (ouazzane , tetouan and chefchaouen) three patients had parents cosanguinity ,and only 4 patients had health insurance the rest benefited from the Medical Insurance Plan for the Financially Underprivileged (RAMED) that allowed them to access to the same care facilities .

Treatment and treatment related complications: Treatment modification was documented in 18 patients who were treated according to the AML-Ma 2011 protocol. All of them suffered significant treatment-related toxicities after the initial induction courses, during

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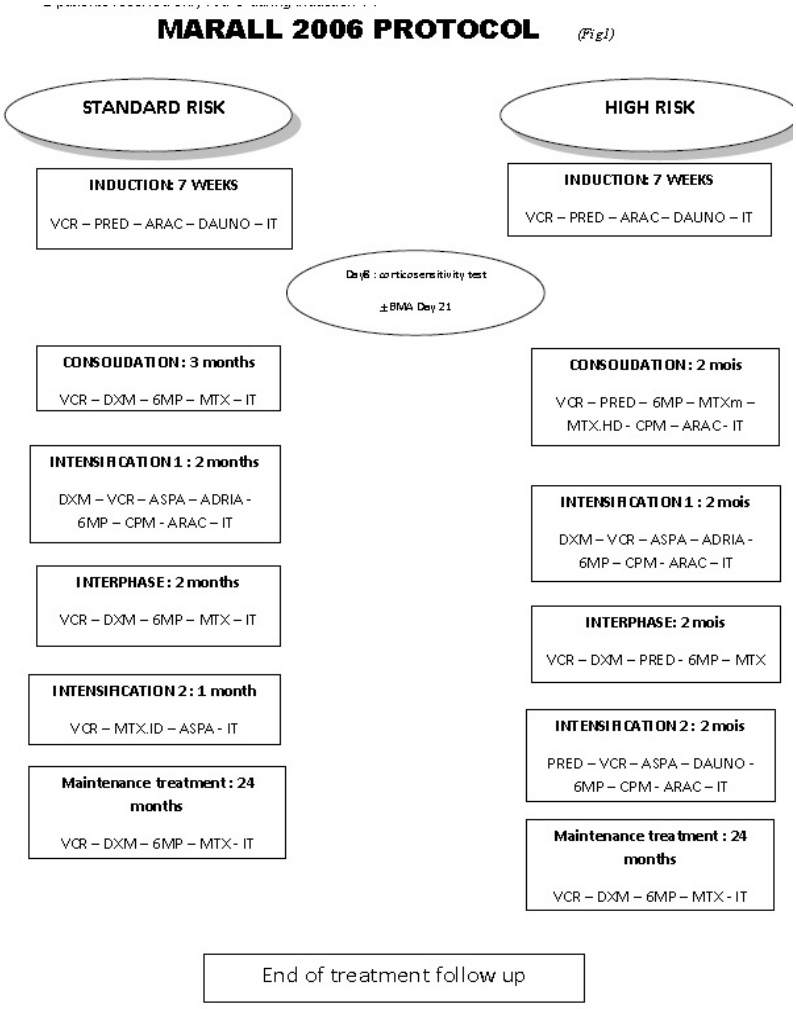

Figure 1: Children with ALL were treated according to MARALL 2006 protocol.

induction 1, 5 patients received only Ara-c and 3 others didn't receive daunomycin, all had 50% dose reduction and subsequently switched to less intensive consolidation treatment. For ALL, all patients had good response to the prednisolone prephase. 9 patients achieved morphologic remission after induction or consolidation and none received hematopoietic stem cell transplant. The most common treatment-related toxicity was severe mucositis (62.5% for ALL and 55% for AML), which responded positively with supportive management. One patient with ALL had severe chemotherapy-induced vomiting and was complicated by reflux oesophagitis and haematemesis which required extended omeprazole and ranitine treatment. Culture proven bacterial or fungal infections were common, being documented in 60% of ALL and 50% of AML patients.

One child with ALL developed hepatitis and jaundice during delayed intensification chemotherapy. The remaining delayed intensification chemotherapy was withheld and intrathecal chemotherapy was omitted subsequently in the maintenance phase. This patient did not have permanent liver damage on follow-up. Two patients with AML developed cellulitis of the hand and of the face for the second patient resulting in compartment syndrome requiring abscess drainage with extended parenteral antibiotic (flucloxacilline)One child with AML and underlying Tetralogy of Fallot experienced Acute lung oedema and pericardial effusion during induction chemotherapy. This patient eventually succumbed as a result of Cardiogenic shock and heart failure. Febrile neutropenia (FN) was common in all AML patients (100%) compared to ALL group (50%) and was defined as an axillary temperature measured as >38°C for once or as >37.5°C for at least one hour in patients who had an absolute neutrophil count (ANC) of <500/mm or who had an ANC between 500 and 1 000/mm3 and whose ANC was expected to decrease below 500/mm^3 in 24-48 hours. 12 of the FN episodes were fever of unknown origin, 30% were microbiologically documented infection. Of the microbiologically documented infections, 40% of them were caused by gram positive bacteria and 60% were by gram negative bacteria. Eight of 25 patients developed invasive fungal infection during treatmen t. FN was the cause of death in 1 patient. Types of antibiotics and Sites of infection are presented in (Tables 1 and 2). There were 10 patients with ALL and 20 with AML.The median age at diagnosis for the latter group was significantly younger (1.7 vs. 7.3 y, P=0.001). Transient myeloproliferative disease (TMD), was documented in one case of AML but none of the ALL patients. Congenital heart disease, the most common malformation associated with DS, was found more commonly in AML than ALL patients (78.9%

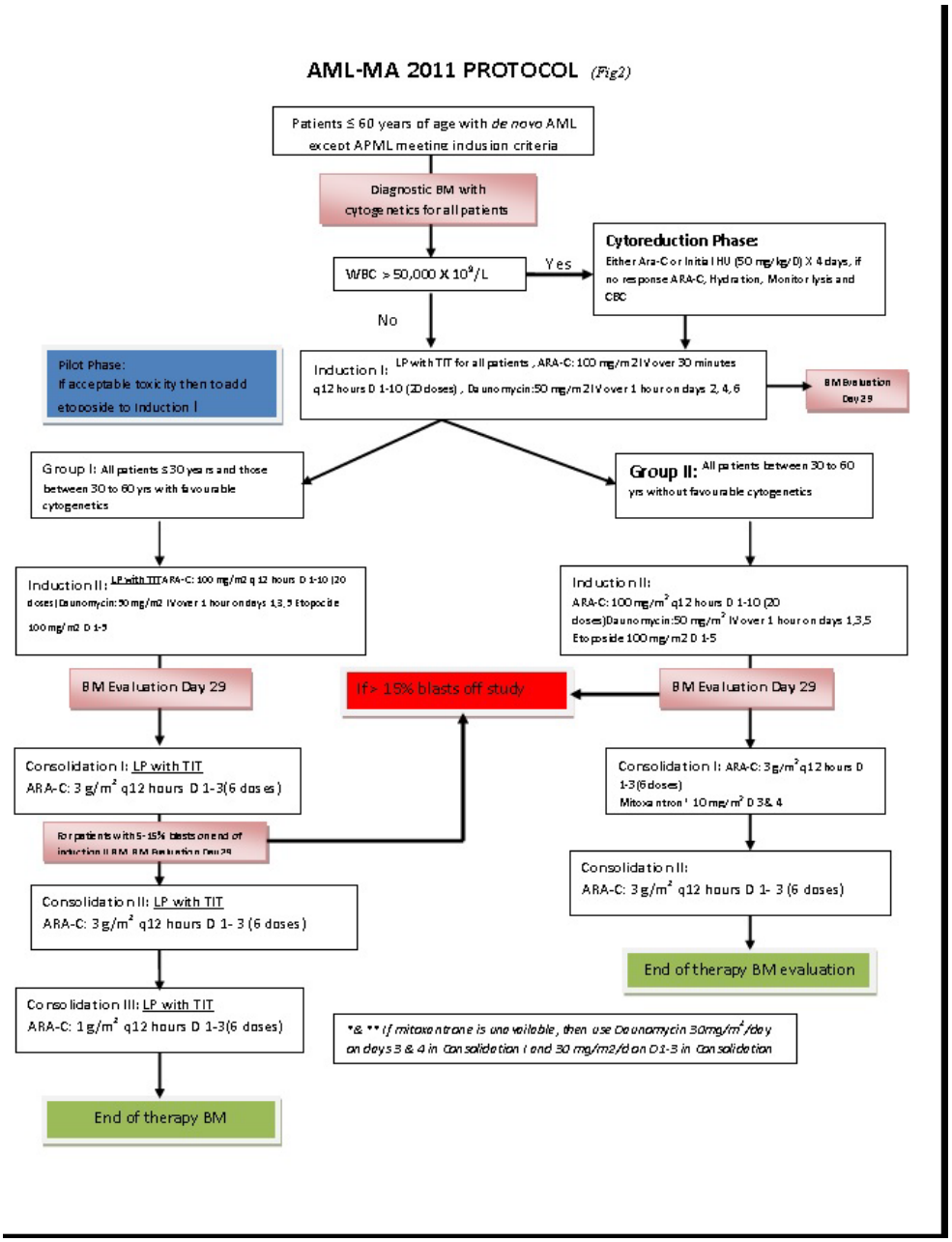

Figure 2: Children with AML were treated according to the AML-MA 2011 protocol.

Antibiotics	N	(%)
Ceftriaxone + Gentamycine	10	40
Ceftazidime + Amikacine	8	32
Metronidazole	3	12
Fluconazole	5	20
Vancomycine	6	24
Other	1	4

Table 1: Types of antibiotics used.

Site	N	(%)
Oral cavity infection	14	56
Respiratory tract infection	9	36
Blood stream infection	5	20
Urinary tract infection	2	8
Skin and soft tissue infection	1	4
Gastrointestinal tract infection	3	12

Table 2: Site of infection.

vs. 33.3%, P=0.026). The following cardiac defects were documented: atrial septal defect (n=12), patent ductus arteriosus (n=10), ventricular septal defect (n=3), atrioventricular canal defect (n=3), Tetralogy of Fallot (n=2), and complex cyanotic heart disease (n=1). Only 2 patients had congenital hypothyroidism . The common presenting features were anemia (51.7%), fever (48.3%), hepatosplenomegaly (41.4%), and bleeding symptoms (37.9%). One child with AML had pericardial effusion and high WBC of 100 000/mm^3 at diagnosis. None of the

Clinical and biological features n (%)			
	DS-ALL (N=10)	DS-AML (N= 20)	Total
Age (y)			
<1	0	1	1
1-3	1 (10)	17 (89.4)	18
4-9	6 (60)	1 (5.2)	7
>10	3 (30)	0	3
Median (range)	7.31 (3.12-15.98)	1.74 (0.61-4.08)	
Sex			
Male	5 (50)	12(60)	17
Female	5 (50)	8(40)	13
Presenting WBC			
<10	6 (60)	13 (65)	19
10-49	4 (40)	6(30)	10
50-99	0	1 (5)	1
>100	0	1 (5)	1
Congenital heart disease			
Yes	3 (33.3)	15 (75)	18
No	6 (66.6)	4 (20)	10
Unknown	1	0	1
Treatment protocol			
Treatment protocol			
MARALL 2006	10 (100)		10
AML-Ma 2011		9(95)	9
Other		1(5)	1
Toxicity			
Septicemia			
Yes	5 (62.5)	8 (40)	13
No	3 (37.5)	7 (35)	10
Unknown	2	5	7
Severe mucositis			
Yes	5 (62.5)	11 (55)	16
No	3 (37.5)	5(25)	8
Unknown	2	4	6
Febrile neutropenia			
Yes	5 (50)	20 (100)	25
No	4 (40)		4
Unknown	1		1
Transfusion			
Yes	5 (62.5)	15 (75)	20
No	3 (37.5)	3 (15)	6
Unknown	2	2	4
Treatment dose modification			
Yes	10 (100)	18 (90)	28
No			
Unknown		2	2

Figure 3: Microbiologically documented infections.

patients had central nervous system involvement at diagnosis. All patients with DS-ALL had B precursor ALL. Five of the 10 patients had additional cytogenetic abnormalities apart from constitutional trisomy 21. None had hyperdiploidy of >50 chromosomes. There was 2 patients with t(8 ;21), t(15 ;17),16q22 fusion and another one had 11q23 fusion. Among the 20 patients with AML, all had bone marrow aspiration classified as myeloid leukemia 10 were classified as FAB M7 subtype , 5 as FAB M6 , 2 patients had M0 (minimallydifferentiated) subtype.

For the 3 remaining the AML pathology could not be further classified.

Ten of the 19 patients had additional cytogenetic abnormalities, including monosomy 7, 5q deletions, and 7q deletions that are more commonly associated with myelodysplastic syndrome.

Outcome: Among the 30 cases we had there were 2 deaths in the ALL group (20%), The first patient had severe neutropenia and septicemia and died of multiorgan failure during intensification chemotherapy. The second patient died from disease relapse after he developed pulmonary tuberculosis during paliative chemotherapy (Table 3).

There were 4 deaths in the AML group (20%) The first was a one-year-old infant admitted with Generalized oedematous syndrome and digestive hemorrhage associated to a severe respiratory distress. He succumbed on the first day of hospitalization.

The second patient died from salmonella septicemia and septic shock during the third day of induction chemotherapy. The other patient was a 2 year-old child with Tetralogy of Fallot and succumbed from Cardiogenic shock and heart failure during induction 1.

The exact cause of death for the last patient was unknown due to incomplete data. There were no relapses among the AML patients. None of the 30 patients developed secondary malignancies.

Study group	Death	Complete remission	Relapse	Abondan of treatment	Lost of sight
AML	4	12	1	1	2
ALL	2	6	2	0	1
Total	6	18	3	1	3

Table 3: Outcomes of study groups.

For patients with DS-ALL the 5-year survival was 40% and respectively 60% for DS-AML Group

Discussion

This review paper covered a 10-year period and included a total of 30 patients with acute leukemia and DS and was mainly representative of the whole north area of Morocco. All of our patients were morrocan and from Arab ethnicity, and our findings would allow comparison with other cohorts to examine for the impact of ethnicity on disease outcome. The health care opportunities in morocco varies from regions to regions and Are mostly centralized in the main cities of the kingdom. Many women would not have had any antenatal care before their late presentation for obstetric care in Rabat or other hospital structure in the area with high-level maternity, this could explain the increased incidence of DS births and led to a proportionate increase in children with DS and acute leukemia.

Majority of our DS-ALL patients belonged to the standard risk group according to age and WBC count at diagnosis. Higher median age at diagnosis of 7.3 years compared with that of 5.6 years for the HKALL 97 cohort [3]. The presenting WBC were all below 50*106/mm^3. None of them had high-risk chromosomal translocations such as t(9;22) or t(4;11), and none had central nervous system involvement.

They were given a 4-drug induction therapy with prednisone , vincristine, Ara-c and Daunomycin and as well as intrathecal methotrexate. Following remission induction, therapy continues with a consolidation phase, an intensification phase, and maintenance. Chemotherapeutics during these phases may include cyclophosphamide, Ara-C, doxorubicin, mercaptopurine, vincristine, methotrexate and continued intrathecal chemotherapy .All patients achieved first remission after induction chemotherapy. Patients who eventually relapsed were all treated according to intermediate risk protocols. It has been documented that patients with DS-ALL has high risk of relapse and treatment-related mortality throughout the treatment period independent of the chemotherapy regime [4]. They are also at higher risk for infection-related mortality throughout all treatment phases [5]. Patients with DS–ALL tend to have poorer outcomes than those with No DS–ALL .One reason for previous treatment failures in children with DS–ALL is that these patients tend to develop toxic reactions to therapies In particular, a severe toxicity to methotrexate has been noted [6]. Methotrexate pharmacokinetics were analyzed retrospectively in children with ALL, comparing 44 with Down syndrome and 87 without the syndrome. Using non-linear mixed effect modeling, no differences in methotrexate pharmacokinetics were found between patients with and without Down syndrome which could explain the significantly higher proportion of children with Down syndrome who experienced methotrexate-induced toxicity.

The authors concluded that the higher toxicities suffered by Down syndrome patients are probably related to pharmacodynamic differences and that intermediate doses of methotrexate (such as 1-3 g/m^2) can be used safely in Down syndrome children with ALL [7].

The increased in vitro sensitivity to chemotherapy observed in Down syndrome patients does not seem extend to those with ALL. Down syndrome lymphoblasts do not demonstrate greater sensitivity than non-Down syndrome cell lines to various chemotherapy agents. This biological characteristic can potentially account for the inferior outcome to therapy described in Down syndrome children with ALL in comparison to the outcome in non-Down syndrome children.

However, no significant differences in cytotoxicity to chemotherapy were found between fibroblasts from patients with or without Down syndrome. Other factors may account for the variation in chemotherapy response and toxicity and the molecular bases that contribute to these differences are not completely understood [8].

Indeed, our DS-ALL patients had poorer outcome than the DS-AML group. Another observation was that a substantial proportion of our patients had dose reduction from the standard ALL protocol, and disease relapse accounted for 1 of the 2 deaths in DS-ALL. However, we could not demonstrate any association between treatment reduction and relapse in our group .DS children with ML have a superior outcome when compared with children without DS who develop AML. Although all 12 DS children with AML enrolled on the original study POG 8498 achieved complete remission and were long survivors, subsequent publications, while noting the continuing evidence for the high curability (75% event-free survival [EFS] for DS-AML) [9].

In our review, the mean age of our patients with DS-AML were younger at presentation as compared with DS-ALL patients (1.74 vs.7.31 y). Distribution of morphological subtypes in AML-DS patients showed a predominance of AMKL-FAB M7 subtype (50%). The outcomes for childhood AML in our study is comparable with results from other study groups. The UK AML trials reported an overall 5-year OS as 65% in non-DS versus 76% in DS children [10]. The BFM group reported 7-year EFS and OS as 78% and 79%, respectively, for ML DS patients for the DS children on NOPHO-AML 93 protocol [11].

All of our patients had chemotherapy reduction using the AML-MA 2011 PROTOCOL , complications related to chemotherapy toxicity were frequent resulting in an increase in treatment-related mortality. We lower treatment intensity compared with the standard AML protocols. During induction 1 course the DS children didn't receive anthracyclines due to The increased risk of anthracycline-induced cardiac toxicity is potentially , although one patient died from congestive heart failure during day 2 of induction . At the time of analysis, all the patients who were treated on this protocol were able to adhere to the regimen without major complications.

On the short term efficacy appeared promising as 12 patients were able to achieve full remission, although long-term outcome is still uncertain. Treatment reduction for DS-AML appeared to have no adverse impact on disease outcome. This suggested that the reduction of treatment intensity was probably beneficial to DS-AML but not DS-ALL patients. The potential for reduced treatment intensity is based on the unique hypersensitivity of myeloid leukemia cells of DS patients to chemotherapy, when compared with AML cells from non-DS individuals, as demonstrated by various investigators [12]. This increased sensitivity to chemotherapy extends to agents with different mechanisms of action. Zwaan and colleagues have reported that myeloid blasts were significantly more sensitive to cytarabine, anthracyclines mitoxantrone, etoposide 6-thioguanine busulfan and vincristine than non-DS AML cells [13].

The major limitation for our study was the small sample size. There was also Poor adherence. To treatment protocols from some patients. Continued improvement of supportive care for these patients may

also be a confounder on the incidence of treatment-related mortality. In contrast, long-term follow-up of these patients would allow better understanding of the late effects of disease and treatment in DS with leukemia. Due to its small sample size. Whether dose reduction of chemotherapy to reduce treatment-related mortality increases relapse remains unknown. The superior outcome in DS became obvious only after the inclusion of high-dose cytarabine in the treatment of childhood AML. Thus, the prevailing opinion is that two or more courses of high-dose cytarabine post–remission induction may be necessary for optimal therapy. However, the 100% EFS reportedby the POG investigators, based on the POG 8498 AML regimen, has not been duplicated in subsequent studies by POG or by other groups [14-15]. Plus the final four courses of conventional dose Ara-C, and sought to intensify the postinduction courses. At the same time, recognition of the unique responsiveness of AML in children with DS lead both to greater enrollment of DS cases on therapeutic studies and the recognition of risk for toxicity and the potential for mortality from infections. Gamis et al. [16] observed no increase in mortality rate in children with DS, but did observe high pulmonary toxicity during induction, including the need for ventilatory support and an increased incidence of mucositis and skin toxicity (perhaps from Ara-C). In our series the deaths occurred in an early phase and cannot be attributed to toxicity of chemotherapy but rather to a late arrival to the service for management.

Conclusion

The prognosis for DS-AML patients was superior to ALL-DS patients. Given the enhanced sensitivity of myeloid leukemic cells in these patients, dose-reductions in ML regimens for DS patients are easier accepted than for ALL regimens. The main side effects include mucositis, and an increased susceptibility to infections wich is mainly associated with high-dose methotrexate (MTX). An important aspect in treating children with DS is whether they have an increased risk of long-term cardiotoxicity following anthracycline exposure, given the fact that a significant proportion of DS children may have a compromised cardiac function because of congenital abnormalities to begin with.

In this study, there was no increased cardiotoxicity in DS children, but these children were treated with reduced dosages of anthracyclines. Finally, as there is still uncertainty in the optimal chemotherapeutic drug dosing for the entire pediatric DS population, new treatment methodologies will be especially crucial to help increase the remission rate for these children. Creating new risk group classifications based on patient cytogenetics may be one way to develop more specific chemotherapeutic drug dosing schedules for particular patient groups. Furthermore, focusing on integration of targeted non-cytotoxic agents, such as monoclonal antibodies may provide a better non-toxic treatment method for all Patients.

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