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Treatment related myeloid malignancies in childhood

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Abstract

Incidence of treatment related AML/MDS (t-AML/MDS) in children is extremely low. Consequently assessment of data from adults and to some extent extrapolation from adults is needed. Epipodophyllotoxin induced t-AML/MDS is more common, which is likely to be related to the shorter latency period, FAB-M4, FAB-M5, APL, balanced karyotypes, 11q23 and 21q22 anomalies, inv(16) and t(15;17) are noted more often. Duration and short interval between administrations of epipodophyllotoxins results in higher incidence of t-AML/MDS. Genetic (karyotypic) make up influence duration of remission, although the relation with overall-survival is less clear. Choice of therapy should be based on co-morbidity and the likelihood to undergo intensive therapy. The majority of children with t-AML/MDS should have a transplantation. A minority of children with t-AML with inv(16), t(8;21) and t(15;19) should be considered for chemotherapy according to de-novo protocols. Monitoring of early response criteria for detection of primary resistance is advised.

Keywords: Leukemia, aml, children, secondary, alkylating agents, epipodophyllotoxins, etoposide

Introduction

Myeloid malignancies represent a number of clonal hematopoietic disorders with extensive production of non-differentiating myeloid precursors cells. Due to infiltration in the bone marrow limiting production of normal cells, anemia, thrombocytopenia and neutropenia are often the first signs of the disease. Myeloid malignancies are mostly denominated as leukemias and myelodysplasia (MDS) and are delineated by the percentage and characteristics of the malignant cells and are classified in the same WHO category. Most patients with myeloid malignancies have no preceding disease. For those patients with a preceding disease, which is related to the development of a myeloid malignancy, a separate entity exists and is defined as "Acute myeloid leukemia and myelodysplastic syndromes, therapy related". A subclassification was based on major related inducing factors; i.e.,1. Alkylating agent/radiation–related type, 2. Topoisomerase II inhibitor–related type; 3. Others [1]. This remaining subclassification; i.e., "others", includes cases related to e.g., fludarabine, chlorambucil and radiotherapy/radioactive isotopes [2-6]. An additional cause of t-AML is immune suppression; e.g., due to azathioprine [7]. Since most patients had combinations of inducing agents this WHO subclassification is currently not seen as relevant [8]. Generally both therapy-related AML of secondary-AML terms are used.

Review

Incidence

Incidence of acute myeloid leukemia in children is low. Based on SEER data an incidence rate of 0.7 cases of AML per 100,000 children in the age group <20 years is noted. No epidemiological data exist on the incidence of t-AML/MDS. St. Jude's Hospital reports on 36 (1%) out of 3,696 children over a 12 year period [9]. Literature data indicate that around 6 to 13% of AML cases, irrespective of age, can be designated as t-AML/MDS [10,11]. In a study on 642 children who had suffered from ALL and who developed a secondary malignancy t-AML/MDS was seen in 255 children; i.e., AML in 186, MDS in 69 children [12]. After a prolonged follow-up after being cured of their primary malignancy, an increment in incidence in secondary malignancies is noted, with a total ratio of observed versus expected cases of 6603 for MDS and 226 for AML [13]. In a follow-up study on 14359 5-year survivors of childhood cancer 1402 patients developed 2703 neoplasms, among them 24 t-AML and 11 undefined non-ALL leukemia, resulting in a standardized increased risk (SIR) of 9.3 for all treatment related malignancies and specific for t-AML/MDS a SIR of 6.0 [14]. In a long follow-up study on 1378 patients surviving pediatric cancer, the standardized mortality rates (SMR) from secondary cancers tend to decrease from 38.1 to 6.19, after follow-up from the first decade to >25 years follow-up after initial diagnosis, respectively. A similar reduction was seen calculating the absolute excess risk (AER; decrease from 1.75 to 1.05 per 1,000 patient years). Only 16% were t-AML/MDS. Explanatory for the lowering of AER and SMR is the increase due to other cancers at older age in the normal population. A factor influencing the observed decrease in incidence rate in more recently treated children is

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the striving to reduce the alkylator dose as well as the trend to irradiate less often, reducing irradiation dosages and limiting irradiation fields [15-17].

Diagnosis

Clinical symptoms and physical findings of t-AML/MDS are to some extent similar to de-novo AML/MDS. Signs of leukemia are more often linked to hyperleukocytosis and cytopenias of normal cells, whereas MDS results in most cases in cytopenias; leading to tiredness, infections and bruises. The primary diagnosis is based on morphology and histochemical staining. Subtyping is done similar to de-novo AML/MDS and based on the FAB-classification. Epiphyllotoxins and anthracyclines/ mitoxantrone related secondary myeloid malignancies are mainly FAB-M4 (among them M4eo~inv (16)), M5 and acute promyelocytic leukemia (APL–FAB- M3~t(15;17)) presenting as acute onset disease. Alkylating agent related t-AML/MDS more often present as FAB-M6 and -M7 subtypes. Secondary myeloid malignancies related to alkylating agents have (in contrast to epipodophyllotoxins related mali-gnancies) a more protracted course presenting initially in many cases as MDS [15]. It was shown that the dominant clone in t-AML as seen after preceding t-MDS is derived by further evolution from the MDS clone [18]. In adults there is a relation on incidence with type of alkylating agent and occurrence of t-AML/MDS. It is claimed that melphalan induced more often secondary AML as compared to cyclophosphamide. Dose relationships were noted for cyclophosphamide [19-21].

Similar to de-novo AML in M4 and M5 subtypes a high frequency of rearrangements of 11q23 anomalies, t(8;21), inv(16) and t(8;16) are noted [22]. Compared to de-novo AML, the incidence of polyclonality is higher in t-AML/MDS. Secondary APL forms a peculiar exception; it has been found to be similar to de-novo APL in respect to morphology, immunology and cytogenetics [23].

Adults

In adults often an initial phase compatible with MDS evolving in to AML is common. In children this is not as usual. In adults the percentage of patients presenting with a t-MDS (in contrast to t-AML) is substantially higher as compared to adults [24]. Higher rates of uncommon AML subtypes such as FAB-M6 and M7, i.e., erythroblastic and megakaryoblastic AML, are noted in t-AML in contrast to de-novo AML. In adults a peak incidence is noted 4-6 years after cytotoxic therapy given for the first malignancy. Occurrence after a latency period as short as 12 months but even ranging to 15-20 years are not uncommon.

Children

It is stated that in children the occurrence of t-AML is negligible 6-years after treatment cessation of the primary disease [25]. Also the latency period to development of t-AML/ MDS was found to be the same for alkylator-induced as for topoisomerase induced myeloid leukaemia [26]. This might in part be related to the age limits restricting the standard follow-up period by paediatricians and is in contrast to findings in adults. The number of patients included in the cited document was also low (n=24) and low-risk t-AML/ MDS related to epipodophyllotoxin cases are absent in the report. In adults epipodophyllotoxins related AML tends to present between 1-4.5 years, and a preceding MDS phase is often lacking, whereas alkyting agents induced-AML often occurs after 1-20 years [10,21,27]. As a result reports on only children may have missed a part of alkylator induced t-AML/ MDS and/or the epipodophyllotoxin related low-risk patients.

Cytogenetics

Distribution of karyotype aberrations is different from de-novo AML since more 11q23 and complex karyotypes are noted [10]. T-AML patients more often have a balanced karyotype as compared to patients with t-MDS [27]. Also in relation to the preceding therapy differences are noted. Alkylating agents are linked more frequently with cytogenetic anomalies involving chromosomes 5 and 7. The latter anomalies were noted in 76% cases in a series of 306 patients, which is substantially higher as compared to de-novo AML [28,29]. Affymetrix mapping confirmed the occurrence of single nucleoside polymorphism (SNP) in a subset of patients with loss of chromosomes 5 and/ or 7, which was associated in that study with prior treatment with alkylating agents [30]. In topoisomerase II inhibitor related secondary AML more balanced translocations are noted; more often involving 11q23 and 21q22. Translocations related with epipodophyllotoxins involving 21q22, inv(16) and t(15;17) have received more often anthracyclines as well [25,31-39]. These findings were also confirmed for children in a study on 20 patients [40]. However, 11q23 and 21q23 abnormalities have been identified in non-anthracycline treated patients as well [9]. Further DNA analysis revealed in epipodophyllotoxin related t-AML/MDS MLL-rearrangements, EML1-1, CBFβ-MYH11and PML-RARα. Whereas in alkylating agent specific genetic aberrations are less specific [15]. It is hypothesized that the differences between alkylator induced and epipodophyllotoxin induced t-AML/MDS in respect both to latency to develop a t-AML and chromosomal findings are related to differences in oncogene alterations. In alkylating agent induced t-AML/ MDS multiple tumor suppressor or oncogenes are needed to induce a malignancy, resulting in imbalanced karyotypes. Epipodophyllotoxins result in balanced karyotypes related to an activation of an oncogene in a dominant fashion [21]. Several pathways more or less specific for either alkylator- or epipodophyllotoxins have been constructed; it is beyond this review to discuss these hypotheses [41].

Risk factors

Secondary myeloid malignancies are in the majority of cases related to cytotoxic chemotherapy and organic compounds such as benzene [42]. Earliest reports date from Hodgkin pat-

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ients receiving mechlorethamine, vincristine, procarbazine and prednisone (MOPP) courses. In patients treated before the age of 16 years, the relative risk of leukemia was about 80 times higher than the control population (relative risk of 321.3). After replacing mechlorethamine by cyclophosphamide a lower SIR of 122 was found. After introducing doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) another reduction was noted [15,43-46]. Cytostatic drugs most commonly linked with secondary malignancies are topoisomerase II inhibitors (epipodophyllotoxins, anthracyclines and anthracenediones) and alkylating agents. Topoismerase inhibitors interfere with the enzymes involved in uncoiling the DNA in order to form single strands. This results in deletions, insertions, inversions and translocations [8]. Additional risk factors related to the use of medication are duration of exposure and cumulative dosage [47]. Cyclophosphamide has been mentioned earlier. In respect to cumulative and duration of administration of epipodophyllotoxins several reports mention the link of a higher cumulative dosage and a higher risk [48,49]. Others do not confirm such a finding, but link the risk to the dosing schedule. They noted that higher cumulative dosages did not result in increased incidence rates, but prolonged administration had a more pronounced effect [50]. Being the most prominent factor of secondary malignancies noted in children; pediatric data are available on the increase related to the dosing interval. Prolonged administration of epipodophyllotoxin twice weekly or weekly was independently associated with the development of secondary AML. The overall cumulative risk of AML at six years was 3.8 percent; but in subgroups treated twice weekly or weekly, the risks were 12.3 percent and 12.4 percent [51]. Alkylating agents act by transferring alkylgroups to oxygen or nitrogen atoms of DNA bases. Alkylating agents with two active sites are additionally capable of cross linking DNA strands. Effects of alkylating agents on SIR are less clearly reported. In most cases they are used in combination with other chemotherapy. As a result the exact effect on induction of t-AML/MDS is less elucidated. It is claimed that anthracenediones (mitoxantrone e.g.,) induce more frequently secondary t-AML as compared to anthracyclines. However, data are mainly based on adults [52-55]. The effects of other agents may be clarified in the future. For instance campthotecans are potential candidates since the mode of action, i.e., blocking topoisomerase I, is quite similar to topoisomerase II inhibitors. It is probable that due to the low number of patients treated with these compounds (in most cases in combination with other drugs) the leukemia inducing effect is still unnoticed [56].

High levels of irradiation and radioactive isotopes are reported to induce secondary myeloid malignancies [6,9,57]. Ionizing irradiation induces the formation of reactive oxygen species through radiolysis of water molecules, which oxidize or deaminate DNA bases and induces DNA strand breakage. Proton irradiation leads to DNA strand breaks as well. It was described that radiotherapy as such is not related to t-AML/MDS. However in combination with chemotherapy there was a clear relation [33,58]. The findings reported by others do not support the finding that radiotherapy given as single treatment modality is not related to induction of t-AML/MDS [27].

Synergy in respect to the induction of second malignancies in relation to other cytostatic drugs and host factors are well known as based on findings in Fanconi anemia, neurofibromatosis type 1 and gluthatione transferase polymorphisms [59-61]. An increase of risk of epipodophyllotoxin induced t-AML/MDS was related to the combination with other anticancer drugs. For asparaginase and alkylating agents, cisplatin and antimetabolites this has been reported as well. In respect to the effects of asparaginase a decrease of protein levels and as consequence a decrease in recombinogenesis activity is relevant in epipodophyllotoxin treatment. Which is explanatory for the increase of t-AML/MDS occurrence if asparaginase is given immediately before epipodophyllotoxin administration [9,15,25,33,37,48,62,63].

Co-medication has been debated to play a role in induction of secondary malignancies. Especially the use of growth factors (G-CSF) and dexrazoxane have been under focus. In adults data on G-CSF are contradictory. An increased risk was found in breast cancer patients diagnosed at a younger age as compared with older patients [52,64,65]. In children with Ewing sarcoma no relation was noted, whereas in ALL patients a relation was suggested [66,67]. In a study by Relling et al., on 412 children treated for ALL receiving etoposide and anthracyclines, 99 had received G-CSF, 284 cyclophosphamide, 58 of these 284 also received cranial irradiation. There were 20 children who developed t-AML/MDS after median interval of 2.3 years (range, 1.0-6.0 years; 16 AML, 3 MDS, and 1 chronic myeloid leukemia). The 6-year cumulative incidence of t-AML was 12.3% (5.3%) Excluding children receiving irradiation, the incidence rate was higher in those receiving G-CSF (P=0.019) [67]. Although G-CSF is mentioned to be linked with the development of secondary malignancy, especially AML, this is at least in adults minimal with an absolute risk increase of 0.43%. In contrast its use resulted in reduction of death (3.4%) probably due to the possibly to give more intensive treatment schedule [68]. Dexrazoxane is used as agent giving cardioprotection to prevent side effects of anthracyclines. The induction of secondary malignancies is claimed by some. Others question such a side effect. As a result the product is only marketed for adults. The debate in children in respect to risk-benefit has not been finalized yet [69-71]. For both G-CSF and dexrazoxane the setting of this drug administered in relation to other carcinogenetic medication is probably of major importance in inducing t-AML/MDS.

Immune-suppression is related with secondary malignancies. Lymphomas are quite common, but AML is relatively scarce. In heart-lung recipients and kidney recipients relative risks of 5.5 and 2.1 for t-AML were reported. Non-DNA as well as DNA damaging immune-suppressants (e.g., azathioprine) are noted to be related with t-AML [7]. In hematopoietic stem

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cell transplantation patients a higher incidence as compared to patients treated without transplantation was reported in several manuscripts. However, administered cytostatic drugs and total body irradiation administered to these patients may be even more important in comparison with the resulting immune deficient state and the extensive cellular proliferation in these procedures [27,72-75]. In a study on 1487 paediatric autologous hematopoietic cell transplantation 35 secondary malignancies were noted; among them 6 cases with t-AML and 7 with t-MDS. For all secondary malignancies these children had a 24 times higher risk for developing a secondary malignancy, for AML and MDS the observed versus expected ratios were 266 and 6603 respectively. Analysis for specific risk factors did not reveal any significances [13].

Some inborn metabolic host factors are also linked with an increased susceptibility for t-AML/MDS. Low thiopurine-methyltransferase activity and polymorphism of a CYP3A4 enzyme results in as DNA-damaging metabolite of epipodophyllotoxins [38,76,77]. Also glutathione-S-transferase, NAD(P)H: quinine oxireductase and polymorphisms of DNA repair genes are linked with an increased occurrence of t-AML/MDS [28,36,78-87]. Extensive reviews on genetic susceptibility and biological pathogenesis were published [21,56,66,82].

Some (often inheritable) anomalies attribute to the development of AML/MDS and AML/MDS without the need for prior therapy. In principle the term secondary AML/MDS is more applicable instead of treatment related AML/MDS. Based on similarities in disease characteristics some reports on t-AML/MDS deal with these anomalies, as well. Examples of genetic predisposition are Down syndrome, Fanconi anemia, Li-Fraumeni syndrome, Leopard syndrome, Noonan syndrome and Costello syndrome. Several of them are related to RAS-MAPK pathways [8,88-94]. The higher incidence of malignancies in relatives of patients with t-AML then in relatives of patients with de-novo AML and the occurrence of new malignancies in cancer patients treated with only surgery can be put forward for existence of yet unidentified factors [91]. As such it is assumed that at least some patients have an inheritable susceptibility to develop t-AML [7].

Patients with specific primary malignancies run an additional risk for t-AML/MDS; e.g., pediatric Hodgkin's lymphoma, osteosarcoma and APL after breast carcinoma [49,95]. The percentage of patients suffering from a specific secondary malignancy is not only related to former therapy; the primary disease itself is related to the distribution of type of malignancy as well. For instance t-AML is rare in chemotherapy treated patients with retinoblastoma treated who are prone to develop second malignancies. It is hypothesized that this is related to the fact that the underlying mutation of the Rb1 gene does not play a role in hematopoietic stem cells [96].

Prognosis

Since AML is more frequent in adults and t-AML/MDS only occurs after a preceding oncogenic exposure t-AML/MDS has a very low incidence in children. As a consequence many data have to be extrapolated from adults. In adults the prognosis of secondary AML is dismal in comparison with de-novo AML. However, remission rates reported range in a single report up to 82%. But in an analysis of 13 different studies an overall CR rate was calculated to be 27%. Survival at 5 years was reported to be less than 10%. The recent study reported by Godley et al., states an overall survival at 1 year of 51%. Overall survival at 1 year was 74% for patients who had achieved a CR, but only 20% for patients who had achieved only a partial remission after induction. After allogeneic stem cell transplantation median survival was 673 days, compared to 399 days for those who had an autologous transplant and 93 days in case no transplantation was done. Overall survival at 1 year was 72%, 75%, and 17% for patients respectively [27,97-101].

The number of children suffering from t-AML/MDS reported in literature is very low [12,102-105]. Tabori et al., reported on 21children with t-AML and 2 with t-MDS. Both event free survival and overall survival were 14%. Leahey et al., report on 11 children. Only 3 survived, resulting in a 3-years survival of 24%. Causes of death were recurrence of primary disease and new malignancies [103]. Sandler reported on 16 children, 9 out of 13 children who achieved complete remission were transplanted. Two transplanted children survived over 2 years, whereas one not transplanted patient survived at least 8 months [104]. One of the larger studies reports on 62 children. Compared to de-novo AML they had a poorer induction rate (50% vs 72%), overall survival (26% vs 47% at 3 years, and event-free survival (21% vs 39% at 3 years) [15]. Children with t-AML/MDS who received intensive-timing induction had better outcomes than those who received standard-timing induction (overall survival 32% vs 0%) [26]. In a study on 642 children who had suffered from ALL and later developed a secondary malignancy t-AML/MDS 5-year survival estimates for AML were 11.2% for 125 patients diagnosed before 2000 and 34.1% for 61 patients diagnosed after 2000 ($P<0.001$); 5-year survival estimates for MDS were 17.1% for 36 patients and 48.2% for 33 patients, respectively. Allogeneic stem-cell transplantation failed to improve outcome of secondary myeloid malignancies after adjusting for waiting time to transplantation [12].

Prognostic factors

Adults

Dismal prognosis is related to age, and co-morbid conditions and restrictions in treatment due to preceding treatments [106-109]. In many cases t-AML/MDS is a fatal condition. Additionally factors are organ and vascular supply injury. Bone marrow function may be severely hampered due to cytostatic use and extensive irradiation [108,110].

In respect to the preceding treatment alkylator related t- AML has a dismal prognosis, due to the more frequent harboring of anomalies of chromosomes 5 and 7. Remission rates of 24 and 26% were noted in t-AML versus 52 and 42% in de-novo

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AML. Long-term survival rates approximate 10% [108,111,112]. On the other hand patients with t-AML due to epipodophyllotoxins are reported to have a better prognosis. In epipodophyllotoxins related cases remission rates are as high as 81%, but ultimate outcome is still low; i.e., 8% at 2-years [104]. In t-AML the expression rate of MDR1 is high. But in contrast to adults expression of the multidrug resistance gene MDR1 in children is expected to be (at least in de-novo AML) non-relevant [113]. Relevance in pediatric t-AML/MDS is undetermined.

Genetics

Prognosis in adults is related to the karyotype observed. Several classifications delineating prognostic groups exist (**Table 1**) [114-116]. A relative old report mentions that patients with t(8;21) (n=26), inv (16) (n=16) and t(15;17) (n=6) have similar outcomes as compared to de-novo AML [117]. Schoch et al., defined, based on data of 93 patients that unfavorable anomalies were 3q21q26, 5q-/-5, 7q-/-7, 11q23, 12p 17p, >2 abnormalities, intermediate anomalies (normal karyotype and other abnormalities) and favorable (i.e., t(15;17), t(8;21) and inv (16)) karyotypes. Unfavorable karyotypes are more frequently noted in t-AML; i.e., favorable , intermediate and unfavorable karyotypes 26%, 28% and 46% respectively. Rates in de-novo patients are 22, 57 and 20% (p<0.001). Matching de-novo with therapy related cases only in patients with secondary AML with t(8;21), inv (16) and t(15;17) a shorter overall survival was noted; higher relapse rate but similar CR rate were noted. Among these karyotypes t(8;21) was found to have the poorest prognosis. Unfavorable and intermediate karyotypes had a similar outcome after matching for these anomalies of secondary versus de-novo patients. It was concluded that karyotypes were influencing survival duration, however ultimate prognosis irrespective of cytogenetic findings was very poor [10]. Similar findings for adults were reported from Chicago, 29 patients with t-AML with favorable cytogenetics had a median survival time of 27 months; those with intermediate cytogenetics had a survival time of 12 months which contrasted with 16 months for de-novo AML. This was however not significant (p=0.19). For t-AML and de-novo AML patients with unfavorable cytogenetics survival was 6 and 7 months, respectively [29,118]. In another report on adult patients from Germany a shorter survival time was noted in t-AML versus de-novo AML. In a later update of their study it was shown that karyotype is a factor in respect to duration of survival, but also in the favorable group 5-years overall survival is below 25% and a plateau is not reached [10,119]. Smith et al., reported similar data, however not all patients had received intensive remission induction chemotherapy. Even patients responding to therapy and patients with favorable karyotypes died either from t-AML or from their primary malignancy. The incidence of unfavorable karyotypes was over two-third, the worst prognosis was noted in patients with anomalies of chromosome 5 and 7 [27]. In a Korean report on outcome in 48 patients multivariate analysis showed that only APL and presence of non-complex karyotypes were related with a more profitable outcome [120]. For APL no differences as compared to de-novo AML were reported [121]. Which once again suggests, similar to the findings in morphological and immunological cell characteristics, that

Table 1. Risk groupings according to cytogenetics in literature.

	Stölzel et al., 2011	Kröger et al., 2009	Litzow et al., 2011		Armand et al., 2007	
			AML	MDS	AML	MDS or AML arising from MDS
Low (Stölzel/Kröger) Favorable (Armand)	t(8;21) or inv(16)	normal and t(8;21), inv 16 or t(15;17	ns	ns	t(8;21) alone inv(16/t(16;16)/del(16q22) with M4 t(15 ;17)	
Intermediate (Stölzel/Kröger) Standard (Armand)	patients not harboring high- or low-risk aberrations	one or two abnormalities not mentioned under low or high risk	ns	ns	Normal Del(9q) t(8 ;21)+del(9q) or complex Trisomy 8 Abnormal 5 or 7 Abnormal 11q23 All others	Normal Abnormal 3q Abnormal 5 Trisomy 8 All others
High (Stölzel/Kröger) Adverse (Armand) Poor (Litzow)	-5/del(5q); -7/del (7q); monosomies of other chromosomes (with exception for the loss of chromosomes X or Y); inv(3q); abn12p; abn11q;+11; +13; +21; +22; t(6;9); t(9;22); t(3; 3); complex aberrant karyotype (≥ three independent abnormalities)	11q; t(6;9); -7; del(7q); del 5q or complex (≥3)	del(5q)/25, 27/del(7q), abn 3q, 9q, 11q, 20q, 21q, 17p, t(6;9), t(9;22) and complex karyotypes (≥3 unrelated abn)	complex (ie, ≥3 anomalies) or chromosome 7 abnormalities	Complex t(9;22) t(6;9)	Abnormal 7 Complex

ns=not specified
*=restricted to post-hematopoietic transplantation patients

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t-APL is similar to the de-novo APL).

FTL3

In respect to FLT3 internal tandem duplications (FLT3-ITD) it was shown that the percentage expressing cells was significantly lower in t-AML, indicating that t-AML leukemogenesis in most cases follows mechanisms different from those seen in de-novo AML. For de-novo AML FTL3-ITD was found to be a risk factor, for t-AML such conclusion was not made [122]. Also nucleophosmin-1 mutations were found to be less frequent in t-AML as compared to de-novo AML and presence was found to be a risk factor in patients below the age of 60 years [116].

Transplantation

In adults undergoing transplantation for t-AML/MDS 2-year survival rates of 30%, relapse rates of 42% and treatment related mortality of 49% were reported in a French study [123]. In a series of 46 patients undergoing transplantation 5-years disease-free survival was 24%, relapse and non-relapse mortality was 31% and 44% respectively. In this cohort no statistical differences existed for patients treated with chemotherapy before conditioning for stem cell transplantation versus those who were not pretreated [124].

Patients after hematopoietic stem cell transplantation for their primary malignancy are at high risk since they have in the majority of cases a history with high dose irradiation and cytostatic use. In a report from the European Society for Blood and Marrow Transplantation t-AML and t-MDS multivariate analysis revealed a better prognosis in case of an age <40 years, normal cytogenetics and a status of CR at the moment of transplantation; overall survival rates were 62%, 33% and 24% at 2 years, respectively. Cytogenetic anomalies were relevant, but sub-analysis on specific anomalies seemed not to be relevant in their prognostic scoring system (**Table 2**) [22].

In multivariable analyses on 2853 adults t-AML was an adverse prognostic factor for death in complete remission but not relapse as compared to de-novo AML. In contrast to older patients the younger patients were more intensively treated and did not show higher induction failures, but more relapse in complete remission. As a result it is suggested that co-morbidity, cumulative toxicity of cancer treatment, inclusive the therapy for the first malignancy may therefore be important factors in the poor outcome of t-AML patients in the early phase of treatment [10,119,122,125]. In a report from Seattle outcome was noted after correction for risk factors in HLA-identical or partially mismatched family hematopoietic transplantation. Relapse probability and relapse-free survival correlated significantly with disease stage and karyotypes. Relapse incidence was lower and relapse-free survival superior (P=0.02) with unrelated donor transplants. Their data also suggest that inferior outcome in patients with t-AML/MDS was related to the frequency of high-risk cytogenetics [126]. Similar findings were reported from the Dana Faber Cancer Institute [114]. A Danish report on 157 adults with t-AML and 473 de-novo AML patients showed in univariate analysis a better outcome for patients not reaching a complete remission. Differences were not significant after correction for age, cytogenetic anomalies, performance status and WBC [127].

Table 2. European society for blood and marrow transplantation risk scoring for t-AML/MDS (Kröger et al.,).

Risk factor	*Number of points*			
Age >40 years	+2			
Not in complete remission	+2			
Abnormal cytogenetics	+1			
Risk group	***Overall survival (2 year)***	***Relapse free survival (2 year)***	***Non-relapse mortality (2 year)***	***Relapse rate (2 years)***
Low (0-1 factors)	96%	58%	22%	20%
Moderate (2-3 factors)	33%	32%	37%	31%
High-risk (4-5 factors)	24%	20%	38%	42%

Children

As already mentioned the data in children are scarce. A major difference is the more frequent relation with epipodophyllotoxins in children as compared with adults. Remission rates are as high as 81%, but ultimate outcome is still low, i.e., 18% at 2-years [104]. In a study on 20 children only 3 children were alive after 1, 12 and 68 months; no correlation was found with chromosomal abnormalities [40]. Hale et al., reported on epipodophyllotoxin induced t-AML in 19 children. Ten patients died from a relapse, and only 4 were alive 3 years after allogeneic transplant [102]. In a report on 38 allogeneic transplanted patients from St Judes Hospital 3-year overall and event free survival were both 15%, the non-relapse mortality was found to be 60% at 3-years. Severe (grade III–IV) acute graft-versus-host disease and relapse rate were 24% and 19%, respectively [128]. A report from the MD Anderson Hospital describes 22 patients from a group of 2589 children treated for a malignancy 2-year survival rates of 20%, 40%, and 25% in children who underwent stem cell transplantation without induction, children transplanted in remission after induction therapy and receiving a stem cell transplantation as salvage therapy, differences were not significant. Risk factors identified were poor/intermediate-risk cytogenetics (p=0.01), lower hemoglobin level (P=0.0001), and t-MDS/AML (vs. de-novo) (p=0.003) [129]. Barnard et al., describe 24 children with t-AML/MDS who were assigned randomly to standard- or intensive-timing induction. A comparison was done with 62 de-novo MDS and 898 de-novo AML children. T-AML/MDS children were older, had lower white blood cell counts and more often MDS (21% vs 7%) and trisomy. None of the patients had the classic t(8;21), t(15;17) and 16q22 anomalies. Patients were randomized for time- and G-CSF- intensification of therapy. Induction rate comparing t-AML/MDS with de-novo AML was lower 50% vs 72%, overall survival was 26% vs 47% at 3 years), and event-free survival was 21% vs 39% at 3 years. T-AML/MDS children who received intensive-timing induction

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had a trend for a better outcomes than those who received standard-timing induction, but this was not significant (overall survival 32% vs 0%, P=0.54). The authors state that most chil-dren with t-AML/MDS have disease resistant to current therapies. Unfortunately they only did univariate analysis and did not correct for specific risk factors [26].

Therapy

Patients with t-AML have generally a poor tolerance for standard chemotherapy. Generally it is stated that patients with t-AML who have a good performance status should be treated similar as patients with de-novo AML. For those patients who have favorable cytogenetic abnormalities, such as t(15;17), inv(16), and t(8;21); intensive chemotherapy is advocated. Hematopoietic stem cell transplantation is advised for unfavorable karyotypes. Supportive care alone may be warranted for those with poor performance status [21,29,98,99]. Recently the European Group for Bone Marrow Transplantation and the Center for International Bone Marrow Transplantation Research devised scores to predict outcome including age, cytogenetics, disease status at transplantation and donor characteristics (**Tables 2** and **3**) [22,115]. The German Alliance Leukemia Study Group devised a similar scoring, but incorporated NPM1 as additional factor and platelet count (**Table 4**) [116]. EFS and OS were, however, quite different applying these scores. Based on these scoring the treatment advises per subgroup can be formulated as mentioned above.

However, whether these scorings are useful in children is doubtful considering the better tolerance of chemotherapy and less co-morbidity in children as compared to adults and the inclusion of age as risk factor in these scorings It is has been stated that most children with t-AML/MDS have disease resistant to current therapies and all should be classified as high-risk patients. This might not be fully appropriate as the advised is based on univariate analysis only and did not correct for specific risk factors [26]. Since epipodophyllotoxin induced t-AML/MDS is the most common form of t-AML/MDS in childhood. For the cases expressing 11q and 22p anomalies this statement is in line with data from adults. However, for those with APL and inv(16) such an advise cannot be given since no or very low numbers of APL and inv(16) cases were among the patients with t-AML/MDS and the advice is not in line with recommendations in adults. In children the general rule not to transplant patients with APL can be adopted, as it is based on the finding that cell characteristics and outcome in this subgroup is similar to de-novo APL [21,95,130]. For non-APL patients with low-risk t-AML/MDS pediatric patients treatment advises could align with advices in adults. As such the presented algorithm can be applied in choosing treatment (**Figure 1**). Those with unfavorable karyotypes should be transplanted; preferably (if feasible) after bringing them in remission. Those with favorable karyotypes (e.g., t(15:17), t(8;21) and inv (16)) could be treated according protocols similar to de-novo AML protocols. Current new protocols use minimal residual disease (MRD) as surrogate marker for resistant disease and adapt treatment accordingly. As a result some children with t-AML/MDS with good risk characteristics will be transplanted in the end. For some transplantation can be withheld. Only a few patients will be sorted in the supportive care category, since physical condition in children is usually better as compared to adults.

Table 3. Center for International Bone Marrow Transplantation Research risk scoring for t-AML/MDS (Litzow et al.,).

Risk factor	Each valid 1 point
Age	>35 year
Poor risk cytogenetics	AML: del(5q)/25, 27/del(7q), abn 3q, 9q, 11q, 20q, 21q, 17p, t(6;9), t(9;22) and complex karyotypes (≥3 unrelated abn) MDS: complex (ie, ≥3 anomalies) or chromosome 7 abnormalities
Disease state	Not in remission at moment of grafting
Donor type	Non-sibling related donor and mismatched donor
Risk group	**Overall survival (5 year)**
No risk factors	50%
1 factor	26%
2 factors	21%
3 factors	10%
4 factors	5%

Table 4. German alliance leukemia study group (Stölzel et al.,).

Risk factor	*Number of points*	
Age >60 years	1	
High risk karyotype	1	
NPM1 wild-type in bone marrow	1	
Platelet count <50x10^9/l in peripheral blood	1	
Risk group	***Overall survival (2 year)***	***Event free survival (2 year)***
Favorable (0-1 factors)	58%	40%
intermediate (2 factors)	28%	21%
High-risk (3-4 factors)	9%	7%

Conclusion

The incidence of treatment related AML/MDS (t-AML/MDS) in children is extremely low. Consequently assessment of data from adults and to some extent extrapolation from adults is needed. Epipodophyllotoxin induced t-AML/MDS is more common in children, which is likely to be related to the shorter latency period to develop this condition. I FAB-M4, FAB-M5, APL, balanced karyotypes, 11q23 and 21q22 anomalies, inv (16) and t(15;17) are noted more often. Duration and short interval between administrations of epipodophyllotoxins in children results in a higher incidence of t-AML/MDS. Genetic (karyotypic) make up is influencing duration of remission, although the relation with overall-survival is less clear. Choice of therapy should be based on co-morbidity and the

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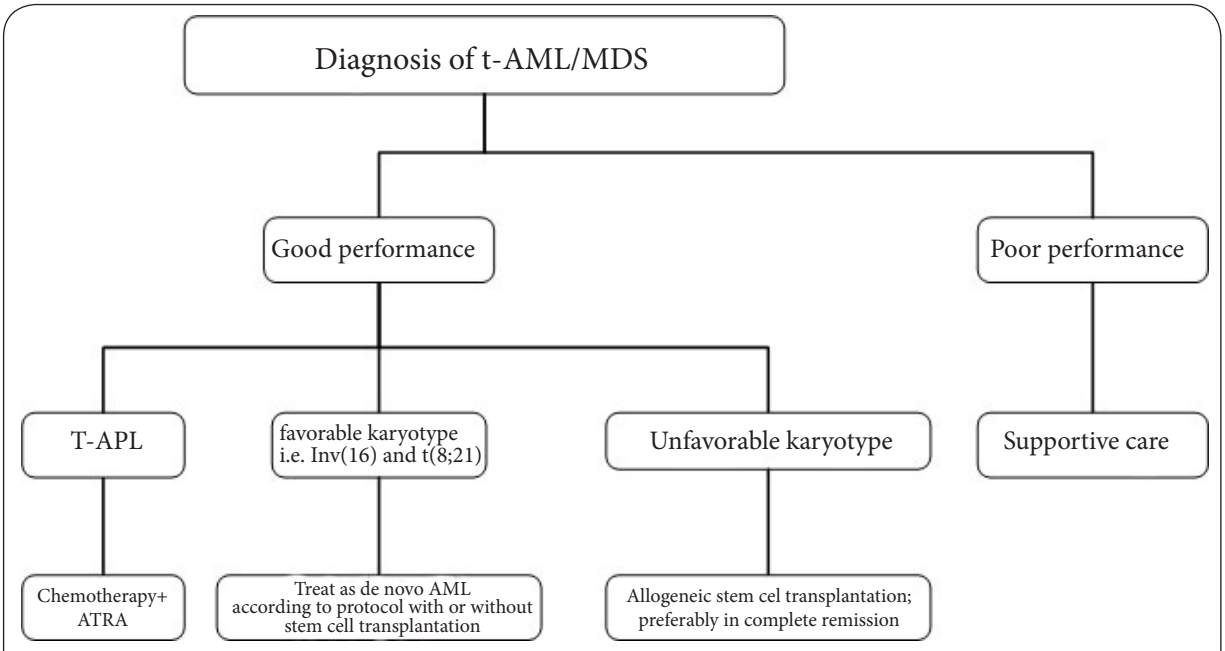

Figure 1. Algorithm for choice of treatment in t-AML/MDS in children.

likelihood to undergo intensive therapy. The majority of children with t-AML/MDS should have hematopoietic stem cell transplantation. A minority of children with t-AML with inv(16), t(8;21) and t(15;19) translocation should be considered for chemotherapy according to de-novo AML protocols. Monitoring of early response criteria for detection of primary resistance is advised.

Competing interests
The author declares that he has no competing interests.

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