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Treatment results for children and adolescents with acute myeloid leukemia in Middle and Eastern European countries

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Acute myeloid leukemia (AML) corresponds to a heterogeneous group of hematologic neoplasms that originate from bone marrow precursors of the myeloid, monocyte, erythroid, and megakaryocytic cell lineages. While acute lymphoblastic leukemia (ALL) remains the most common childhood malignancy, AML comprises only about 4.8 % of all pediatric cancers in Europe. However, although an orphan disease and despite of remarkable advances during the past decades in both the management and the understanding of the biology and molecular genetics of childhood AML, it still remains one of the most frequent causes of death in children and adolescents with cancer.

The major causes for treatment failure are (a) the development of resistance of AML cells to various chemotherapeutic agents and (b) treatment-related mortality. Therefore, ultimate care for a child with AML must consist of a treatment that is both: efficient and safe. This does not only require efficient antineoplastic agents to which the individual AML responds, but also a medical infrastructure that provides professional management of pediatric oncological emergencies or side effects of the intensive treatment, respectively (e.g. hemorrhages as a result of hyperleukocytosis or infections during neutropenia) on the one hand, as well as appropriate supportive care modalities (such as the availability of blood products) on the other.

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The key of success in treating pediatric leukemias in high-income Western European countries during the past decades has been the conduct of clinical studies, the concept of which is based on the comparative testing of the effectiveness of multimodal treatment concepts (rather than on studying the efficacy of a single drug) as well as on patient stratification into specific risk groups according to the individual morphology, histochemistry, immunophenotype and genetic subtype of the disease. Hence, the continuous optimization of intensive therapy in conjunction with effective supportive care based on such standardized, risk-adapted treatment protocols led to an increase in survival rates for Western European pediatric AML patients from less than 10 % to about 70 % over the last 40 years [1].

In Middle and Eastern Europe, the standards of medical care have improved since 1990. However, overall, the standardized, risk-adapted treatment regimens according to multicenter protocols, for example as developed by the Berlin-Frankfurt-Muenster (BFM)-Study Group for treatment of childhood ALL (ALL IC-BFM 2002 trial [2]), is not yet a routine approach for the management of AML in Middle or Eastern Europe. Despite a relatively good standard of general pediatric care in some of these countries, one of the underlying problems so far has been that the pediatric oncology frequently suffered from lack of financial resources not only for research and specific diagnostic procedures but also and most importantly for the costly treatment such as anticancer drugs, antibiotics, etc. A certain tradition of treating AML patients according to modified versions of published AML-BFM protocols, however, has certainly been maintained for many years by various treatment centers in this part of the world, but publication of the results have been, so far, rather rare [3]. This might be partially due to the fact that until recently the communicative network between East-

ern and Western pediatric oncologists was thin because of the long lasting communist regime in the East.

This *memo* edition aims at further improving this network by giving an overview on past, present, and future challenges of establishing standards for the management of childhood AML in Middle and Eastern European countries. The particular prognostic impact of using standardized multicenter treatment protocols is outlined based on the positive Western European experience, followed by various articles presenting Eastern European results and experience in the diagnosis and treatment of childhood AML—with more to follow in the next issue of *memo*.

Historical background

Treatment of childhood AML in Western Europe: the trials of the Berlin-Frankfurt-Muenster (BFM) AML study group

The AML-BFM strategy was initially based on the BFM approach to treatment of ALL. The first AML trial in Germany was performed in 1978 followed by various subsequent studies. Chemotherapeutic agents showing highest efficacy were cytarabine and anthracyclines, a combination of which was chosen for induction and consolidation, followed by preventive cranial irradiation and maintenance therapy. The resulting remission rate of 80 % as well as 5-year survival rate of 40 % represented a significant improvement compared to less than 10 % of survival prior to the initial study in the 1970s. The 5-year survival was further increased to currently 70 %, and even 90 % in the subgroup of core-binding factor leukemias by using an intensified and continuously optimized treatment schedule in 5 subsequent trials [4]. In the first AML-BFM studies performed during the 1980s, early death rates due to bleeding complications were high—especially for patients with monocytic leukemias and those with hyperleukocytosis [5]. Special recommendations were propagated and led to a reduction of these fatal events [6]. With the introduction of the AML-specific intensive induction regimen "ADE" (cytarabine, daunorubicin, etoposide) in study AML-BFM 83, the outcome was improved significantly [7], in particular for a subgroup of AML patients that was later defined as the standard risk group [8]. The 1990s saw both the introduction of another efficient intensification and the reduction of treatment toxicity: in study AML-BFM 93, which was performed in collaboration with the Austrian group, second induction with high-dose cytarabine/mitoxantrone (HAM) showed to be of particular benefit for high-risk patients. Additionally, the results of study AML-BFM 98 indicated that the 6-week consolidation could be replaced by two short cycles of high drug intensity with the advantage of not leading to higher cumulative doses but to similar survival rates, higher tolerability, and lower toxicity when compared to the results of the initial 6-week consolidation regimen [9]. In study AML-BFM 2004, survival rates were raised again. This was mainly due to optimized therapy management achieved by performing early treatment intensification in patients whose AML showed unfavorable response as well as by better supportive care. In addition, the treatment concepts for patients with AML-relapse or -nonresponse to therapy were improved [4, 10].

Taken together, the AML-BFM Study Group always used the experience gained from the previous study to optimize the subsequent one. Combined with continuously improved diagnostic procedures and supportive care regimens as well as with the permanently rising experience of the medical staff involved, this approach was crucial for the stepwise and considerable increase of long-term survival of pediatric AML patients who have been treated according to these six subsequent AML-BFM protocols.

Treatment of childhood AML in Middle and Eastern Europe

Due to the gaping health care quality and health care standards in the different Middle/Eastern European countries, the preconditions of treating childhood AML were severely heterogenous at the beginning of the1990s. According to the Automated Childhood Cancer Information System (ACCIS), a project funded by the European Union (EU), the probability of 5-year overall survival of children with cancer in Eastern Europe was about 64 % in the 1990s versus 75 % in the West [11]. It was also shown that enrolment into clinical trials was more consistent in Western than in Eastern European countries. This tendency is ongoing because the EU Clinical Trials Directive has made conducting clinical trials more difficult [12]. More regulatory requirements and more personal resources are needed, e.g. health professionals trained in Good Clinical Practice [13] to improve this situation.

Although steady advances have been made in managing childhood AML in the majority of Middle/Eastern European countries such as Poland, Czech Republic, Slovakia, Hungary, and Serbia during the past two decades (Table 1), further improvement of prognosis still strongly requires optimization of the current medical infrastructure. This includes the establishment of professional multidisciplinary caregiver teams as well as the availability of adequate diagnostic, therapeutic, and supportive care equipment in every appointed treatment center.

In this issue of *memo*, reports from groups in Poland [14], Czech Republic [15], Hungary [16], Slovakia [17], and Serbia [18] will further introduce the history of the treatment of childhood AML in each country during the last 10–30 years. They show that new diagnostic methods have been introduced and that patients were classified into risk groups. A clearly positive tendency is seen when comparing the recent results with the previous ones. Survival rate in childhood AML have been lagging behind those in Western countries mainly due to higher rates of early death and deaths due to treatment-related

Table 1 Results of patients treated in Middle/Eastern European countries since the years 2000 and 2004

	Czech Republic AML BFM 2004 [15]		Poland AML-BFM 2004 interim [14]		Hungary AML-BFM 98 since 2001[a] [16]		Slovakia AML-BFM 2004 interim since 2004 [17]		Serbia AML-BFM 87, 93, 98 and 2004 interim since 2000 [18]	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Number of patients	57		237		112		73		106	
Early death (defined as death during the first 42 days from start of treatment)	3	5	11	4	14	13	5	7	12	11
Non-responders	1	2	19	9	16?		3	4	7	7
CR achieved	53	93	207	87	77?	69	65	89	87	82
Death in CCR (chemo/after HSCT in CR1)	2/0	4	11/3	6	8/12		5	7	9	11
Relapse	16	30		36	21	19	26	38	20	23
Secondary malignancies	2	4	0	0	1		1	1		
Total group pOS (5 years)	42	74		63		48 (4 years)		52		59
Total group pEFS (5 years)	33	56		52		45 (4 years)		47		50
SR pEFS (5 years)		67		55				63		
HR pEFS (5 years)		49		51				40		

CR complete remission, *CCR* continuous complete remission, *HR* high risk, *HSCT* hematopoietic stem cell transplantation, *EFS* event-free survival, *OS* overall survival, *SR* standard risk
[a]data were incomplete

toxicity during intensification. However, improvement was seen recently especially in the Czech Republic and in Poland, countries with an already longer lasting tradition of conducting clinical trials. Also, certain epidemiological aspects such as a higher percentage of children with acute promyelocytic leukemia (FAB M3) in Serbia, Slovakia, and the Czech Republic (13–18 %) compared to those in Germany and Austria (7 %) have been revealed in these studies and need future evaluation.

In summary, this *memo* issue emphasizes that despite facing major political, ethnical, and socioeconomic obstacles, pediatric oncologists and hematologists have done their very best and succeeded to improve the survival rates of children and adolescents with AML in Middle and Eastern Europe. A major challenge for the future will be to further optimize the pediatric oncological and hematological infrastructure as well as the interactive professional network between East and West. A closer collaboration in performing clinical trials has already been started between the AML-BFM group and the Czech group since the 1990s and recently also with the Slovakia group.

Conflict of interest

The authors declare that there is no conflict of interest.

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