Acute Lymphoblastic Leukemia in Adolescents and Young Adults: A Single Center Experience in Russia

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OBJECTIVES

Background: Adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL) constitute a distinct population from children and older adults. Based on patterns of referral, they may be treated by either pediatric or adult hematologists. As a group, AYA with ALL have a worse overall survival (OS) and event-free survival (EFS) compared to that achieved by younger children. Original pediatric protocols ALL-MB 91 and 2002 have shown high efficiency of treatment of children in Russia. As a hypothesis we have assumed that outcomes for AYAs treated at adult and pediatric institutions will be equivalent when using therapy based on that used in pediatric cooperative group protocols.

The purpose of the study was to assess the efficacy and toxicity pediatric protocols ALL-MB 91 and 2002 for adolescents and AYA with ALL.

PATIENTS AND METHODS

Enrollment on the study began in December 1997. Inclusion of patients (pts) in protocol ALL-BFM 90 (n = 43) was completed in September 2005 and ALL-MB 91/2002 – March 2008 (n = 34). In protocols ALL-MB 91/2002 the pts receive four drug induction with dexametasone 6 mg/m2 daily for 36 days, daunorubicin 45 mg/m2 for 2 doses, vincristine 2 mg weekly for 5 doses and and intrathecal (IT) cytarabine and IT methotrexate and IT prednisolone weekly for 5 doses. Consolidation therapy included L-asparaginase in a constant dose of 10000 ME/m2 weekly for 18 doses and 6-merkaptopurine 50 mg/m2 (100%) daily and methotrexate 30 mg/m2 (100%) weekly with weekly doses adjusted according to white blood cell count. Central nervous system (CNS) irradiation is performed for pts with CNS involvement at diagnosis and for patients with T-cell ALL and a high presenting white blood cell count. Traditional maintenance was carried out up to 24 months. The protocol ALL-BFM 90 called for the purpose of comparison as an effective standard therapy.

Table 1. Distribution of AYA with ALL on therapy

Risk Group:	ALL-BFM 90m		ALL-MB 91/2002		Total:	
	Abs.	%	Abs.	%	Abs.	%
Standard	10	23	18	53	28	36
Medium	22	51	8	24	30	39
High	11	26	8	24	19	25

RESULTS

Table 2. Clinical features of AYA with ALL

Parameters:	ALL-BFM 90m		ALL-MB 91/2002		Total:	
	Abs.	%	Abs.	%	Abs.	%
Age (years)	20.3 (15-28)		18.8 (15-35)		19.3 (15-35)	
Male	27	63	20	59	47	61
WBC≥50.000	16	37	6	18	22	29
T-ALL	18	42	6	18	22	29
Ph+	4/22	18	3/22	14	7/44	16
CNS+	8	19	3	9	11	14

78 (m – 8, f – 30) pts have been enrolled. 77 pts are valuable (1 withdrew on day 1 of therapy). The median age is 19.3 years (range 15–35). 37 (86%) pts are in complete remission (CR) on the protocol ALL-BFM 90 vs. 29 (88%) pts – ALL-MB 91/2002. Respectively 3 (7%) and 3 (9%) pts died in the induction. 3 (7%) and 1 (3%) pts is refractory to therapy. 5 (12%) and 1 (3%) pts died in CR from significant toxicities. Respectively 9 (21%) and 3 (9%) pts relapsed. 4 (33%) pts have CNS relapse, and 6 (50%) have bone marrow relapse. 6-years event free survival (6y-EFS) has 54 vs.77% (median of observation 5.7 years, $p > 0.05$), and 6-years overall survival (6y-OS) has 65 vs. 82% ($p > 0.05$) respectively. Myelosuppression toxicities of ALL-MB 91/2002 protocols have less significant compared with the ALL-BFM 90. In postremission period the most frequent significant toxicities are neutropenia Grade 4 (21 vs. 66%, $p < 0.05$), and thrombocytopenia Grade 4 (0 vs. 62%, $p < 0.05$), and infectious Grade 3–4 (32 vs. 55%, $p > 0.05$).

Table 3. Outcome of AYA with ALL

Parameters:	ALL-BFM 90m		ALL-MB 91/2002		Total:	
	Abs.	%	Abs.	%	Abs.	%
Early death	3	7	3	9	6	8
Refractory	3	7	1	3	4	5
CR	37	86	29	88	66	87
Relapse	9	21	3	9	12	16
Death in CR	5	12	1	3	6	8
Lost follow up	1	2	1	3	2	3
6y-EFS	0.54 ± 0.08		0.77 ± 0.10		0.64 ± 0.06	
6y-OS	0.65 ± 0.07		0.82 ± 0.09		0.73 ± 0.06	

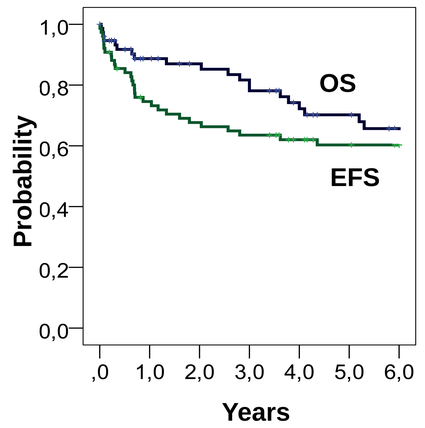

Fig.1. 6-years event free survival (EFS) and overal survival (OS)of AYA with ALL

CONCLUSIONS

AYA have improved outcomes when pediatric ALL therapeutic regimens are used. The reasons for this difference are not fully known. Possible the dose intensity and drug selection may be driving much of the outcome differences. Adult ALL protocols are designed to be tolerable to patients across a wide age range and therefore younger patients receive less treatment. Further research on the biological differences between patients of different ages using microarray analysis or gene profiling can help us better understand these features. Possible new therapeutic targets for AYA with ALL will be found.

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