

Acute Lymphoblastic Leukemia: Treatment

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Complete remission (CR) rates in adults with acute lymphoblastic leukemia (ALL) are 63%-86% (Table 1), usually achieved with combination chemotherapy including vincristine, prednisone, and an anthracycline, with or without L-asparaginase, cytosine arabinoside and cyclophosphamide. Consolidation therapy consists mostly of intense therapy with high-dose cytosine arabinoside and/or high-dose methotrexate in various combinations.⁽¹⁾ The superiority of one or another regimen has, up to now, not been proven in randomised adult ALL trials. As post-induction consolidation, recent prospective randomised studies compare allogeneic bone marrow transplantation (BMT) or autologous BMT versus chemotherapy.

Table 1. Results of chemotherapy in adult ALL in recent large studies.

Group	Year	N	Median age	CR	MRD (months)	LFS
SWOG2	1989	168	28	68%	23	30% at 7y
MDACC3	1990	105	30	84%	22	34% at 5y
MSKCC4	1990	199	25	82%	28	33% at 18y
GATLA5	1991	145	29	78%	28	34% at 6y
JALSG6	1991	117	38	81%		30% at 4y
Swedish ALL7	1991	113	38	77%		
CALGB 80118	1991	277	33	64%	21	29% at 9y
CALGB 85139	1991	164	32	64%	11	18% at 3y
EORTC10	1992	106	27	74%	32	40% at 8y
L+B+V11	1992	212	27	71%	23	32% at 10y
Finnish group12	1992	51	29	82%	13	17% at 6y
FGTALL13	1993	573	33	76%	20	32% at 3y
GMALL 0114	1993	368	25	74%	24	35% at 10y
GMALL 0214	1993	562	28	75%	27	39% at 7y
UKALL IX15	1993	266		68%		22% at 8y
Hong Kong16	1994	50	28	86%	22	13% at 5y
HOVON17	1994	130	35	74%		26% at 3y
Japan18	1994	84	33	63%	14	24% at 7y
		82	36	65%	17	31% at 7y
Verona19	1994	86	33	79%	32	35% at 6y
Vienna20	1994	61	29	85%	41	44% at 5y
CALGB21	1995	197	32	85%	32	30% at 5y
GIMEMA22	1996	358	31	79%	20	25% at 10y

Study Groups: SWOG, Southwest Oncology Group; MDACC, M D Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center; GATLA, Argentine Group

for Treatment of Acute Leukemia; JALSG, Japan Adult Leukemia Study Group; CALGB, Cancer and Leukemia Group B; EORTC, European Organisation for Research and Treatment of Cancer; L+B+V, London (St. Bartholomew's Hospital) + Bergamo (Ospedale Riuniti) + Vicenza (Ospedale San Bartolo); FGTALL, French Group for Treatment of Adult Acute Lymphoblastic Leukemia; GMALL, German multicentre trials in adult ALL; UKALL, United Kingdom ALL trials; HOVON, Dutch study Group; GIMEMA, Gruppo Italiano Malattie Ematologiche Maligne Adulpo

Leukemia-free survival (LFS) rates at three or more years in a large series of nearly 4,500 patients range from 13% to 44%. This wide variation is most probably due not only to variations in therapeutic regimens but also to different inclusion and exclusion criteria. Also the frequency of BMT will influence the outcome. Although there is no substantial improvement in the overall cure rate of about 30%, there are significant changes in ALL subgroups.

Prognostic Factors

Prognostic factors known to influence the survival of adult ALL patients are cytogenetic abnormalities, immunophenotype, the initial white blood cell (WBC) count, time to CR, organ involvement, e.g., CNS or mediastinal tumour, and other variables. The only impact on CR rate is age, showing a strong inverse relationship (Table 2)

Table 2. Outcome of adult ALL according to subgroups*

Subgroup	Incidence	No. pts.	CR rate*	MRD* (mo.)	LFS*
Overall		4474	75% (63% - 86%)	23 (11 - 41)	31% (13% - 44%)
Age					
15 - 20			82% - 95%		32% - 65%**
20 - 50			80%		35%
50 - 60			36% - 63%		20%
>60			33% - 65%		0% - 10%
Subtype					
T-ALL	24%	621	81%	25	46%
pre-pre-B-ALL	11%				
common ALL	57%	881	80%	22	30%
B-ALL	3%	89	77%		58%
My+ ALL	29%	258	62%		30%
Cytogenetics					
Ph<</BCR-ABL+	24%	352	66%	9	0% - 16%

Risk group			
High	70%	8 - 13	0% - 25%
Low	30%	>24	50%

* Pooled data from published studies

** Results from pediatric studies

Age

As for achievement of CR, age has the greatest impact on the outcome of adult ALL. Adolescents in some pediatric ALL studies can approach a CR rate of 95% and a LFS of 65%. Survival decreases continuously with increasing age, to a survival rate of less than 10% in patients above 60 years. The poor outcome in elderly ALL patients may have several causes. First of all there is an accumulation of adverse risk factors, e.g., a higher frequency of Ph-ALL. Also, older patients have a lower tolerability to the applied chemotherapy due to an increase in hematological and non-hematological toxicity. However, even elderly ALL patients who can tolerate an intensive chemotherapy, e.g., high-dose cytosine arabinoside/ mitoxantrone, still have a poorer outcome. Differences in the pharmacology of the cytostatic drugs, e.g., of methotrexate⁽²³⁾ or 6-mercaptopurine, and also a higher expression of the multidrug resistance (MDR1)-associated membrane protein (p-170)^(24, 25) might be an explanation. The inferior outcome of ALL patients above 50 years, and the even more inferior outcome for patients above 60 years, together with the fact that the incidence of ALL increases in these age groups shows that to achieve overall improvement new treatment strategies are needed for these patients, e.g., repeated, moderate dose consolidation cycles or expansion of autologous bone marrow transplantation to elderly patients up to 60 years or more.

Immunophenotype

T-ALL, usually associated with male predominance (73%), high WBC count > 30,000 (62%), mediastinal mass (50%), CNS infiltration (15%), formerly had a poor outcome in children as well as in adults. The median remission duration (MRD) was 10 months or less. Results for adult T-ALL have improved, with CR rates of more than 80% and LFS of 45% or more. Sufficient in vivo and in vitro evidence has accumulated that cyclophosphamide and cytosine arabinoside are mainly responsible for this improvement. The inclusion of pulses of these two drugs during continuation chemotherapy was beneficial in childhood T-ALL. Also, in adult ALL the combination of cytosine arabinoside and cyclophosphamide added to the conventional drugs improved the CR rate and LFS rate in the T-ALL subtype. The earlier form, pre-T-ALL (CD7, cyCD3, CD), has had a poor prognosis⁽²⁶⁾ compared to the more mature form of T-ALL (CD7, cyCD3, CD2), probably due to a higher expression of MDR.⁽²⁷⁾ The optimal duration of treatment for T-ALL, where the majority of relapses occur within 1-2 years but also observed up to 3-4 years, remains unsolved.

B-lineage ALL comprises, according to the stage of differentiation, the subtypes pre-pre-B-ALL, common ALL, pre-B-ALL and mature B-ALL.

Pre-pre-B-ALL was associated with a poor outcome in children, especially in infants and also in adults. In recent adult ALL studies it seems that the prognosis can be improved by the use of intensive treatment regimens to a survival rate of more than 40% at 4 years. One third of the adult ALL patients with the pre-pre-B-ALL subtype have the translocation t(4;11), and the prognosis for these patients has also improved significantly.⁽²⁸⁾

Common ALL is the most frequent subtype in adults (55%) as well as in children (65%). The outcome for adult common ALL patients has not changed very much in recent years, and the survival remains approximately 30%. This may be partly explained by the fact that about 45% of adult patients with c-ALL are Ph/BCR-ABL positive ALLs whose prognosis remains poor. However, even for the adult c-ALL patients who are Ph/BCR-ABL negative, results have not greatly improved. In particular, these patients relapse in most studies over a period of up to 5-7 years or even later. There is no evidence that short intensive consolidation cycles with high-dose cytosine arabinoside in combination have a substantial benefit. Ongoing randomised trials will show whether these patients profit from a transplantation in first CR.

The outcome for pre-B-ALL is similar to that for common ALL.

Mature B-ALL is associated with male predominance (83%), often lymphadenopathy (77%), younger age < 35 years (66%), mediastinal mass (3%), CNS involvement (9%), abdominal tumour masses, and renal and/or bone involvement. In earlier trials, remission rates for adult B-ALL were low and remission duration and survival poor. In 11 studies with a total of 63 patients, the weighted mean CR rate was 33% and most patients relapsed rapidly reflected by the MRD of 9 months and the low survival rate.⁽¹⁾ In childhood B-ALL, the outcome has significantly improved, with CR rates of 81%-96% and LFS rates of up to 80%. The drugs responsible for this improvement are fractionated high-dose cyclophosphamide, high-dose methotrexate (0.5 to 8 g/m²) and high-dose cytosine arabinoside. In addition these regimens contain cytostatic drugs such as adriamycin, conventional dose cytosine arabinoside, teniposide, vincristine, prednisone and etoposide. When these childhood protocols were applied in adult patients with B-ALL, results were also improved. The CR rates in nine such studies have a weighted mean of 77% and the LFS rate a weighted mean of 58%. In the two recent largest adult studies for B-ALL by the GMALL group, the CR rates were 63% and 74%, LFS rates 50% and 71% and survival rates 49% and 51%.⁽²⁹⁾ In the childhood as well as in the adult B-ALL treated with the regimens above, relapses occur almost exclusively within the first year and thereafter the patients can be considered to be cured. Thus maintenance therapy is no longer indicated for this subtype.

Myeloid antigen positive ALL. With the current more detailed immunological analysis, increasing numbers of patients with myeloid antigen positive (My+) ALL can be detected. Common to these leukemias is that in addition to the markers specific for ALL, the myeloid markers CD13, CD14, CD15, CD33 and CDw65, may be expressed on 20% or more of the cells. Whether My+ ALL has an adverse impact on outcome is controversial. The few adult studies available indicate an inferior outcome for My+ ALL patients, both for CR rate and for LFS, but in a recent GMALL analysis the LFS rate is similar to that for My- common ALL.

Philadelphia chromosome/BCR-ABL positive ALL is the subgroup of ALL having the worst prognosis in children as well as in adults. Ph-ALL is diagnosed by chromosome analysis as well as the new detection of BCR-ABL rearrangements by molecular analysis. The incidence in adults with ALL reaches 20%-25%. The weighted mean CR rate for Ph/BCR-ABL positive ALL in eight recent studies was 66% and is now approaching 75%. However, the MRD is still short - only 7-11 months - and the survival rate of 0%-16% at 3 to 5 years is extremely poor.

How to improve the prognosis for Ph/BCR-ABL positive ALL patients remains unanswered. Under investigation are intensified chemotherapy, e.g., high-dose cytosine arabinoside in combination with other drugs, allogeneic BMT, autologous BMT with a variety of purging methods and mismatched/unrelated donor marrow transplantation (MUD). Also maintenance with α -interferon, either alone or in combination with interleukin-2, and experimental approaches such as in vitro purging with antisense oligonucleotides, use of hematopoietic growth factors, priming and modulation of multidrug resistance are currently under investigation.

Bone Marrow Transplantation

BMT plays an essential part in intensive consolidation treatment of adult ALL (Table 3). However, the optimal strategies for the integration of BMT are as yet unsolved. For patients in first CR, an allogeneic BMT is considered either for all patients or is restricted to high-risk patients as in the GMALL studies. In patients without a donor, the role of autologous transplantation is explored in several studies in a randomised comparison with chemotherapy. The role of unrelated BMT is even less resolved but indicated for very high risk patients such as those with Ph/bcr-abl-positive ALL who have an extremely low curative chance with chemotherapy alone. Whether autologous or unrelated BMT is superior for patients without a donor remains unclear and should be evaluated in prospective trials. For practical reasons, if a donor cannot be found within a period of 3-4 months, autologous transplantation is considered.

Table 3. Recent Results of Bone Marrow Transplantation in Adult ALL.

BMT	Disease Stage	N	Relapse Incidence	LFS
Allogeneic	CR1	875	29% (10% - 50%)	45% (21% - 61%)
	CR2	104	64% (62% - 71%)	26% (15% - 41%)
	Rel./refr.	231	71% (57% - 78%)	18% (12% - 32%)
Autologous	CR1	759	57% (27% - 67%)	43% (15% - 75%)
	CR2	465	74% (69% - 88%)	28% (10% - 31%)
	Rel./refr.	27	90%	8%
MUD (mostly children)		65	16%	39% (23% - 53%)

The outcome for patients transplanted in first CR by allogeneic or autologous BMT is - surprisingly - similar. The reason is a higher treatment-related mortality in allogeneic BMT and a higher relapse rate in autologous BMT. Both give room for improvement by better supportive care and, for autologous BMT, by better purging methods. In addition, the optimal conditioning regimen for ALL, e.g., with total body irradiation or not, and to what extent the outcome is influenced by the graft-versus-leukemia effect have not yet been established.

The survival after chemotherapy for relapsed or refractory patients in adult ALL is very poor (< 5%), and all these patients are candidates for BMT. The recent approach - allogeneic BMT at the beginning of first relapse without induction therapy to avoid treatment delay, time loss by resistance to treatment therapy or complications - is under investigation and seems promising.

Conclusion

Acute lymphoblastic leukemia consists of distinct subgroups. Subgroup adjusted treatment regimens for T-ALL or B-ALL can significantly improve the outcome. In B-ALL the CR and LFS rates could not only be improved but also the duration of treatment considerably reduced from the conventional regimens of 2-21/2 years to schedules lasting only three to four months. Also in T-ALL, whether a shorter treatment period, e.g., 1 year, is sufficient has to be evaluated. Common ALL, corresponding to standard-risk children with ALL, is still a subgroup for which longer treatment (2 years) is apparently needed. For common ALL, as well as for the other subtypes, how long the optimal treatment should be can probably be based in the near future on monitoring of minimal residual disease. The role of BMT in first CR, either for all patients or for selected high-risk patients, is under investigation. In particular, it has to be determined whether autologous BMT, most probably with purging, or unrelated BMT is superior for high-risk patients without a related donor.

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