I17 Treatment of acute lymphoblastic leukemia in adults

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Recent treatment strategies in adult ALL mainly include (1) intensification of induction and consolidation chemotherapy, (2) molecular targeting, particularly in Ph/bcr abl pos- ALL, (3) antibody therapy and (4) extension of stem cell transplantation (SCT). New diagnostic tools are used to refine definition of prognostic subgroups and to develop a new risk stratification. They include (5) evaluation of minimal residual disease (MRD) and (6) microarray techniques.

Keywords: Acute lymphoblastic leukemia; Molecular targeting; Antibody therapy; Ph/bcrabl ALL; Minimal residual disease; Prognostic factors; Stem cell transplantation

Standard therapy: Standard therapy of ALL consists of intensive chemotherapy starting with induction followed by consolidation cycles and a prolonged maintenance therapy up to a total duration of $2\frac{1}{2}$ years. SCT is part of consolidation therapy in most trials. In addition prophylaxis of CNS relapse with intrathecal therapy, systemic high-dose therapy and CNS irradiation is part of the backbone of treatment in ALL (reviewed in ref. [1]).

Induction therapy: Standard drugs for induction of adult ALL are at least a steroid, vincristine and an anthracycline. Recently in many trials prednisone was replaced by *dexamethasone* (DEXA) based on pediatric results with a decreased CNS relapse rate and improved survival [2]. The DEXA schedule has to be considered carefully since continuous application of higher doses may lead to long-term complications [2] and to increased morbidity and mortality due to infections [3]. The most frequently used anthracycline is *daunorubicin* (DNR). Many groups have replaced weekly applications by higher doses of DNR (45–80 mg/m^2) on subsequent days. Promising results of smaller trials could not always be reproduced. One reason is the increased hematologic toxicity of these regimens. Thus it remains open whether intensified anthracyclines are beneficial – for all subgroups and particularly in terms of molecular remission. The application of *cyclophosphamide* up-front may be of benefit as well [4,5], although not confirmed in a randomized trial [6]. The majority of studies now include *asparaginase* (ASP) in induction therapy. Most studies use native *E. coli* asparaginase which is replaced in some trials by the prolonged-action pegylated Asparaginase. In induction ASP is often given parallel to steroids in patients with cytopenia and may induce additional toxicities such as coagulation disorders and hepatopathies. Supportive care is of increasing importance during induction – including the concomitant application of *G-CSF* throughout chemotherapy [3,5].

With current regimens the remission rate in ALL is 85–90% (Table 1) with low failure rates and a variable early mortality up to 11% increasing with age. Options for an increase of CR are limited in adult ALL. Therefore in the future an increase of molecular CR rates is the most important goal. It may be defined as a level of MRD below the detection limit of 10^{-4} (0.01%); the frequency of molecular CR in adult ALL ranges from 40% in high-risk ALL to 60–70% in standard-risk ALL.

Consolidation therapy: Intensive consolidation is standard in the treatment of ALL, although consolidation cycles in large studies are very variable and it is impossible to evaluate their individual efficacy. In general it seems that intensive application of high-dose methotrexate (HDMTX) is beneficial. From pediatric ALL trials there is increasing evidence that intensified application of ASP leads to improved overall results [7,8]. Several studies have also demonstrated that a modified induction (reinduction) improves outcome. The role of cytarabine HD anthracylines and podophyllotoxins HD in consolidation remains open. Overall in adult ALL stricter adherence to protocols with fewer delays, dose reductions and omission of drugs due to toxicities would be an important contribution to therapeutic progress.

Maintenance therapy: Maintenance even after intensive induction and consolidation is still standard

Table 1: Results of large trials in adult ALL

Study	Year	N	CR Rate	Early death	Survival
CALGB 9111, *USA* [5]	1998	198	85%	8%	40% (3 y)
LALA 87, *France* [9]	2000	572	76%	9%	27% (10 y)
NILG 08/96, *Italy* [10]	2001	121	84%	8%	48% (5 y)
GMALL 05/93, *Germany* [11]	2001	1163	83%	n.r.	35% (5 y)
JALSG-ALL93, *Japan* [12]	2002	263	78%	6%	30% (6 y)
UCLA, *USA* [13]	2002	84	93%	1%	47% (5 y)
Sweden [14]	2002	153	75%	n.r.	28% (5 y)
GIMEMA 0288, *Italy* [6]	2002	767	82%	11%	27% (9 y)
MD Anderson, *USA* [15]	2004	288	92%	5%	38% (5 y)
EORTC ALL-3, *Europe* [16]	2004	340	74%	n.r.	36%* (6 y)
LALA 94, *France* [17]	2004	922	84%	5%	36% (5 y)
GOELAL02, *France* [18]	2004	198	86%	2%	41% (6 y)
MRC XII/ ECOG E 2993, *UK-USA* [19]	2005	1521	91%	n.r.	38% (5 y)
GIMEMA 0496, *Italy* [20]	2005	450	80%	n.r.	33% (5 y)
Pethema ALL-93, *Spain* [21]	2005	222	82%	6%	34% (5 y)
Weighted mean		7262	84%	7%	35%

for ALL patients since all attempts to omit it led to inferior long-term outcome. Therefore some groups even prolong maintenance therapy beyond 2 years of total treatment duration. MTX preferably given intravenously (i.v.) and mercaptopurine (MP) given orally are the backbone of maintenance. The role of intensification cycles during maintenance remains to be determined.

CNS prophylaxis: In protocols with intensive intrathecal (i.th.) therapy and systemic HD therapy the rate if CNS relapses in adult ALL is below 5%. Only few trials still rely on CNS irradiation. However the CNS prophylaxis consisting of triple Dexa i.th. (MTX; AraC), CNS irradiation (24 Gy) and systematic HD-MTX and HD-AraC cycles leads to a reduction of the CNS relapse rate to 2% in the GMALL trial 07/03 (personal communication). Risk factors for CNS disease such as elevated WBC or LDH, traumatic lumbar punctures and phenotypes such as mature B-ALL and T-ALL are well known. Therefore risk adapted approaches to prophylaxis seem to be reasonable [15].

Targeted therapies:

Molecular therapy of Ph/BCR-ABL positive (Ph+) ALL: Similarly as in CML the bcr-abl fusion gene is the major pathogenetic factor in Ph+ ALL based on an increased tyrosine kinase (TK) activity. Imatinib is the first specific inhibitor of this mechanism. A phase-II trial demonstrated a CR rate of 29% in relapsed/refractory Ph+ ALL with Imatinib as single drug [22]. Despite the rapid development of relapse which occurs within weeks in many patients, some of them could be transferred to SCT [23] closely controlled by quantitative PCR. Treatment can generally be performed on outpatient basis and has very limited side effects.

- In *younger patients* Imatinib when given conducted with intensive chemotherapy resulted in a substantial increase in the CR rate to 90% or more in several trials. Therefore studies with parallel application of chemotherapy and Imatinib were started leading to CR rates above 91–96%. Even more impressive is that the molecular CR rates, which pre-Imatinib were less than 10%, increased to 38–50% [24,25–27]. All studies reported an improved OS of 55–65% compared to 15% in studies before the Imatinib era. No trial described increased toxicity compared to chemotherapy alone or negative effects on subsequent SCT.
- In *older patients* with de novo Ph+ ALL, treatment results were extremely poor with particularly high induction mortality. Therefore induction chemotherapy was replaced by single-drug therapy with Imatinib. The remission rate was 92% in an Italian trial [28]. The German study group (GMALL) conducted a randomised trial comparing dose-reduced chemotherapy and Imatinib monotherapy. After induction all patients received chemotherapy combined with Imatinib. The remission rate for Imatinib was 93% compared to 54% with chemotherapy [29]. The survival was superior to previous trials without Imatinib but in both arms the relapse rate was high and there was no difference in outcome.

Frequent controls of MRD often lead to early detection of molecular resistance or molecular relapse. Additional treatment can then be initiated before overt relapse. Nowadays in addition the search for mutations of the TK domain is required since these mutations confer resistance to Imatinib and partly to the 2nd-generation TK-inhibitors Dasatinib and Nilotinib [30,31]. Both drugs have increased efficacy compared to Imatinib and are active in the majority of mutations – though not in the T315I mutation. The remission rates achieved with these drugs in patients with failure to Imatinib are approximately 30%. They are currently evaluated in relapse treatment, but trials for de novo Ph+ ALL are starting.

Antibody therapy: ALL blast cells express a variety of specific antigens such as CD20, CD19, CD22, CD33 and CD52 which may serve as targets for treatment with monoclonal antibodies (MoAb). MoAb therapy is an attractive approach since it is targeted, subtype specific and compared to chemotherapy has different mechanisms of action and side effects. Application may be most promising in status of MRD. The *anti-CD20* antibody has been succesfully integrated in therapy of mature B-ALL. It is now also explored in several pilot studies for CD20-positive B-precursor ALL. In a GMALL protocol for elderly patients Rituximab is added before chemotherapy cycles starting from induction for a total of 8 applications. Also the combination of Hyper-CVAD regimen with Rituximab in B-precursor ALL was feasible and a favourable outcome of CD20 positive ALL was reported (reviewed in ref. [32]). Several studies with *anti-CD52* are ongoing, either in relapse or in status of MRD.

Stem cell transplantation (SCT): SCT has gained an increasingly important role in the treatment of adult ALL. Although the majority of large prospective studies in adult ALL addressed the issue of indications for SCT in first CR, scheduling and procedures are still not defined satisfactory. To circumvent the problem with comparability of SCT and chemotherapy several groups have invented prospective trials with a "genetic" randomisation offering allogeneic (allo) SCT in CR1 to all patients with a sibling donor. The study results certainly depend on the compared "conventional" treatment approach. Some groups scheduled autologous (auto)