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Treatment of childhood acute lymphoblastic leukemia after the first relapse: curative strategies

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Despite the intensity of first-line chemotherapy in the treatment of childhood acute lymphoblastic leukemia (ALL), this strategy is not able to cure all patients so that roughly 25% of ALL children suffer from relapse, mostly within the first 5 years from diagnosis.

Every year in Italy the AIEOP (*Associazione Italiana di Ematologia ed Oncologia Pediatrica*) registers about 80 pediatric patients who experience a first ALL relapse but in the last decade it has not been possible to set up a common strategy for treating these relapses because some controversial points need to be solved.

One of the aims of this article is to present the current opinion concerning the strategy for managing ALL relapse and to discuss the possibility of reaching a consensus on the following aspects: a) the optimal second-line treatment; b) the role of hematopoietic stem cell transplantation (HSCT); c) the possibility of designing a common relapse protocol and setting up a common data base in order to assess the results of a co-operative study homogeneously; d) the possibility of joining with other international prospective co-operative studies.

The optimal second-line treatment: rationale and general design

Results of treatment with chemotherapy in children after an ALL relapse remain unsatisfactory worldwide, especially in early relapses and in heavily pretreated patients. Only patients with a late relapse (>30 months after the diagnosis) or with an isolated extramedullary relapse have reasonable chances of cure after second-line chemotherapy. Results can be improved by allogeneic bone marrow transplantation (AlloBMT) when a suitable donor is available. Chemotherapy for first ALL relapse should thus take into account the treatment given as first-line therapy and BMT options.

Patients with ALL currently enrolled in AIEOP studies are treated with intensive chemotherapy schedules. About 80% of them are stratified as standard or intermediate risk patients; these patients receive protracted intensive chemotherapy and do not receive cranial radiotherapy unless there is a central nervous system involvement at diagnosis (<2%). High risk patients (20%) also receive intensive rotational chemotherapy and cranial radiotherapy.

Protocols used in the last decade have been very similar to BFM protocols[1,2] and thus the BFM experience in the treatment of ALL relapses provides important information for AIEOP too. Since 1983 the BFM group has been treating ALL relapses with intensive chemotherapy blocks of non-cross-resistant antineoplastic agents, cranial or craniospinal radiotherapy and maintenance therapy.[3,4] The BFM group has classified ALL relapses as very early, early or late according to time from diagnosis to relapse (< 18; > 18 and < 30; > 30 months, respectively) and has shown that about 2/3 of the small fraction of children with late extramedullary relapse and about 1/3 of those with early extramedullary relapses or late non-T marrow relapses or early combined non-T relapses can be rescued by chemotherapy; conversely, bone marrow relapses occurring earlier or with T-immunophenotype can be rescued only by BMT. The concept that after intensive front-line chemotherapy only late ALL relapses have good chances of being rescued by chemotherapy is confirmed by results obtained by other institutional or co-operative groups.[5,6]

The AIEOP approach (1998 AIEOP guidelines) for treatment of ALL relapses has been developed in this context. According to this strategy ALL relapses are defined as standard risk (non-T-ALL relapsing >30 months after diagnosis), intermediate risk (extramedullary relapses occurring <30 months after diagnosis) or high risk (bone marrow relapses occurring < 30 months after the diagnosis and all relapses of T-ALL).

The large majority of standard risk ALL relapses occur in patients treated with front-line therapies for non-high risk ALL. These patients are not heavily pre-treated and have a high probability (about 90%) of obtaining a second complete remission (CR) after a treatment with standard ALL front-line chemotherapy. According-

ly, induction therapy for standard risk ALL relapse consists of four weeks of prednisone, four weekly doses of vincristine and idarubicin, 8 doses of asparaginase (every three days) and intrathecal chemotherapy; after achieving complete remission, three intensive chemotherapy blocks are administered as consolidation therapy; in patients not undergoing BMT, treatment is continued with a reinduction phase (i.e. BFM protocol II modified in that idarubicin is substituted for daunomycin), cranial radiotherapy and maintenance with rotational combination chemotherapy[5-7] for a total treatment duration of two years.

In the AIEOP experience, patients with intermediate risk ALL relapses (early or very early extramedullary relapses) have a poor outcome and are thus treated with the same chemotherapy approach adopted for high risk ALL relapses. Induction therapy for these patiens consists of a single high dose of idarubicin (40 mg/m^2) and high dose arabinoside cytosine (ARA-C) (3 g/m^2/day x 5).[5] Seventy-four patients have been treated with this schedule with 82% of them obtaining a second CR. Early mortality and resistance rates have been respectively 10% and 8%. Although the CR rate is satisfactory, these patients have a very high probability of developing a second very early relapse. While waiting for BMT, a consolidation phase consisting of six weeks of chemotherapy (prednisone, vincristine, L-asparaginase (L-ASP), teniposide, and intrathecal therapy) used in the R11 study as induction therapy,[5] followed by three intensive chemotherapy blocks has been administered to these patients. As expected, however, 25% of the patients who achieved a second CR relapsed in this phase, suggesting that treatment used may be inadequate and that BMT should be performed as soon as possible. For patients not undergoing BMT and remaining in CR, chemotherapy after consolidation phase is continued as for standard risk patients.

The role of different types of HSCT: past, present and future

The decision to perform allogeneic matched family or unrelated donor (MFD /MUD) HSCT, autologous peripheral or marrow or cord blood HSCT depends on many factors which can be considered strong predictors of the outcome of the relapsed patients as has emerged from a number of literature reports that deserve some comments.

Sites and time of relapse

Different sites of relapse and the tempo of the relapse may be the most important factors predicting the outcome after a first relapse.

Except for late isolated extramedullary relapse (over 6 months from therapy withdrawal) in which chemotherapy alone plays a favorable role,[8-10] all other kinds of relapses (isolated/combined medullary particularly) taking place during therapy or within 30 months of the diagnosis of ALL seem to benefit more from different HSCTs than from chemotherapy.

The overall probability of disease-free survival (DFS), as derived from multicenter studies over the last 10 years, ranges from 30 to 60%[11-21] with some advantage for AlloMFD HSCT compared with other kinds of HSCT[10-20]). The AIEOP and GITMO (*Gruppo Italiano Trapianto di Midollo Osseo*) groups demonstrated a significant advantage of AlloMFD HSCT over chemotherapy only in early medullary relapse patients[18] and again an advantage in terms of DFS between AlloMFD HSCT and autologous HSCT for childhood ALL in 2nd complete remission treated with the same conditioning regimen.[20]

The difference between chemotherapy and AlloMFD HSCT for patients who experienced a late marrow relapse (45% DFS vs 65%),[15-17] i.e. over 30 months from diagnosis, was evident but not statistically significant.

In summary the current opinion is that the earlier the relapse the more difficult is to obtain and maintain a second CR. In this sense transplantation procedures should be considered as elective therapeutic options in order to eradicate a resistant disease.

Immunophenotype, cytogenetics, biologic characteristics of relapsed patients

There is no doubt that patients with T-cell ALL relapses have a poor prognosis. While any kind of chemotherapy is unsuccessful for them, some promising results can be obtained with transplant strategies following this priority cascade: AlloMFD HSCT, MUD or Haplo HSCT, cord blood HSCT, autologous HSCT.

One biological predictor of negative outcome could be the number of peripheral blood blast cells ($\geq$ 1/µL to <10,000 µL or >10,000 µL) at the time of relapse according to POG or BFM group experience[4,6] so that one could justify AlloMFD or MUD HSCT even in patients with late relapse. On the other hand the absence of peripheral blast cells at relapse has been associated with a 10-year event-free surivival (EFS) of 64% suggesting that these patients are not candidates for HSCT.[22]

The MLL rearrangement or a BCR-ABL positive relapse makes patients elective candidates for the above cascade of HSCT due to the documented particularly poor prognosis in patients treated by chemotherapy only.[23] Tel-AML1 fusion, the molecular characteristic of approximately 25% of B-lineage ALL patients at diagnosis,[24] should be otherwise considered as a good outcome marker even in relapsed patients. This particular subset of patients experience very late relapse, and get and maintain an excellent 2nd CR undergoing chemotherapy only.

Availability and role of MUD HSCT compared with other HSCTs

AlloMFD HSCT is currently a limited transplant option because only 20 to 30% of relapsed patients have an HLA A-B and DR identical sibling donor. HSCT from a MUD has become a feasible procedure capable of curing a significant proportion of children with ALL and lacking an HLA identical family donor.

Recently Balduzzi,[25] Davis,[26] Oakhill,[27] Heslop[28] and

others reported a 2-3 year EFS between 40% to 53% for ALL children in 2nd CR treated with MUD HSCT.

In particular in Oakhill's study there was no significant difference in outcome between patients who received fully matched unrelated marrow and those who received partially mismatched marrow. The study by Heslop *et al.* demonstrated that there was no difference between ALL relapsed children undergoing AlloMFD HSCT and MUD HSCT.

All these studies reported the outcome of selected cohorts of patients with ALL who actually received a MUD HSCT. Recently the AIEOP reported on the outcome of 192 consecutive children with 2nd CR ALL for whom the search for a MUD was activated. One of the aims of this study was to overcome the biases related to the allocation of patients to different therapeutic options.[29] The probability of finding a MUD within 6 months after search activation was 21% (SE 5) and 37% (SE 5) before and after 1995, respectively ($p = 0.01$). The major obstacle to the success of the search was a second relapse. The 6-month probability of relapse during the search was 39% (SE 3.9). Treatment effectively assigned to patients was dependent not only on donor availability, but also on the course of the disease during the search: 83 out of 192 children found a MUD but only 73 were given a MUD HSCT; the remaining 10 children lost their eligibility to this procedure because of progressive disease and died. Nineteen out of the 73 (38%) children undergoing a MUD HSCT survived in complete remission. Of the 109 patients who did not find a suitable donor, 70 underwent chemotherapy alone but only 5 of them (7%) survived without leukemia, while the remaining 39 children were given other types of HSCTs and only 13 of them survived in complete remission.

Recently, cord blood HSCT has been shown to be feasible and has yielded some encouraging preliminary results.[30,31]

In this setting the evidence of quite similar results between cord blood HSCT and MUD HSCT, when applied to patients with malignancies, is particularly interesting.

For selected relapsed patients for whom AlloMFD HSCT or MUD HSCT is not possible, autologous HSCT may offer a chance of cure. Retrospective single center studies[32] demonstrated the efficacy of autologous HSCT for late relapsed B-precursor ALL (over 2 years from diagnosis) with a 3-year EFS of 53% and the same result was confirmed afterwards by the same group[33] when autologous HSCT was compared with AlloMFD HSCT (53% EFS vs. 47%).

Autologous HSCT for ALL children in 2nd CR performed by the AIEOP group[34] yielded an 8-year EFS of 34% indicating, also by univariate analysis, an advantage for isolated extramedullary relapse vs BM relapse (68% EFS vs 18%) and for patients undergoing total body irradiation (TBI) conditioning regimens vs. no TBI (48% EFS vs 15%).

An Italian single center study[35] recently demonstrated a promising result in ALL children in 2nd CR when rescued both with autologous HSCT and a particularly efficient purging technique such as monoclonal antibodies and double selection of CD34 peripheral blood stem cells: the PCR negative infused product gave a 2-year probability of EFS of 89%. Our experience addresses the possible advantage of autologous HSCT procedures when additional modifications of autografting methods, including *in vitro* purging or post-transplant immunomodulation, are applied.

A BFM matched–pair analysis in childhood ALL in 2nd CR treated by autologous HSCT and chemotherapy demonstrated an overall 9-year EFS of 32% vs. 26%[36] Multicenter retrospective studies comparing MUD HSCT vs. autologous HSCT[37,38] in a mixed 2nd CR ALL series (adults and children) came to controversial conclusions due to the excessive toxicity in unrelated transplantation which limited the apparent superiority of this former procedure vs autologous HSCT.

Recently it has been reported that matching HLA class I and class II alleles of the donor and recipient can significantly improve the outcome after MUD HSCT,[39] but the best transplantation strategy is to carry out this transplant, possibly within 3-4 months from the beginning of the search. This is the reason why, in the absence of a fully compatible donor, a one antigen mismatched donor is acceptable too.[40] If no MUD or cord blood units are available within 3 to 5 months from the beginning of the search , a haploidentical HSCT should be offered to patients who are in second remission after an early relapse.

Pre- and post-HSCT factors which can play some role in the outcome of childhood ALL in 2nd CR

The quality of 2nd CR obtained after an intensive second line therapy remains the golden standard for applying successfully whatever subsequent consolidation therapy (chemotherapy or any kind of HSCT). Molecular monitoring of minimal residual disease is now available and could have an important role in future strategies for treating relapses.[41]

Transplant procedures such as conditioning regimens including total body irradiation together with high doses of several drugs (cytoxan, VP-16, Ara-C, vincristine) should be tested in multicenter prospective and/or randomized studies in order to understand the role of different drugs in eradicating the leukemic clone.

Careful evaluation of the best conditioning regimen to adopt should be done by transplant teams in order to lessen so-called transplant-related mortality and late effects. In this respect, continuous improvement of support treatment over the last 10 years seems to have provided better results in terms of short- and long-term quality of life, and indeed non-myeloablative regimens represent a recent field of interest in order to decrease transplant toxicity and mortality in particular subsets of patients.

Recently some clinical studies have shown that allogeneic engraftment can be accomplished by non–myeloablative regimens based predominantly on fludarabine and/or low–dose TBI.[42] These experiences are giv-

ing rise to the concept that allogeneic non-myeloablative transplants are much better tolerated than standard conditioning regimens, both in adults and in children. Limited toxicity, prompt engraftment, and stable and full chimerism were obtained in more than 90% of the recipients. To date this approach has been adopted in advanced stages of malignant diseases and in heavily pretreated patients; for these reasons its real capacity to control the underlying disease has been probably underestimated. The few data concerning patients with early relapse and minimal residual disease are more interesting and similar to the data obtained with myeloablative regimens.[43,44] One can hypothesize that children with late medullary relapse or isolated extramedullary relapse and an HLA identical family donor might undergo a non-myeloablative regimen.

Last but not least an emerging favorable factor in transplantation strategy could be the increase of graft-versus-leukemia effect, which has also been demonstrated by the AIEOP group,[45] by the immunomodulatory effect of the graft-versus-host in the early post-transplant phase. The possibility of eradicating minimal residual disease was in fact demonstrated in patients receiving low dose cyclosporin A (CyA) vs. standard dose CyA as graft-versus-host disease (GVHD) prophylaxis which resulted in a decrease of the overall relapse rate.

Possibility of setting up a common relapse protocol and data base for the AIEOP group

During the last 10 years the first line treatment for children with newly diagnosed ALL has been administered according to three consecutive AIEOP protocols, which adopted BFM-based chemotherapy.[46-48] Between January 1988 and April 1998, 3,015 consecutive children were centrally registered at diagnosis and followed up yearly. By December 1999, 857 consecutive children had experienced an event, including in 581 cases an isolated bone marrow relapse. In most cases salvage treatment was given on the basis of single institution decisions according to either AIEOP or BFM guidelines for treatment of relapsed patients.[3, 49-51] If, in the future, we can set up a common relapse protocol it will be easier for the AIEOP Registry to collect data prospectively on relapsed patients[52,53] and possibly improve the results.

The principal eligibility criteria for entering such a study should be the attainment of second CR after a common relapse protocol. Subsequently, a treatment arm such as chemotherapy or any kind of HSCT should be assigned according to common decisions based mainly on time from diagnosis to relapse and on site of relapse. Such a collaborative study requires a good relationship between clinicians involved in the front-line protocols and in the transplantation program.

Possibility of joining with other international study groups for a common co-operative relapse study

In 1996 the Pediatric Working Party of the *European Group for Bone Marrow Transplantation* (EBMT) reached a consensus on HSCT indications for childhood ALL.[54] The need for a prospective relapse study in childhood ALL is urgent and this is the reason why the EBMT and the I-BFM-SG tried to set up this kind of project last year. The common eligibility criteria and the common conditioning regimen to apply for AlloBMT patients constitute the principal conditions for entering patients in this study. The priority *cascade* of different kinds of transplantations (AlloMFD, MUD, haploidentical, cord blood and autologous HSCT) should be accepted by all the participating centers in order to validate all the results coming from different procedures according to an intention-to-treat analysis. A common data base is going to be set up and should pool some relevant information on all the patients eligible for the relapse protocol so that each group will periodically provide the basic data to the co-ordination unit in order to make the data management feasible. The principal aim of a co-operative prospective study of this type should be to avoid many different experiences which can result in a waste of time and effort. We think that the actual existence of co-operative study groups such as the EBMT, I-BFM-SG and AIEOP will allow this common relapse study to be carried out successfully as were the studies on myelodysplastic syndromes and childhood very high risk ALL in first CR.

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Editorial note

A workshop on *Hematopoietic stem cell transplantation in pediatric oncologic-hematologic and autoimmune diseases* was held in Trieste, Italy, on November 24-25, 2000. The journal supplement containing all presentations[1-17] is available at our website at the URL: http://www.haematologica.it/trieste.html; a hard copy is available free of charge upon request through our editorial office.

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