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13

Hematopoietic Stem Cell Transplantation for Adult Acute Lymphoblastic Leukaemia

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1. Introduction

The most recent clinical trials on adult acute lymphoid leukaemia (ALL) have shown complete remission and disease-free survival (DFS) rates of 80-85% and 30-40%, respectively (Annino, *et al*, Durrant, *et al*, Kantarjian, *et al*, Larson, *et al*, Ribera, *et al*, Rowe). Intensified consolidation, particularly with high-dose methotrexate and high-dose cytarabine, may be one of the reasons for the improved outcome in recent series (Bassan and Hoelzer, Hoelzer and Gokbuget, Kebriaei and Larson). In addition, risk-adapted and subtype-oriented therapy may have contributed to this better outcome. However, the long term outcome of adult patients is still dismal, with approximately one third of the cases only being cured. At present, therapeutic options include conventional chemotherapy (CHT), high dose therapy with autologous and, especially, allogeneic stem cells transplantation (SCT) and, for certain subsets, such as *BCR-ABL1*$^+$ ALL, specific targeted therapy (Piccaluga, *et al*).
Although SCT has been used in adult ALL for more than 20 years, its role remains controversial as demonstrated by conflicting results in various studies. Previous case-controlled studies did not show that allogeneic SCT (alloSCT) provided any advantage over CHT (Horowitz, *et al*, Zhang, *et al*) while in some studies there was an advantage, but restricted to young adults (Oh, *et al*). The number of controlled published or ongoing trials is remarkably small and some of them did not include both standard-risk and high-risk patients. Thus, it is difficult to draw definitive conclusions from their results. In fact, while some authors did not report any differences between alloSCT and chemotherapy or autologous SCT (ASCT)(Gupta, *et al*, Labar, *et al*), others only found differences favouring allogeneic SCT in standard risk (Goldstone, *et al*) or high-risk ALL patients (Sebban, *et al*, Thiebaut, *et al*, Thomas, *et al*).

In this article, the Authors reviewed data concerning alloSCT in adult ALL and discuss current controversial and possible perspectives.

2. Rationale for allogeneic SCT: the graft versus leukaemia effect in ALL

Initial studies were conduced in patients with advanced stage disease, aiming to overcome drug resistance by intensifying the dose of CHT and rescuing patients with syngeneic or allogeneic haemopoietic stem cells (SC) (Fefer, *et al*, Thomas, *et al*). In the first study, 16 patients with refractory ALL received high dose therapy followed by infusion of syngeneic bone marrow (Fefer, *et al*). Six out of these patients achieved a durable remission, demonstrating the efficacy and the potential curative effect of high dose therapy in ALL. On the other hand, the role of donor-derived immunologic anti-leukaemic effect - so called "graft versus leukaemia" (GVL) effect – was first established in animal models (Chester, *et al*). The first evidence of GVL effect in humans was actually demonstrated in ALL patients treated with alloSCT (Mathe, *et al*, Thomas, *et al*). In this series, patients who developed grade ≥2 graft versus host disease (GVHD) had a significantly lower relapse rate after transplant if compared with patients with grade 1 or no GVHD or with those who received syngeneic bone marrow ($p<0.01$). Subsequent studies further underlined this phenomenon (Doney, *et al*, Horowitz, *et al*, Lee, *et al*), although its relevance is less convincing than in myeloproliferative diseases such as chronic myeloid leukaemia, or chronic lymphoproliferative disease and possibly lymphomas.

3. Designation of risk factors in ALL

There is a considerable variation in the relapse risk which can be predicted by various risk factors (Table 1) (Hoelzer D 2002, Moorman, *et al*), including unfavourable cytogenetics,

	Good	*Adverse*
Age	15-35* 35-50	>50-60
WBC at diagnosis	<30x10^9/L (B-ALL) <100x10^9/L (T-ALL)	>30x10^9/L (B-ALL) >100x10^9/L (T-ALL)

Cytogenetics	del(9p)
	high hyperdiploidy
		t(9;22);
		t(4;11);
		t(8;14)
		hypodiploidy/almost triploidy
		complex karyotype

Time to CR	< 4 weeks	> 4 weeks
Immunophenotype	Pre-B Common Thymic	Pro-B Pro-T Pre-T Mature T
MRD	Negative Stable during follow up	Persistent (≥10^{-3}) after induction Increasing during treatment/follow up

* Special benefit appear to be related in this group to the application of paediatric (i.e. intensified) regimens
** intermediate prognosis
WBC = white blood cells

Table 1. Prognostic factors in adult ALL

poor/slow response to induction CHT, leukocyte count at diagnosis and phenotype. Accordingly, patients can be stratified as standard-risk (no risk factors) or high risk (one or more risk factors) with 45-60% vs less than 30% DFS, respectively (Hoelzer D). In particular, detection of minimal residual disease (MRD) after treatment was shown to be associated with impending relapse, independent of any other risk factor (Bassan, *et al*, Mortuza, *et al*)(Gazzola A et al, submitted). According to some investigators the status of MRD may be sufficient for stratification and the role conventional clinical risk factors appears questionable. [29]

4. Preparative regiments

4.1 Ablative regimens

Conditioning regimens used for alloSCT must ideally: 1) achieve adequate immunosuppression of the recipient to prevent rejection of the donor SC, and 2) destroy residual malignant cells while causing minimal toxicity. Most preparative regimens for ALL use total body irradiation (TBI) and cyclophosphamide (Cy) while some centres use etoposide and cytosine arabinoside (Ara-C) in addition to or instead of Cy. Busulphan-cyclophosphamide (BU/Cy) has also been used to avoid radiation but an IBMTR study showed an inferior outcome with this regimen with a 3-year probability of DFS of 35% versus 50% when TBI and Cy were used (Davies, *et al*). Because most chemo-radiation regimens are at the limits of toxicity, any further dose escalation in an attempt to reduce the risk of relapse would probably increase the regimen-related toxicity to unacceptable levels, particularly in older or heavily pretreated patients. The addition of biological agents like monoclonal antibodies or radioconjugates to conventional conditioning regimens can potentially provide an augmented anti-leukaemic effect without increasing treatment related toxicity.

4.2 Non-myeloablative regimens

High-dose CHT and alloSCT carry substantial treatment related morbidity and mortality in older patients (>50 years), those with compromised organ function (e.g., congestive heart failure), coexisting infections, or those who were heavily pre-treated prior to SCT. In all of these patients, treatment-related mortality can exceed 50%, making them ineligible for SCT. More recently, new strategies for allografting have explored an approach of less intensive conditioning therapy with the aim of allowing partial engraftment of donor immune and haematopoietic systems with eventual replacement of the host's own haematopoiesis and immunity. A variety of regimens based on low-dose TBI or fludarabine are increasingly used (Giralt, *et al*, Khouri, *et al*, Slavin, *et al*, Storb, *et al*). Such reduced intensity conditioning (RIC) regimens may be more suitable for patients with indolent malignancies where there is sufficient time for a graft versus malignancy effect to operate. Patient with acute leukaemia who have active disease transplanted with non-myeloablative regimens have a high relapse rate. Another major problem with submyeloablative regimens is an increased rate of graft failure ranging from 5% to 30% versus 1% to 5% in patients undergoing full myeloablation prior to alloSCT. The use of lymphodepleting antibodies or a combination of monoclonal antibodies in addition to cytotoxic or immunosuppressive drugs could potentially decrease rejection rates (Brenner, *et al*, Kottaridis, *et al*).

Examples of preparative regimens used in ALL are summarized in Table 2.

Author	Regimen
Thomas et al 1982	Cy 120 mg/Kg + TBI (SD 10 Gy)
Vitale et al. 1983	Cy 120 mg/Kg + fractioned TBI (2 Gy x6)
Tutschka et al. 1987	BU 16 mg/Kg + Cy 120 mg/Kg
Blume et al. 1993	Etoposide/TBI vs. BU/Cy
Rowe et al. 2001	Etoposide/TBI
Bieri et al. 2001	TBI at different doses*

BU = busulfan; Cy = cyclophosphamide; SD = single dose

* retrospective comparison

Table 2. Examples of preparative regimens adopted in ALL

5. Allogeneic stem cell transplantation for Ph-negative ALL

Many factors need to be considered before recommending alloSCT including:
1. Cure rate with conventional CHT;
2. Transplant related mortality (TRM) and morbidity;
3. Cure rate with alloSCT.

As TRM and cure rates strongly depend on the disease phase at the time of transplant, different phases will be considered separately in our description.

5.1 Acute lymphoid leukaemia (ALL) in first remission

As the risk of transplant related mortality needs to be balanced against potential cure with standard CHT alone, alloSCT as post-consolidation therapy is favoured in patients who are at a high risk of relapse after standard CHT. While in children the likelihood of cure with modern intensive CHT range is 70–80% (Pui and Evans), in adults with ALL the cure rate with CHT is only 25–40% and, despite the intensification of CHT regimens, the majority of patients will relapse and die of their disease (Bassan and Hoelzer). In particular, the presence of any risk factor (Table 1) reduces the chance of long-term DFS with CHT to between 15% and 25%, making the patient a candidate for allografting in first remission (CR1). In fact, alloSCT in CR1 was suggested to provide a better anti-leukaemic effect and to improve patients' outcome compared with a conventional post-remission CHT regimen.

Retrospective studies evaluating the role of alloSCT in CR1 were encouraging with DFS ranging between 40 and 63% and relapse rates of 10-40% (Barrett, *et al*, Blume, *et al*, Blume, *et al*, Chao, *et al*, De Witte, *et al*, Thomas, *et al*, Vernant, *et al*, Vey, *et al*). However, most of the studies were small (with less than 50 patients each) and were limited by selection bias (see Table 3 for details). In addition, few studies retrospectively compared alloSCT vs. autologous SCT (ASCT) or CHT in ALL performed in CR1. None of these studies showed an improved survival in transplanted patients (Table 4). In particular, Horowitz and Colleagues, on behalf of the IBMTR, reported the outcome of adult ALL patients (aged 15-45 years) treated with intensive CHT (IC, N=484) vs. allogeneic SCT (N=251) in CR1 (Horowitz, *et al*).

Allografted patients had significantly reduced risk of relapse (26% vs. 59%). However, the DFS was not superior after SCT, reflecting the higher mortality rate observed after SCT (38% vs. 4%) (Horowitz, *et al*).

Author	Number of patients/ characteristics	Age	GVHD grade 2-4 (%)	TRM (%)	RR (%)	5-y DFS (%)
Blume et al. 1987	38	16-41	31	26	16	63
Vernant et al. 1988	27	15-36	44	30	11	59
Barrett et al. 1989	243	16-48	40	37	30	39
Chao et al. 1991	53/high risk	1-45	11	28	10	61
Vey et al. 1994	29	16-41	27	29	10	62
De Witte et al. 1994	22/high risk	15-51	NA	23	23	58

GVHD=graft versus host disease
TRM=transplant related mortality
RR=relapse risk
5-y DFS=disease free survival at 5 years

Table 3. Retrospective non-comparative studies considering alloSCT in ALL

Only few studies prospectively compared alloSCT to other post-remission strategies in ALL (Table 4) (Attal, *et al*, Fielding, *et al*, Fiere, *et al*, Goldstone, *et al*, Hunault, *et al*, Rowe, Sebban, *et al*, Thiebaut, *et al*), (Labar, *et al*). The BGMT group conduced a prospective trial evaluated alloSCT vs. ASCT in CR1. According to *genetic randomization*, patients with (n = 43) or without an HLA-identical sibling (n = 77) were assigned to receive allogeneic or autologous SCT, respectively. The 3-year post-CR probability of DFS was significantly higher in the HLA-identical sibling group than in the non-HLA-identical sibling group (68% v 26%; P<0.001) (Attal, *et al*). Recently, the 10-year follow-up results confirmed the marked superiority of alloSCT to CHT in terms of survival (44 vs 11%, P=0.009)(Marks, *et al*).
The prospective randomized LALA87 trial compared alloSCT vs. ASCT/CHT. Patients aged 15-40 years who achieved CR and had a matched related donor were assigned to allograft, whereas those without a donor were randomized to receive ASCT vs CHT. Seventy-six percent (436/572 evaluable patients) achieved CR. Intention to treat analysis, comparing patients assigned to alloSCT (N=116) vs. ASCT/CHT, showed increased survival in allografted patients (10 years overall survival – OS- 46% vs. 31%, p=0.04). In high risk patients, the advantage was more evident (44% vs. 115, p=0.009). On the contrary, standard risk patients did not significantly benefit from SCT (p=0.06) (Thiebaut, *et al*).
The GOELAL02 trial evaluated the impact in high risk ALL patients of early alloSCT or delayed unpurged ASCT for patients who had no HLA–matched sibling donor or who were older than 50 years. Among 198 patients, the median age was 33 years. The CR rate was 80% with standard induction therapy. AlloSCT was performed after 2 consolidation courses while ASCT was delayed after 1 additional reinduction. Intensified conditioning regimen before transplantation included etoposide, cyclophosphamide, and total body irradiation (TBI). Median follow-up was 5.1 years. The median overall survival (OS) was 29 months, with a 6-year OS of 41%. On an intent-to-treat analysis for patients younger than 50 years, alloSCT significantly improved the 6-year OS (75% versus 40% after ASCT; *P* = .0027). On the other hand, randomized interferon-α maintenance had no effect on relapse or survival after ASCT (Hunault, *et al*).

In the EORTC ALL-3 study, Labar and collegues evaluated the role of alloSCT based on a genetic randomization.(Labar, *et al*). Patients achieving CR and having an HLA-identical sibling were intended for alloSCT after completion of consolidation while the remaining ones were randomized to receive either ASCT or maintenance. Among 68 patients in the donor arm the transplantation was performed in 47 cases. According to the intention-to-treat analysis the incidence of relapse at 6 years was decreased (38% vs. 56%) while the incidence non-relapse mortality increased (24% vs. 7%) in the "donor" compared with "no donor" arm. The probability of DFS was superimposable (38% vs. 37%, respectively). Among 116 patients lacking a donor only 45 were randomized making the vs. maintenance comparison statistically underpowered.

Recently, Ribera and Colleagues reported on 222 high risk ALL patients enrolled in the PETHEMA ALL-93 trial (Ribera, *et al*). All received a standard five-drug/five-week induction course. Patients in CR with an HLA identical family donor were assigned to alloSCT (n=84) and the remaining were randomized to ASCT (n=50) or to delayed intensification followed by maintenance CHT up to 2 years in complete remission (n=48). Overall, 183 patients achieved complete remission (82%). With a median follow-up of 70 months, the median DFS and OS were 17 and 23 months, respectively. The 5-year DFS and OS were 35% (95% CI, 30%- 41%) and 34% (95% CI, 28%-39%), respectively. Patients allocated to the CHT, allogeneic and autologous SCT were comparable in the main pre-treatment ALL characteristics and the rate of response to therapy. Intention-to-treat analysis showed no differences between patients according to whether they had or did not have a donor in DFS (39%, 95% CI 30-48% vs. 33%, 95% CI 23-41%) and OS (44%, 95% CI 35- 52% vs. 35%, 95% CI 25-44%), as well as for autologous SCT vs. CHT comparisons (DFS: 40%, 95% CI 28-52% vs. 51%, 95% CI 37-67%; overall survival: 43%, 95% CI 29-58% vs. 52%, 95% CI 39-65%). No differences were observed when the analysis was made on the basis of the treatment actually performed (Ribera, *et al*).

More recently, the final results of the MRC UKALL XII/ECOG 2993 protocol were available, regarding a large prospective randomized study aiming to establish the best post-remission therapy for adult ALL (Avivi and Goldstone, Rowe, *et al*, Rowe). In this study, patients (N=1,646) received 2 phases of induction and, if in remission, were assigned to allogeneic transplantation if they had a compatible sibling donor. Other patients were randomized to chemotherapy for 2.5 years versus an ASCT. A donor versus no-donor analysis showed that Ph- patients with a donor had a 5-year improved OS (53% versus 45%; p = .01), and the relapse rate was significantly lower (p ≤ .001). The survival difference was significant in standard-risk patients, but not in high-risk patients due to a high treatment related mortality (TRM) in the high-risk donor group. Interestingly, patients randomized to chemotherapy had a higher 5-year OS (46%) than those randomized to autologous transplantation (37%; p = .03) (Goldstone, *et al*). Importantly, a dedicated analysis was carried on Ph+ cases (N=267) (Fielding, *et al*). In this setting, in the comparison of the outcome after any alloSCT with the outcome after chemotherapy alone, OS (p = .001), EFS (p < .001), and RFS (P < .001) were all significantly superior for patients receiving any alloSCT over those receiving chemotherapy alone. Of note, there was a marked difference in the cause of death between alloSCT and chemotherapy recipients. Whereas the leading cause of death in chemotherapy treated patients was relapse, the leading cause of death after transplantation was TRM, which was 27% after sibling-SCT and 39% after VUD-SCT (Fielding, *et al*).

Author	Post-remission therapy	Number of patients	Age	TRM (%)	RR (%)	5-y DFS
Blaise et al. 1990	Allo vs. Auto	25 vs. 22	4-36 vs. 7-47	20 vs. 9	9 vs. 57	71 vs. 40
Horowitz et al. 1991	Allo vs. CHT	234 vs. 484	15-45 vs. 15-45	39 vs. 4	26 vs. 59	44 vs. 38
Attal et al. 1995	Allo vs. Auto	43 vs. 77	15-55 vs. 15-55	12 vs. 2	12 vs. 62	68 vs. 26 (3-y)
Oh et al. 1998	Allo vs. CHT	127 vs. 38	<30	32 vs. 3	22 vs. 69	30 vs. 30
	Allo vs. CHT	87 vs. 38	>30	NA	37 vs. 70	30 vs. 26
Fiere et al. 1993	Allo vs. Auto vs. CHT	116 vs. 95 vs. 96	15-40 vs. 15-50	18	37	46 vs. 39 vs. 32
Fiere et al.1998	Allo vs. Auto vs. CHT	116 vs. 95 vs. 96	15-40 vs. 15-50	NA	NA	46 vs. 34 vs. 30
Rowe et al. 2001	Allo vs. Auto/CHT	190 vs. 253	15-50 vs. 15-50	NA	24 vs. 60	52 vs. 36
Hunault 2004	Allo vs. Auto*	41 vs. 115	15-52 vs. 15-57	15 vs. 3	10 vs. 49	75 vs. 38
Labar et al. 2004	Allo vs. (Auto or CHT)	68 vs. 116	<50	24 v.7	38 vs. 56	38 vs. 37
Ribera et al. 2006	Allo vs. Auto vs. CHT	84 vs. 50 vs. 48	16-49 vs. 15-50 vs. 15-50	8 vs. 3 vs. 0	62 vs. 57 vs. 46	44 vs. 54 vs. 45
Goldstone et al. 2009	Allo vs. CHT/ASCT	443 vs. 588	<54 vs. < 64	36-20% vs. 14-7%	24% vs. 49%	53% vs. 45%§

* early alloSCT vs. delayed ASCT
TRM=transplant related mortality
RR=relapse risk
5-y DFS=disease free survival at 5 years
§ Overall survival

Table 4. Studies comparing alloSCT vs. CHT/ASCT in ALL

5.2 ALL in second remission

More than 50% of adult ALL patients will relapse after initial CR. Half of these patients will actually obtain a second CR (CR2) following re-induction therapy. However, CR2 is not durable and only less of 10% of the patients will be cured with CHT or ASCT. By contrast, DFS after alloSCT performed in CR2 approaches 25-38% (Avivi and Goldstone, Herzig, *et al*, Thomas, *et al*). Indeed, alloSCT appears to be the best option for patients in CR2, irrespectively of the initial risk factors. However, unfortunately, no randomized trials compared alloSCT and CHT in this setting. Noteworthy, the outcome of alloSCT in CR2 is also affected by CR1 duration, being definitely better when CR1 was longer than 24 months (Forman, Kersey, *et al*, Thomas, *et al*).

5.3 ALL after second relapse or primary induction failure

Once patients are beyond second remission, the results of all allografting procedures worsen considerably, with only 10–15% of patients becoming long-term disease-free survivors (Goldman, *et al*, Storb, *et al*). Similarly, the outcome with transplant is poor with only 10–

15% DFS for patients who fail primary induction therapy. However, though these results are not brilliant, SCT still offers the only prospect of cure (Biggs, *et al*). Biggs et al reported 23% DFS in 38 ALL patients treated with alloSCT for primary induction failure disease; the 3 years probability of persistent/recurrent disease was 59% (Biggs, *et al*). The result is, however, encouraging with almost one quarter of patients rescued after initial treatment failure. On the other hand, it should be considered that 26% of the cases in this study were aged under 19 years (and 8 less under 10) and 39% achieved a partial remission before transplant. TRM was significantly higher in patients older than 30 years or with poor performance status (PS). Thus, it appears that 10-20% of patients who fail to achieve CR after induction can benefit from alloSCT; however, patients to be referred to this procedure should be carefully selected basing on age and PS.

6. Stem cell transplantation for Ph+ ALL

The presence of Ph chromosome is one of the most relevant adverse prognostic factors in ALL. To date, alloSCT is the unique approach which can be considered as potentially curative, thus being the treatment of choice in adult Ph+ ALL (Avivi and Goldstone, Barrett, *et al*, Chao, *et al*, Dombret, *et al*, Fielding, *et al*, Ottmann and Pfeifer, Piccaluga, *et al*, Piccaluga, *et al*). Twenty-seven to 65% long-term survival has been reported for patients undergoing alloSCT in first complete remission (CR1), (Avivi and Goldstone, Fielding, *et al*). Unfortunately, relapse occurs in approximately 30% of patients, representing the primary cause of treatment failure together with treatment-related mortality, which increases with age and advanced disease (Avivi and Goldstone, Martin and Gajewski). Achievement and maintenance of a CR prior to SCT is an important prerequisite for a favourable outcome after SCT (Wassmann, *et al*). In fact, when performed further than first remission, only a small minority of patients can be cured by alloSCT; nevertheless, in such cases, although

Author	N	TRM	REL	Outcome
Barret et al, 1992	33 22	42% 40%	34% 32%	38% at 2 years (DFS) 41%
Chao et al, 1995	38	NA	NA	46% (CR1) at 2 years (DFS) 28% (>CR1)
Snyder et al, 1999	23	30%	12%	65% at 3 years (DFS)
Goldstone et al, 2001	72	37% (Sib) vs 43% (VUD)	32%	42% at 5 years (DFS)
Dombret et al, 2002	56	25%	37%	37% at 3 years (OS)
Fielding et al, 2009	267	27% (Sib.) vs. 39% (VUD)	32%	41%-36%* at 5 years (EFS) 44%-36%* at 5 years (OS)

N= number of patients
TRM= transplant related mortality
REL= relapse rate
DFS= disease free survival
CR1= first complete remission
* Sibling donor vs. VUD

Table 5. Results of allogeneic stem cells transplantation in adult Ph+ ALL

the probability of success is limited, alloSCT may be still curative in a subset of patients and it remains the treatment of choice (Garcia-Manero and Thomas). The probability of DFS (DFS) at 2 years after alloSCT in second or third remission or as salvage therapy for refractory disease has been reported to be 17% and 5%, respectively (Cornelissen, *et al*). In patients failing allogeneic SCT, further treatment is rarely successful. With this regard, the availability of novel tyrosine-kinase inhibitors (TKI), including imatinib, dasatinib and nilotinib, has became of great interest (Piccaluga, *et al*). In fact, TKI either can be added to CHT potentially increasing the number of patients to be referred to alloSCT in CR1 (Wassmann, *et al*), and constitutes a possible salvage treatment in case of relapse after alloSCT (Olavarria, *et al*, Wassmann, *et al*).
Results with allogeneic stem cells transplantation are summarized in Table 5 (Avivi and Goldstone, Barrett, *et al*, Chao, *et al*, Fielding, *et al*, Snyder, *et al*).

7. Source of stem cell for allogeneic transplantation

7.1 Bone marrow versus mobilized peripheral blood

Cytokine-mobilized allogeneic peripheral blood stem cell (PBSC) harvest has become an alternative to bone marrow as a source of stem cells for matched-sibling transplants. Early phase II studies showed that this source of stem cells resulted in faster engraftment, no increase in acute GVHD (perhaps due to a G-CSF-mediated shift to Th2 helper cells) but an increased incidence of chronic GVHD (Bensinger, *et al*, Korbling, *et al*). A prospective randomized study of allogeneic PBSC compared to marrow showed a 2-year actuarial overall survival of 54% in patients receiving marrow compared with 66% in those receiving PBSCs (Bensinger, *et al*). Differences in survival were significant for patients with unfavourable-risk diseases but not for those with favourable-risk diseases (Bensinger, *et al*). Faster engraftment, similar GVHD and improvement in overall survival was also reported in a Canadian and New Zealand study (Couban, *et al*). In a retrospective multivariate analysis from the IBMTR comparing the results of 288 HLA-identical sibling blood stem cell transplants with the results of 536 HLA-identical sibling bone marrow transplants, the relapse incidence between the two transplant groups did not differ significantly (Champlin, *et al*). However, treatment-related mortality rates were lower and leukaemia-free survival rates were higher with use of blood stem cell transplants in patients with advanced versus early leukaemia (Champlin, *et al*). While the results of more studies should become available over the next few years, the current experience suggests that peripheral blood should be the preferred source of stem cells for patients with high-risk disease and/or advanced phase. For patients with low-risk disease, the increased risk of chronic GVHD needs to be balanced against the risk of relapse.

7.2 Alternative donor sources

Most patients do not have a suitable histocompatible sibling donor for an allograft and the use of alternative donors such as voluntary unrelated donor (VUD), haploidentical donor and umbilical cord blood (UCB) grafts. As regards VUD, the results are actually comparable to those obtained with matched sibling donors and many groups routinely refer to this source for patients in CR1. Conversely, to date, the other two options have been mainly reserved for patients in ≥CR2. Few large-scale studies compare these forms of alternative donor transplantation and the choice of stem cell source will also be influenced by clinical

urgency and the time taken to procure haematopoietic stem cells. Single centre results must be analysed carefully when deciding what plan to recommend in the individual patient.
If a matched donor is not available, some data indicate that a single antigen mismatched family donor allograft may result in the same outcome as using a matched UD, but a perspective randomized comparison has never been performed. In general, if there is no molecularly matched UD, then a single allele mismatched UD, an UCB donor or a haploidentical stem cell donor could be considered as possible alternative (Marks, *et al*).
In this regard, few small studies focused on the use of UCB in ALL, and basing on these data it is difficult to advise investigators how to approach potential patients. Small patient numbers, heterogeneity of remission status, variability of matching and incomplete information about UCB cell dose make data summary difficult. In general, these results are promising, but relapse remains a significant issue as well as does engraftment failure. Somewhere between 20 and 50% of patients in CR1 and an occasional CR2 patient can become long-term survivors. Double UCB transplants or intra-bone SC infusion (Castello, *et al*) may represent an advance, particularly addressing the issue of engraftment.
Haploidentical transplant have the major advantage of donor availability and results have been possibly improved. In particular, the high rejection rate and incidence of severe GVHD are reduced by combining high-intensity conditioning and an infusion of a large dose of purified SC in adult ALL patients transplanted in CR1 or CR2. These data, however, have not been corroborated in multi-centre trials, and a variety of opportunistic infections continue to plague this approach that does not appear useful in the setting of advanced disease. Further avenues of improvement include the exploration of killer cell immunoglobulin-like receptor (KIR) mismatching between donor grafts and recipients.
Data on alternative donor source in ALL have been recently reviewed by Marks et al (Marks, *et al*) and are summarized in Tables 6-7.

8. Post transplant strategies to improve clinical outcome

8.1 GVHD prophylaxis

GVHD results from alloreactivity between donor and recipient. The two major prophylactic regimens employed to prevent this complication are pharmacological (administration of immunosuppressive drugs), and immunological (in vitro T-cell depletion). The standard pharmacologic prophylaxis has been cyclosporine (CsA) and short-course methotrexate, but recent studies suggest that the incidence of GVHD may be lower if FK506 is substituted for CsA (Nash, *et al*). MMF also shows promise in animal models, and its combination with CsA is being evaluated in clinical trials. Ex vivo T-cell depletion reduces the risk of both acute and chronic GVHD and may allow higher tolerance of mismatching but may also increase the risk of rejection and delay immune reconstitution. A confounding feature for interpreting the value of T-cell depletion is that a variety of methodologies are employed to remove T cells, including physical methods, poly- and mono-clonal antibodies. Some techniques produce a pan-T depletion, whereas others use antibodies with more restricted T-subset specificities. An IBMTR study showed a better outcome when antibodies with narrow specificities are used (Champlin, *et al*).

8.2 Reducing the risk of relapse

The major cause of failure after transplant for ALL is relapse. The outcome of patients who relapse after allogeneic SCT is very poor. Remissions are possible with standard CHT but

are not durable. Those who relapse more than 1-year post-transplant are more likely to achieve a further remission. Donor leukocyte infusions have been used but their success rate in patients with ALL is much lower than in patients with myeloid malignancies (Porter and Antin). Strategies to reduce the risk of relapse include intensifying conditioning regimens, altering the timing of transplant and augmenting the graft versus leukaemia effect. The risk of relapse may also be reduced by more precisely defining the biological risk factors that justify transplant in first remission, thus circumventing the possibility of selecting for leukaemia resistance during prolonged CHT. Patients who receive an alloSCT for ALL and develop graft versus host disease (GVHD) have a lower probability of relapse than patients who do not suffer this complication. A recent study showed that in patients with high levels of minimal residual disease (MRD) pre-transplant, the presence of acute or chronic GVHD may be needed to prevent relapse(Uzunel, *et al*). The likely explanation for this observations is that the alloreactive T cells in the donor graft are able to destroy residual host leukaemia cells. In support of this contention, administering lower doses of CsA reduces the relapse risk and improves DFS in children undergoing SCT for leukaemia (Locatelli, *et al*). Adoptive immunotherapy with donor mononuclear cells is less successful in ALL than in the myeloid leukaemias, although there is some evidence that use of immunostimulatory cytokines such as IL2 may amplify graft versus leukaemia mechanisms and induce remissions in patients who have failed to respond to donor lymphocyte infusions. Immune modulation post-transplant may therefore be a therapeutic alternative to reduce the risk of relapse. One means of reducing the risk of GVHD is to administer antigen-specific cytotoxic T-cell lines (CTL) lines when a specific antigen is known. Potential targets include minor antigens differentially expressed on haemopoietic cells (Mutis, *et al*) or lineage specific antigens, such as WTI or proteinase 3 (Ohminami, *et al*). Such lines could potentially mediate cytotoxic activity directed at recipient haemopoiesis (and leukaemia) but not donor haemopoiesis. An alternative approach when a tumour antigen is not defined is to increase the immunogenicity of the tumour and allow selection of the tumour antigen by responding immune system effector cells. This approach has shown efficacy in a number of animal models using molecules that modify antigen presentation such as Class I MHC molecules or GMCSF, co-stimulatory molecules such as B7 or T-cell activation factors such as IL2. For example pre B ALL cells lack B7-1(CD80) and induce allo-specific T-cell anergy. If ALL cells are transduced with B7, their antigen presentation capacity is improved and they are able to generate autologous leukaemia-specific CTL lines from marrow from the majority of patients (Cardoso, *et al*). Murine data also suggests that combination of molecules acting on different phases of the immune response may produce increased anti-tumour activity (Dilloo, *et al*) and this approach is currently being tested in a clinical trial in patients with ALL (Rousseau, *et al*).

9. Autologous stem cell transplantation

The role of in adults with ALL has not been clearly defined. Prospective studies comparing with alloSCT in high-risk patients demonstrated increased risk of relapse and reduced probability of survival in the autologous setting (Attal, *et al*, Hunault, *et al*). Trials comparing with maintenance chemotherapy did not show survival benefit from high-dose treatment, however, a pooled analysis of three subsequent trials by the French group (LALA-85/87/94) suggested that ASCT may contribute to decreased risk of relapse (66% vs. 78%, p=0.05) (Dhedin, *et al*, Labar, *et al*, Ribera, *et al*, Thiebaut, *et al*). In the MRC UKALLXII/ECOG 2993

study investigators tested if ASCT may be administered instead of consolidation + maintenance for patients lacking an HLA-identical sibling, irrespective of the presence of risk factors. OS was significantly worse in the ASCT compared to chemotherapy arm (46% vs. 37% at 5 years, p=0.03) leading to conclusion that early ASCT cannot substitute consolidation.

Disappointing results of prospective trials evaluating the role of ASCT led to a general tendency to abandon this treatment option in adults with ALL. It must be stressed, however, that in view of current knowledge design of the studies could have been suboptimal. First of all, the trials have been conducted before the era of routine MRD assessment. Low tumor burden is prerequisite of successful ASCT as in other conditions the transplant material may be contaminated by residual leukemic blasts leading to their re-transplantation and early relapse. Evaluation of MRD status in bone marrow reflecting the tumor load may therefore be crucial for selection of patients who could benefit from ASCT. Indeed, in a retrospective analysis by the European Working Group for Adult ALL, the MRD level was demonstrated the most important prognostic factor with DFS of 58% for patients with MRD<0.1% vs. 19% for those with MRD ≥0.1% in bone marrow (p=0.0002) (Giebel, *et al*). In a setting of 123 ASCT recipients with HR ALL, the incidence of non-relapse mortality was 2.4%. In the analysis of a selected group of 50 patients in whom the MRD was evaluated with sufficient sensitivity to define the MRD status as negative at the level of 0.01%, the 5-years probability of DFS was 69%.

In so far conducted prospective trials ASCT was administered instead of either maintenance or consolidation + maintenance and was considered the last stage of the treatment. There is, however, another option, which has not been prospectively tested i.e. incorporating ASCT in consolidation, followed by maintenance. Interim analysis of a retrospective study by the Central and Eastern Leukemia Group indicate significantly increased probability of the DFS if maintenance based on mercaptopurine + methotrexate was administered after ASCT (70% vs. 38% at 5 years, p=0.03). The effect was independent on the MRD status (HR=2.6, p=0.007) (unpublished data).

Finally, ASCT followed by interferon alpha administration has been shown to be quite effective for Ph+ patients (Piccaluga, *et al*, Visani, *et al*).

Taken together, ASCT is associated with low risk of transplant-related mortality and morbidity. Its efficacy should still be prospectively evaluated in patients with low MRD level, with post-transplant maintenance as an option.

10. Conclusion

Data from clinical trials trying to compare alloSCT and other post-remission therapies for ALL patients in CR1 are sometimes difficult to interpret because of varying proportions of patients with different risk factors in each study (some of them are actually limited to high risk patients as many centres do not include alloSCT in the therapeutic program of standard risk patients in CR1). Prospective randomized studies have been carried out by various cooperative groups. These studies have compared patients with HLA identical siblings assigned to the allogeneic SCT group to those without HLA identical sibs assigned to either a standard chemotherapy or ASCT group. However, as up to 70% of adults with ALL cannot be allocated to SCT because of a lack of a matched related sibling, comorbidities, or severe infections, an objective and unbiased comparison among treatments is difficult (Avivi and Goldstone, Martin and Gajewski, Popat, *et al*). A major limitation of these studies is that

the proportion of patients in the allogeneic SCT group actually undergoing transplant varies from study to study. Despite this limitation, a donor versus no donor comparison is the best way to answer the question about role of allogeneic SCT in first remission, even though the so called "genetic randomization" (based on the availability of HLA-matched donor) is not a proper randomization. In addition, in some studies, patients receiving ASCT/CHT included cases over 50 years not suitable for alloSCT. Notable features of all these studies include a high treatment related mortality and a lower risk of relapse in allogeneic transplant arm. On the other hand, the most recent study from the MRC/ECOG group (MRC UKALL XII/ECOG E2993) (Fielding, *et al*, Goldstone, *et al*) represented the largest series in which the role of alloSCT in ALL was prospectively evaluated. Indeed, in this study alloSCT was shown to provide the best outcome specially in standard risk patients, thus offering a strong indication to this procedure in the majority of ALL cases.

On the other hand, the randomized studies so far available did not compare alloSCT to the most recent risk-adapted, intensified consolidation schedules, which provided significant benefits in terms of both relapse free and overall survival in standard risk ALL cases (Bassan and Hoelzer). In addition, not all the patients can benefit from it, at present. Thus, optimizing SCT strategies (see above) as well as improving post SCT therapy are necessary. In this light, the possible interventions regards either cellular therapies and pharmacological approaches. For example, the development of grade ≥2 GVHD is correlated with reduced relapse rate but relevant morbidity and mortality are related to GVHD. Thus, future strategies should consider graft manipulation aiming to maintain GVL effect though reducing GVHD and TRM.

Finally, the presence of minimal residual disease after SCT is associated with impending relapse. Thus, careful MRD monitoring after SCT should be performed and treatment of molecular relapse should be considered. In this setting, targeted therapy, such as TKI and interferon alpha (Piccaluga, *et al*) or novel TKI for Ph+ ALL, FLT3 inhibitors for MLL^+ cases, nelarabine/forodesine for T-ALL and, more in general, monoclonal antibodies (anti-CD19, anti-CD20, anti-CD22 and anti-CD33) surely warrants further evaluation in clinical trials.

Accordingly, based on the currently available data, allogeneic SCT is a reasonable treatment option for adults with high-risk and possibly standard risk ALL in CR1. Patients in CR2 with matched donor should be probably always referred to alloSCT unless major clinical contraindications are recorded. Finally, refractory patients as well as cases beyond CR2 should be carefully evaluated and selected for alloSCT basing on age, PS and amount of previous CHT.

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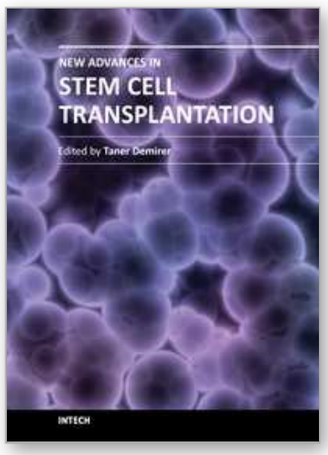

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