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Cellular Therapy of ALL

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1. Introduction

There are almost 6000 cases of acute lymphoblastic leukemia (ALL) diagnosed annually in the United States. Approximately two-thirds occur in children and adolescents making ALL the most common cancer in that age group.[1] The remaining third occurs in the adult population with the incidence increasing beyond age 50. The biology of the disease with advancing age confers a worse prognosis than with childhood ALL as the incidence of "very high risk" cytogenetic categories, such as Philadelphia chromosome–positive (Ph+) ALL, is much higher in the older population.[2] Treatment of childhood ALL has in general been relatively successful with five-year event-free survival rates ranging from 70 to 83% in developed countries, with an overall cure rate of approximately 80%. The experience with adult ALL has been far less successful with reported cure rates rarely exceeding 40% despite the use of hematopoietic stem cell transplantation (HSCT).[3] Historically there have been two separate approaches for treatment of adult patients, transplantation-based or attempts to optimize chemotherapy reserving transplantation only for patients who are Ph+.[4-8] Prior to the last decade, allogeneic transplantation in adult patients with ALL in first remission was reserved for patients who were Ph+ or those with advanced disease.[9] The recently published results from the landmark UKALL XII/ECOG E2993 trial compared these treatment options posing the question of whether the allogeneic graft versus leukemia (GVL) effect, could improve the outcome for all suitable adult patients.[10] The trial analysis, which will be discussed in detail later in the chapter, concluded that sibling donor allogeneic HSCT was superior to chemotherapy alone in standard risk first remission ALL patients with respect to overall survival.

Achieving a complete remission (CR) with induction chemotherapy is crucial for a favorable outcome in adult patients with ALL. Furthermore, relapse from complete remission is associated with dismal survival and overall only one-third of adult patients who achieve complete remission will survive 5 years. Thus prevention of relapse is vital for long-term survival. Strategy employed to maintain remission includes autologous and allogeneic HSCT. In the case of allogeneic HSCT, evidence is mounting that not only related donor but also matched unrelated donor and umbilical cord blood sources are equivalent options when overall survival is considered. Historically, it was felt that both autologous and allogeneic transplant could improve survival on the basis of phase two data.[11] More recently, this concept has been challenged by the findings of the UKALL XII/ECOG E2993 trial.[10] Phase two data demonstrated favorable leukemia free survival (LFS) with human

leukocyte antigen (HLA)-matched sibling allogeneic HSCT in ALL in first or later CR. Considering that only one-third of patients have a matched sibling donor, other graft alternatives have to be considered including autologous transplant (auto), matched unrelated donor (MUD), umbilical cord blood (UCB) and haploidentical-related donors. Although transplant related mortality (TRM) is low with autologous transplant, typically less than 5%, the overall survival (OS) is disappointing due to an unacceptably high risk of relapse and because of these findings, enthusiasm for autologous HSCT has decreased over the past few years. In contrast, the appealing aspects of allogeneic transplantation, including the potential for an immune mediated GVL effect has been associated with decreased relapse rates and improved LFS.[11]

2. Graft versus leukemia

The GVL effect in recipients of allogeneic HSCT is an anecdotally described and statistically demonstrated phenomenon. The GVL effect is statistically evident by demonstration of a higher relapse rate after autologous or syngeneic HSCT compared to allogeneic HSCT. There is also a lower incidence of relapse in patients who experience graft versus host disease (GVHD), as well as increased relapse rates in recipients of T-cell-depleted marrow grafts. Both single institution and registry data provide evidence of an allogeneic GVL effect with relapse rates lower in patients who developed GVHD than in those who did not.[12, 13] The occurrence of acute, chronic or both forms of GVHD correlated with the best disease free survival (DFS).

Doney and colleagues described a study of 192 patients with ALL, mostly transplanted in second remission (CR2). They evaluated the probability of relapse among patients with or without GVHD.[12] Relapse was significantly higher in the group that had grade 0-I GVHD. In fact, in patients without significant GVHD, the actuarial risk of relapse approached 80% versus 40% in those who developed grade II or above. Subsequently, this observation was confirmed for both relapse and overall DFS by Appelbaum et al.[13] Passweg reported a study of 1132 patients with T-cell or B-cell ALL, which showed a decreased rate of relapse in patients with both acute and chronic GVHD.[14]

These data support the idea that T-cells in the graft mediate a potent GVL effect in patients with ALL. Augmenting the GVL effect may be possible by developing antigen-specific T-cell immunotherapy for patients with ALL.[13, 15-18]

3. Minimal residual disease

As mentioned previously, one of the most important prognostic factors in patients with ALL is the achievement of CR after induction chemotherapy, in addition to age and cytogenetic abnormalities at the time of diagnosis. These factors directly reflect the chemosensitivity of the disease. Consequently, a longer time to achieve CR during induction is an indicator of relative chemoresistance. Several studies have shown that patients who need more than one cycle of induction chemotherapy have a poor long-term prognosis and a shorter duration of remission.[19-21] Historically, clinical trials have defined success of induction chemotherapeutic regimens on the basis of morphology.

With the advent of ever more sensitive molecular and immunophenotypical methods, a single blast cell in 10,000 normal cells can now be reliably detected. Using these techniques a majority of patients with ALL will have markers identified that can be used to detect

minimal residual disease (MRD) at different times throughout the treatment course. The presence of MRD as detected by these methods allows for the identification of groups at risk for relapse. MRD studies might be useful for identifying high-risk groups of patients who might benefit from early transplantation and also provide guidance to help determine the most suitable conditioning regimen.[22]

Bassan and colleagues reported results of the Northern Italy Leukemia Group (NILG) study 09/00 of 280 patients with ALL. Adequate probes for MRD detection were obtained in 223 patients (88%) with a single marker in 61% and two probes in 39%.[23] A sensitivity level of 10^{-4} or higher was found in 94% of these patients and data was available on 79% of patients who completed the first stage of treatment. The presence of MRD was the strongest predictor of LFS and bone marrow relapse in the multivariate model used. Detection of MRD was associated with hazard ratios of 5.88 for DFS and 5.33 for bone marrow relapse (p=0.001). The study used risk-adapted therapy based upon MRD detection.

Study	Year	No. Evaluable/ Studied (%)	Risk Subsets	MRD Study*	Survival/DFS of MRD Negative v Positive; Study Conclusions
Retrospective/descriptive MRD analysis					
MRC[109]	2010	161/NR	SR/HR BCP	RQ-PCR; < 10^{-4} at 1-9 months	DFS 74% v 30% at 5 years (P = .002) MRD at end of phase II induction best predictor of relapse (P = .0002) HSCT partially active in MRD-positive
PALG[110]	2008	116/132 (87.8%)	SR/HR BCP/TCP	IF; < 0.1% at end of induction	DFS 61% v 17% at 3 years (P = .0002) MRD best predictor of relapse (P < .001), higher value in SR and BCP
GRAALL[111]	2009	212/507 (41.8%)	SR/HR BCP/TCP	RQ-PCR; < 10^{-4} at end of induction/1st consolidation	DFS 82% at 3 years (84% after HSCT censoring) v relapse rate 56% (P < .001) MRD best predictor of relapse (P < .001) HSCT not needed in MRD negative, partially active in MRD positive
Prospective MRD analysis for therapy optimization†					
GMALL[24, 112]	2006, 2009	479/NR	SR/HR BCP/TCP	RQ-PCR; negative/<10^{-4} at end of induction I-II and 1st consolidation	SR: survival 67% v 38% at 5 years (P < .001) HR: survival 66% v 42% at 5 years (P = .003) MRD negative at days 11 and 24 (relapse risk 0%) v MRD positive until week 16 (relapse risk 94%) HSCT not needed in SR MRD negative and partially active in SR/HR MRD positive
NILG[23]	2009	223/253 (88.1%)	SR/HR BCP/TCP	RQ-PCR; < 10^{-4} at week 16, negative at week 22	DFS 72% v 14% at 5 years (P = .0000) MRD at weeks 10 to 22 best predictor of relapse (P < .0001) HSCT not needed in MRD negative and partially active in MRD positive
PETHEMA[113]	2009	156/202 (77.2%)	HR BCP/TCP	IF; < 0.1% at end of consolidation	DFS 54% at 4 years v 31% at 2 years (P = .043) MRD best predictor of relapse (P = .007) HSCT not needed in MRD negative and partially active in MRD positive

NOTE. Adapted from Bassan et al.[33]

Abbreviations: MRD, minimal residual disease; ALL, acute lymphoblastic leukemia; DFS, disease-free survival; MRC, Medical Research Council; NR, not reported; SR, standard risk; HR, high risk; BCP, B-cell precursor ALL; RQ-PCR, real-time quantitative polymerase chain reaction; HSCT, hematopoietic stem-cell transplantation; PALG, Polish Adult Leukemia Group; TCP, T-cell precursor ALL; IF, immunofluorescence study (flow cytometry); GRAALL, Group for Research on Adult ALL; GMALL, German Multicenter Study Group for Adult ALL; NILG, Northern Italy Leukemia Group; PETHEMA, Programa Espanol de Tratamiento en Hematologia; CR, complete response.

*Method and definition criteria for MRD negativity.

†GMALL: reporting MRD study results in 479 of 1,489 total study patients (CR 89%); includes pilot phase with two probes with sensitivity 10^{-4}; MRD-oriented therapy (treatment stopped after 1 year in MRD negative, only pilot phase; intensification/HSCT in MRD positive); NILG: 280 study patients, 253 evaluated for MRD probe(s), 142 for risk-oriented (n = 30) or MRD-oriented (n = 112) therapy (maintenance in MRD negative; intensification/HSCT in MRD positive); PETHEMA: 253 study patients, 156 of 202 in CR reported MRD evaluable, 100 at end of consolidation (maintenance in MRD negative; HSCT in MRD positive).

Table 1. Clinical Significance of MRD Analysis in Adult ALL (selection of recent representative studies, mainly Ph- patients)

In an earlier study by the German study group GMALL, 196 patients with standard risk-ALL had their MRD status monitored prospectively.[24] At week 16 of therapy, subsets of patients could be identified with very different outcomes. Twenty three percent of patients who had MRD detectable until week 16 and beyond had a 3-year relapse rate of 94% whereas no relapses occurred in 10% of the patients who had a rapid decline to undetectable levels when measured at days 11 and 24. Other studies have also shown similar trends (Table 1).

Studies in MRD have also been performed in the pediatric population. A recent study used polymerase chain reaction (PCR) amplification of antigen-receptor genes to detect 1 leukemic cell per 100,000 normal mononuclear cells (0.001%).[25] Stow and colleagues examined 455 pediatric patients and compared 2 cohorts based on MRD levels at day 46 of therapy. Those patients with MRD < 0.001% had a 5 year risk of relapse of 5% compared with 13% for those with MRD levels of < 0.01% but > 0.001% (p < 0.047).

These studies show that a higher level of MRD either after consolidation chemotherapy or a rising level during treatment might predict for a higher relapse rate. Inversely, a low level of MRD might identify a group of patients who do not necessarily need transplantation, or perhaps can wait until there is clear evidence of rising levels of MRD before further therapy is initiated.[24, 26-28] In the future, MRD might be used to further refine the treatment options for patients with ALL, and may better define which patients should undergo transplantation.

4. Who should receive a HSCT?

Established predictors of poor long-term outcome in ALL patients undergoing aggressive chemotherapy have been used to determine which patients should proceed to transplantation in first remission. In the pediatric population, transplantation is reserved for the patients with the worst prognosis, whereas the adult patient is much more likely to benefit from allogeneic HSCT and the procedure is performed more frequently. Patients with high risk features are known to have a greater risk of relapse and have historically undergone HSCT in first remission (CR1) if they were deemed transplant candidates.[19, 29-31] High-risk features include: age greater than 35 years, leukocyte count > 30,000/μL for B-cell and > 100,000/μL in T-cell origin, non T-cell phenotype, lack of mediastinal adenopathy, poor performance status at diagnosis, t(9;22), t(4;11), t(1;19) or t(8;14). Patients who require more than four weeks of induction therapy to achieve remission or who have detectable molecular or immunophenotypical evidence of disease while in remission also have a poorer prognosis.[32]

The results of the UKALL XII/ ECOG E2993 trial demonstrated superior survival in standard risk patients who underwent allogeneic HSCT. Many centers have taken this as conclusive evidence that all patients with standard risk disease in CR 1 should undergo allogeneic HSCT, if they are suitable candidates and a suitable donor is available.[10] Whether allogeneic transplant should be performed in all ALL patients in CR 1 is debatable, given the excellent outcome observed with chemotherapy alone in subsets such as young males with standard risk T-ALL. The reduction of relapse risk with allogeneic HSCT is definitely superior to chemotherapy alone or autologous transplant.[5, 10, 33-37] Given the uncertainty, patient education and choice must be a priority for clinicians who treat such individuals.

Adolescents and young adults (AYA), ages 16-30, or subsets thereof appear to have less favorable outcome than younger pediatric patients. However, retrospective analyses comparing pediatric and adult therapy of ALL in AYA, have shown significantly better results with pediatric treatment protocols with survival rates at 5 years of 67% to 78% compared to 34% to 41% with adult protocols.[36, 38-42] The question of the applicability of pediatric style therapy is being formally tested in clinical trial to define the toxicity and feasibility of the pediatric approach to therapy in AYA. The CALGB is conducting study 10403 (http://www.clinicaltrials.gov ID:NCT00558519), which treats ALL patients 16 to 39 years of age on one arm of the Children's Oncology Group (COG) AALL0232 protocol. As the CALGB and COG protocols are running concurrently patient specific data from both trials will be used to compare the outcome of AYA treated in the pediatric and adult settings. Investigators at the Dana Farber Cancer Institute are conducting a phase 2 clinical trial that investigates the safety and efficacy of a pediatric regimen which includes pegylated L-asparaginase in patients age 18-50 (Study 06-254).[22] If the outcome appears to be improved by the application of the pediatric approach to therapy of ALL then subsequent trials might compare allogeneic transplant to pediatric chemotherapy regimens in a prospective fashion.

Although pediatric style treatment when retrospectively compared to adult therapy has created an interesting hypothesis, the UKALL XII/ECOG E2993 trial showed that in every age group up to 40 years, including those younger than 20, there was an OS advantage to having a donor. There is thus insufficient evidence at this point to conclude that allogeneic transplantation in CR1 should be abandoned in this age group, including those with high-risk disease.[22]

In patients with ALL greater than 50 years of age, treatment related mortality increases and the effectiveness of therapy decreases, as noted in previous studies and the UKALL XII/ECOG E2993 trial. The age at which the TRM exceeds the reduction in relapse risk may even be as low as age 35 to 40 years. A recent meta-analysis that included the UKALL XII/ECOG E2993 data also showed a survival advantage for standard risk patients and a non-significant survival advantage for high-risk patients.[43] This may be due in part to the fact that older patients have more high-risk features. These prospective trials have used full-intensity myeloablative conditioning regimens that include total body irradiation (TBI), whereas reduced intensity conditioning (RIC) might allow for the therapeutic benefit of a GVL effect with less transplant related toxicity. Reduced TRM with RIC regimens might permit allogeneic transplantation in older patients.[22] Conditioning regimens, including RIC regimens, are reviewed in more detail later in the chapter.

In patients with B-ALL that express CD20, the addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy, might increase the survival rate by 20% to 30% to approximately 80%.[44, 45] In these patients, relapse tends to occur within the first year and a half after achieving remission. There are no validated prognostic factors that predict relapse. Thus the detection of MRD in CR1 might select patients for allogeneic HSCT since maintenance chemotherapy is associated with a high risk of relapse.[33]

Until more effective non-transplant therapy is developed for adult ALL, risk adapted selection of patients for allogeneic HSCT will likely increase. The co-morbid status, age of the patient and MRD status will most likely dictate the type of conditioning regimen selected for transplantation.[10] A summary of overall results of HSCT in adults with ALL can be found in table 2.

HSCT and Disease Stage	No.	DFS/OS*		Relapse*		TRM*		Decision	Recommendation
		No.	%	No.	%	No.	%		
Sibling donor									
CR1	1,100	50	21-71	24	10-50	27	12-42	HSCT v CHT	Comparable results; HSCT probably superior in HR
CR2	1,019	31	16-60	48	62-71	29	40-75		HSCT superior
Relapsed/refractory	216	18	8-33	75	60-77	47	46-47		
Matched unrelated donor									
CR1	318	39	32-51	10	6-19	47	32-54	Sibling v matched unrelated	Comparable results
> CR2	231	27	17-28	8†		75†			
Autologous									
CR1	1,369	42	15-65	51	27-68	5	0-8	Autologous v CHT	Comparable results
CR2	258	21	20-27	70	59-75	18		Autologous v allogeneic	Advantage for allogeneic
Non-myeloablative, all stages	132	23	0-50	47	30-56	42	10-72	RIC v TBI-based regimens	Advantage for TBI-based full intensity conditioning

NOTE. Adapted from Bassan et al.[33]
Abbreviations: HSCT, hematopoietic stem-cell transplantation; ALL, acute lymphoblastic leukemia; DFS, disease-free survival; OS, overall survival; TRM, transplantation-related mortality; CR1, first complete response; CHT, chemotherapy; HR, high risk; CR2, second complete response; RIC, reduced intensity conditioning; TBI, total body irradiation.
*Weighted mean and range of published studies.
†One study.

Table 2. Overall Results of HSCT in Adult ALL and Current Recommendations

5. Types of HSCT

Since 2000, there have been at least 10 trials that have compared the outcome of patients with ALL with high-risk features based upon related donor availability. [4, 7, 46, 47] Seven out of ten studies demonstrated statistically significant improvement in LFS with allografts. TRM varied considerably between 9% and 44% with the highest reported in the LALA-87 trial in sibling donor allogeneic HSCT compared to 2% to 24% in autologous transplant.[7] A meta-analysis was performed of all prospective trials, 1274 total patients, which confirmed a beneficial effect of allogeneic sibling HSCT.[48] Patients in the sibling donor group showed better survival, which was even more pronounced in the patients with high-risk features. The UKALL XII/ECOG E2993 trial reported its findings to prospectively determine what the optimal therapy should be for adult patients with newly diagnosed ALL. In individuals with standard risk ALL, defined as age < 30 years, Philadelphia chromosome negative and low white blood cell count at presentation, OS in allogeneic HSCT recipients was found to be superior to chemotherapy in CR1. The greatest benefit was apparent in patients < 30 years as higher TRM negated the benefit of a lower relapse rate in older patients.

HLA-matched unrelated donor transplantation is another HSCT option for patients with ALL. In high-risk ALL, matched unrelated donors have been used when matched siblings were not available, and there is preliminary evidence that a well-matched unrelated donor may be comparable to a sibling donor.[49] There have been no prospective randomized trials that investigate the use of this type of transplant compared to autologous transplant. In a large retrospective analysis from the Center for International Bone Marrow Transplant research (CIBMTR), outcome and toxicity of 712 patients < 50 years of age in CR1 or CR2 were compared based upon type of HSCT (517 MUD, 195 autologous).[50] TRM was significantly higher in the MUD treatment group as compared to those patients who underwent autologous transplant (p=0.004). The CIBMTR also performed a long-term update analysis that confirmed similar 5-year survival for patients in CR1 after MUD and autologous transplant (38% versus 39%), but superior 5-year survival after MUD transplantation in CR2 (30% versus 14%).[11] The rate of relapse was significantly different between the two types of transplant: 20% in CR1 and 25% in ≥ CR2 for MUD versus 58% in CR1 and 81% in ≥ CR2 in autologous transplant (P=<0.0001).

There have been two recent studies that compared the outcomes of MUD and sibling allogeneic transplantation.[8, 51] In these studies, HLA class I and II high resolution typing was used for most of the patients, which reflects more closely the current standard of donor selection. The first study found that disease free survival (DFS) for adults with high-risk ALL in CR1 is similar between siblings and MUD HSCT. The second study included 84 high-risk patients and showed a 3-year survival of 46% in patients who received a sibling allogeneic transplant versus 44% for those treated with MUD transplantation. There was no relevant difference noted in TRM rate (27% and 26%, respectively). These reports support comparable results whether the allogeneic donor is related or unrelated. Recent reports that present comparable outcomes after related and unrelated HSCT are not based on intention-to-treat analyses and need to be interpreted appropriately. Despite the widespread perception of a similar outcome, it is common practice for a discrepant approach in the policy of many transplant centers.[9]

Umbilical cord blood (UCB) transplantation is now a standard option for management of pediatric ALL. UCB grafts that are partially mismatched have been used without causing excessive GVHD or graft rejection. This may be a consequence of the naïve immune status of T-cells in the UCB unit. Collection of UCB from ethnic and racially underrepresented populations in the donor pool might increase the availability of allogeneic HSCT as a treatment option for these groups.[11] Since the collection of UCB is possible from every healthy live birth with no potential harm to the donor, this option is potentially unlimited as donation is uncomplicated. UCB samples are also prescreened for infection, HLA-typed and cryopreserved and are thus quickly available for transplantation. Three studies examined UCB transplantation in adults with different types of hematological malignancy and a meta-analysis was performed.[52] There were 316 total adults who received UCB transplant versus 996 patients who underwent mostly fully matched unrelated donor transplantation without in vitro T-cell depletion. The TRM and DFS were not statistically different between the two groups despite more HLA-disparity in the UCB transplant patients. This meta-analysis represents the most cogent data available for comparison of UCB and MUD transplantation. Logistical difficulty associated with designing and conducting a randomized comparison of UCB and MUD transplantation makes this comparison unlikely in the future.

Mismatched related donor and haploidentical HSCT is an experimental therapy whose usefulness is being explored in patients with very high-risk and late stage disease who do not have an HLA-matched sibling or alternative donor available.[22] The advantage of haploidentical HSCT is both real and theoretical. The most obvious advantage is the almost universal availability of a related donor who is at least haplotype identical to the patient in need of the transplant. Such donors are usually available quickly, and can serve as repeat donors in the event of engraftment failure or as donors of lymphocytes in order to convert mixed chimerism to full donor hematopoiesis or to treat disease relapse. A more potent graft versus tumor effect is also a theoretically attractive benefit from this type of transplant.[53]

6. Why Allogeneic HSCT?

6.1 UKALL XII/ECOG E2993

In 1993, the UK Medical Research Council (MRC) and the Eastern Cooperative Oncology Group (ECOG) of the United States collaboratively developed a large study to ask two fundamental questions regarding ALL.[10] Given that GVL was first described in adult ALL and given published data supporting allogeneic transplantation in first CR for Ph+ and

other high risk patients; could the allogeneic effect improve the outcome for all suitable adult patients?[8, 54] The second question was, given the fact that protracted consolidation/maintenance therapy has been the mainstay of treatment for ALL, based on data mostly extrapolated from pediatric experience, could single autologous transplantation replace extended maintenance therapy? The UKALL XII/ECOG E2993 trial was designed so that all adult patients with a matched sibling donor would receive an allogeneic HSCT. The patients without a donor would be randomized to an autologous HSCT versus consolidation and maintenance chemotherapy. Maintenance therapy consisted of vincristine 1.4 mg/m² intravenously every 3 months, prednisone 60 mg/m² orally for 5 days every 3 months, 6-mercaptopurine 75 mg/m² orally each day, and methotrexate 20 mg/m² orally or intravenously once a week. Maintenance therapy was to continue for a total of 2.5 years from the start of intensification therapy.

Prior to randomization, all patients received intensification with high dose methotrexate. The primary outcome of the study was OS. Other measures of outcome to be assessed were event free survival (EFS) and non-relapse mortality defined as time to death censored at relapse.

A total of 1929 patients were recruited from 1993 to 2006, with 16 excluded, as pathology review did not substantiate the diagnosis of ALL. All patients age 15-59 with newly diagnosed ALL were included, including Ph+ patients. They received identical induction therapy, irrespective of risk assessment, including central nervous system (CNS) prophylaxis and treatment of CNS disease if present at diagnosis. In 2003, the upper age limit was increased to 64 and the upper age limit for allogeneic transplant was increased to 54. Patients that were Ph+ were also offered MUD transplantation.

High risk in this study was defined as patients older than 35 years, having a high WBC count at diagnosis (≥ 30 x10^9/L for B lineage and ≥ 100 x 10^9 /L for T lineage) and patients with t(9;22). All other patients were deemed standard risk. The median follow-up in this study was 4 years, 11 months. The OS of the 1913 patients at 5 years was 39% and was 43% for patients who were Ph- (Figure 1A and 1B) and there was no difference in survival between patients entered through MRC or ECOG (Figure 1C). Figure 1D demonstrates the overall survival benefit when all patients on study are included in this analysis with a 5-year survival of 53% (95% CI = 48% - 58%) for patients with a donor versus 45% (95% CI = 40% - 49%) for patients without a donor (p = 0.1). The high-risk patients had an OS of 41% versus 35% for donor versus no donor, respectively, which was not statistically significant; however, the OS was significantly improved in the standard risk patients, 62% versus 52% for donor versus no donor, respectively (p = 0.02) for survival at 5 years (Figure 1E and 1F). The relapse rate was significantly reduced in both risk groups who underwent allogeneic HSCT, confirming the potency of the graft versus leukemia effect in allogeneic transplantation.

There were 456 patients in the study that were randomized to the chemotherapy versus autologous transplantation arm of which 16 were Ph+. The patients who were randomized to receive chemotherapy had significantly improved 5 year EFS (41% versus 32%; p = 0.02) and OS (46% versus 37%; p = 0.03) (Figure 2A and 2B). The 5-year survival for chemotherapy versus autologous transplantation among the high-risk patients was 37% versus 31%, respectively and was 56% versus 46%, respectively for the standard risk patients (Figure 2C and 2D). Non-relapse mortality was 16% for the autologous versus 8% for the chemotherapy group (Figure 2E).
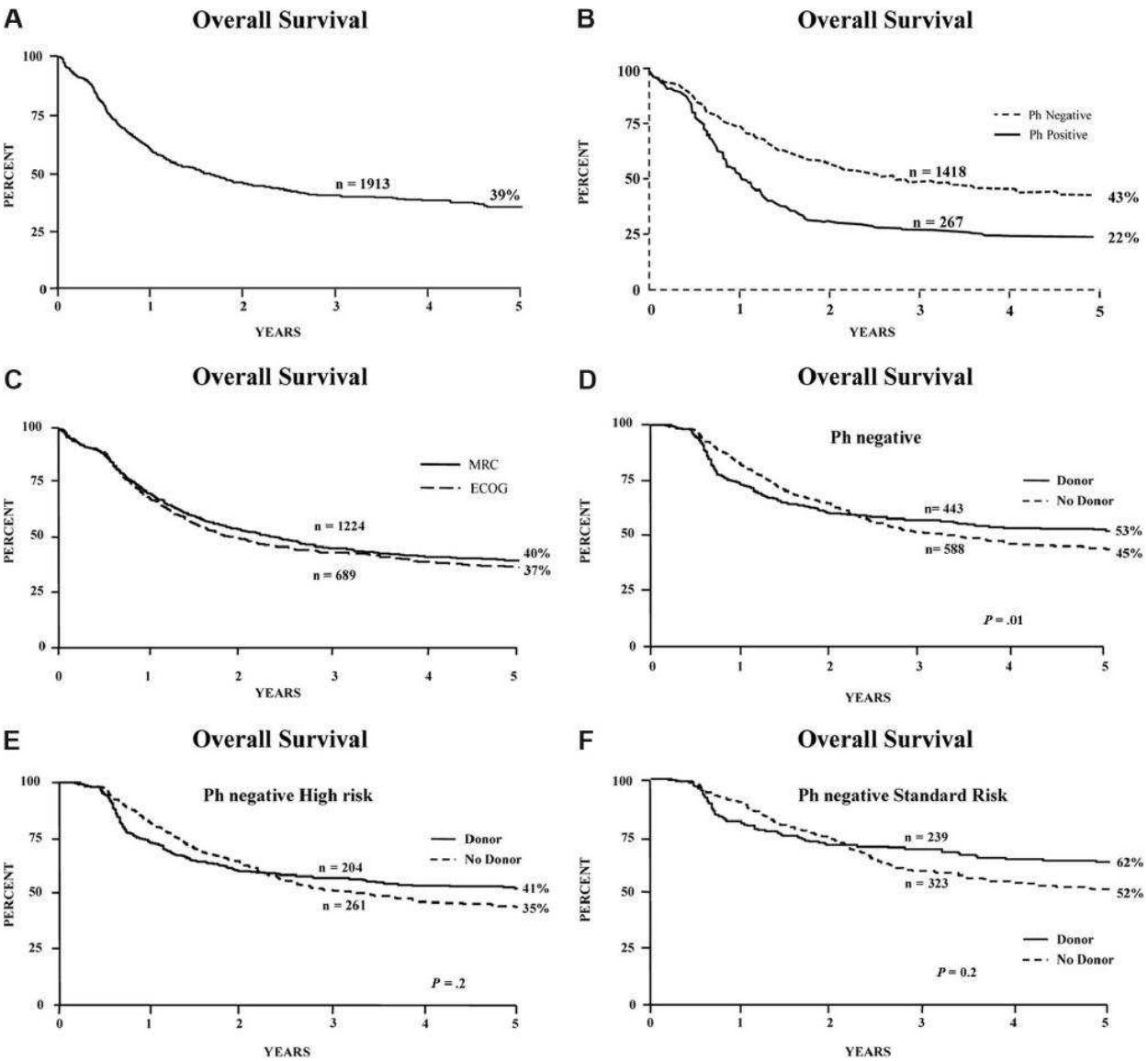
Note: Adapted from Goldstone, et al.[10]

Fig. 1. Survival of patients and donor versus no-donor analysis. Overall survival from diagnosis for (A) all patients entered on the study, including Ph-positive; (B) Ph-negative and Ph-positive patients; (C) patients entered via MRC or ECOG; (D) donor versus no-donor for all Ph-negative patients; (E) donor versus no-donor for Ph-negative patients with high risk; and (F) donor versus no-donor for Ph-negative patients with standard risk.

After reviewing the data and noting that patients randomized to chemotherapy had a better outcome than those undergoing autologous transplantation, an analysis was made that compared patients with a donor versus those without to investigate the effect of allogeneic transplantation versus chemotherapy alone. There was a superior OS noted for the patients with a donor, in the standard risk patients, with a 5-year survival of 62% for those with a donor versus 52% for those without. This same benefit could not be demonstrated for the high-risk patients. In high-risk patients, the donor versus no donor comparison showed a 5 year OS of 41% versus 35% which was not statistically significant. This finding questions the need for immediate allogeneic transplantation in high-risk patients, however for high-risk patients allogeneic transplantation remains the standard of care.
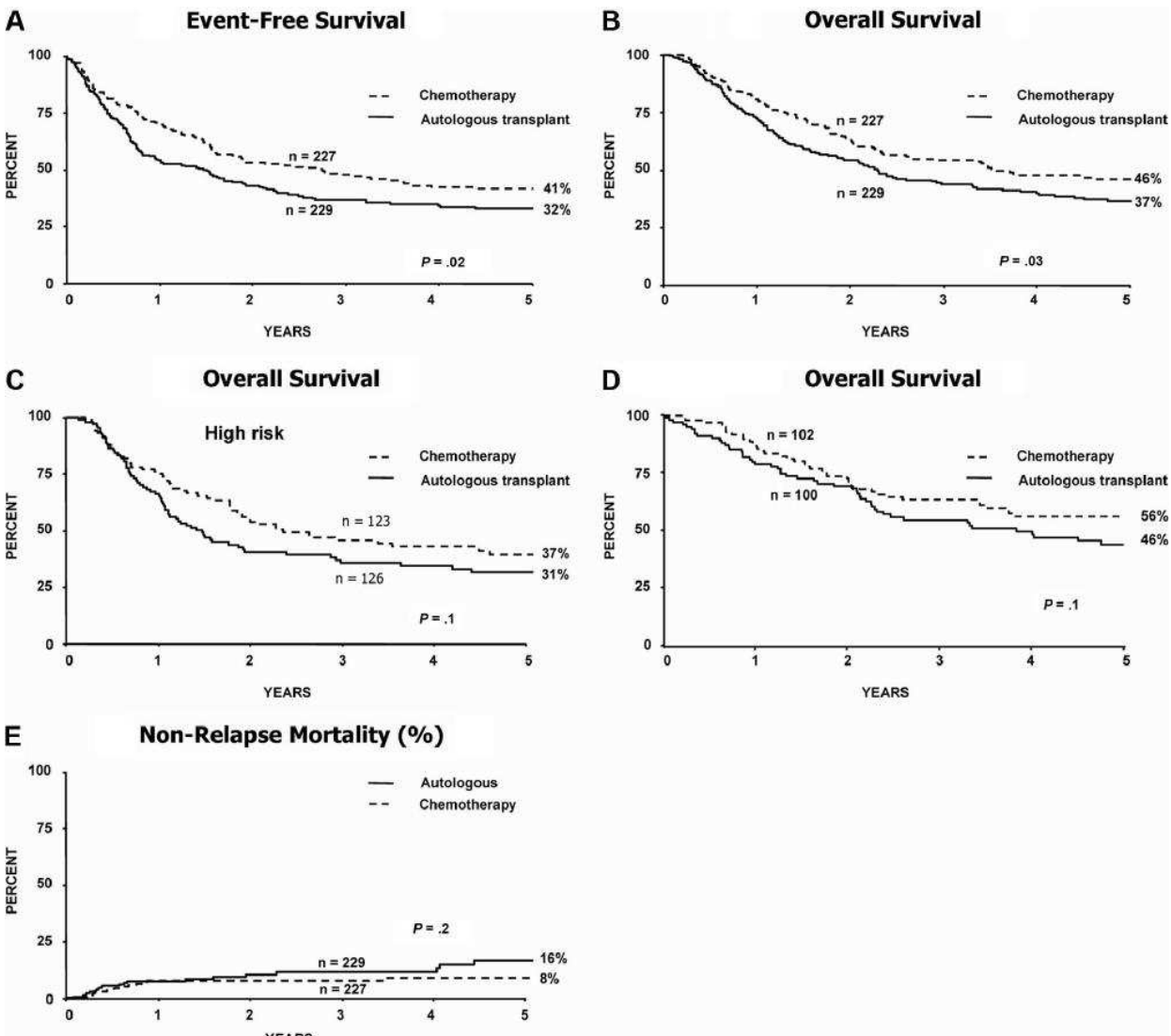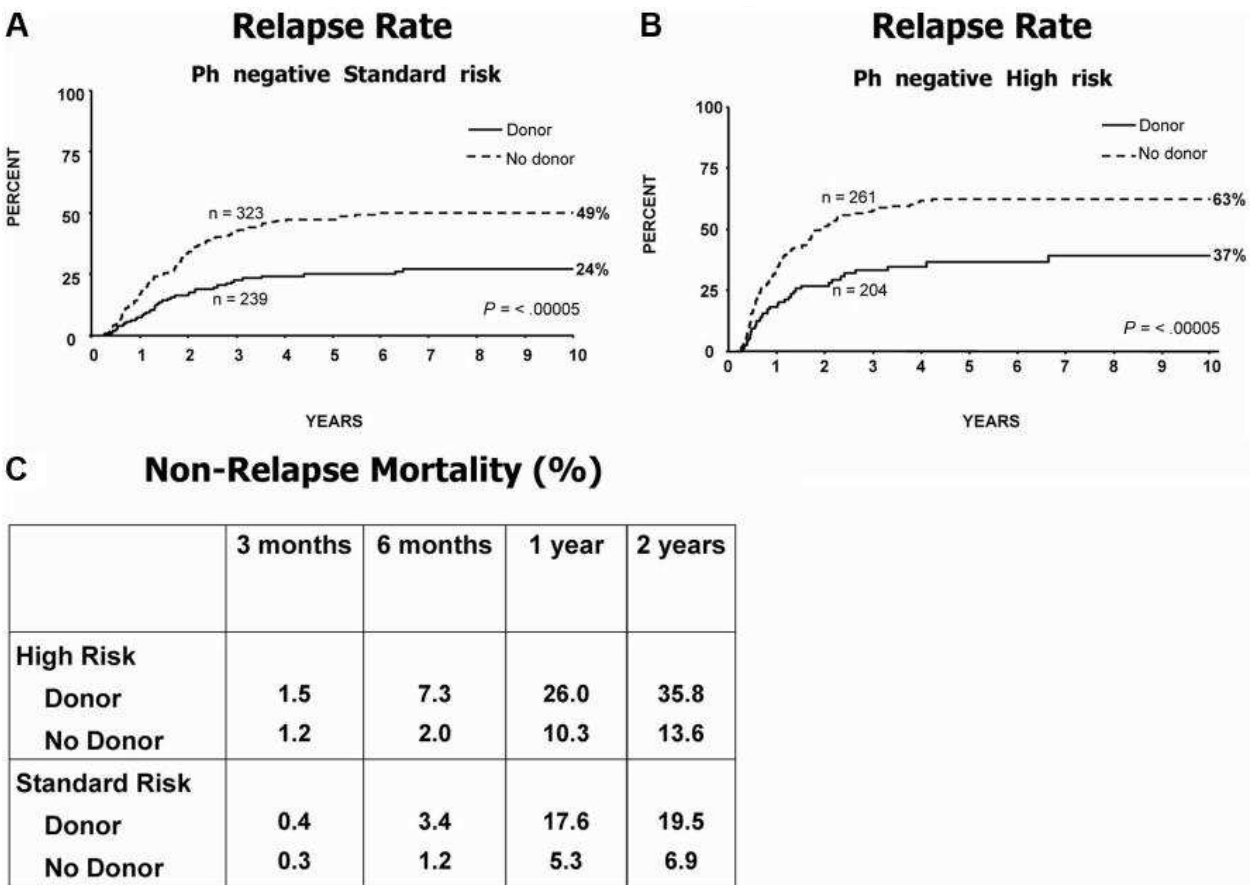
Note: Adapted from Goldstone, et al.10

Fig. 2. Randomized chemotherapy versus autologous transplantation, measured from time of randomization. (A) Event-free survival for all patients. (B) Overall survival for all (C) high-risk patients and (D) standard-risk patients. (E) Nonrelapse mortality for all patients undergoing chemotherapy or autologous transplantation.

One of the most noteworthy findings of the UKALL XII/ECOG E2993 trial was the potent anti-leukemic effect seen in adults who received allogeneic transplantation as demonstrated by a significantly reduced relapse rate. TRM in the high-risk patients was 36%, which is considered to be unacceptably high. In the low-risk group with a donor the TRM was 20%. However the high-risk group was older than the standard-risk group and would be expected to suffer more TRM. The TRM in the standard-risk group was 7% for no donor but rose to 14% in the high-risk group with no donor. The most benefit was seen in patients with standard risk disease where allogeneic transplant demonstrated a significant survival advantage over those who underwent conventional chemotherapy (Figure 3A, 3B and 3C). There have been small studies of autologous transplantation reported.[4-7, 55] Review of the data shows no clearly increased anti-leukemic benefit over conventional chemotherapy. The

UKALL XII/ECOG E2993 trial showed an inferior outcome for autologous transplantation as compared to chemotherapy and thus autologous HSCT cannot be recommended as the preferred modality. The study concluded that allogeneic transplantation is the treatment of choice for adults with standard risk disease in remission and provides the greatest chance for long-term survival.

A **Relapse Rate** — Ph negative Standard risk

B **Relapse Rate** — Ph negative High risk

C **Non-Relapse Mortality (%)**

	3 months	6 months	1 year	2 years
High Risk				
Donor	1.5	7.3	26.0	35.8
No Donor	1.2	2.0	10.3	13.6
Standard Risk				
Donor	0.4	3.4	17.6	19.5
No Donor	0.3	1.2	5.3	6.9

Note: Adapted from Goldstone, et al.10

Fig. 3. Relapse on study and mortality not associated with relapse. Relapse rate for (A) Ph-negative patients at standard risk; (B) Ph-negative patients at high risk; and (C) nonrelapse mortality for high-risk and standard-risk patients. Note the underlying mortality at 1 and 2 years among the no-donor group.

7. Philadelphia positive ALL

ALL with t(9;22), also referred to as Philadelphia chromosome positive (Ph+), historically has a lower rate of CR and lower long-term OS than Ph negative disease. Ph+ ALL accounts for approximately one fourth of all adult ALL. Historically, clinical trials typically would assign this group to the very-high-risk treatment arms and most physicians treating outside of a clinical trial would recommend myeloablative HSCT. With the advent of tyrosine kinase inhibitors (TKI), there is now the question of whether HSCT is still necessary in this patient population.[49] There have been two large studies performed that support the overall benefit of a sibling transplant in unselected patients with Ph+ ALL in the pre-TKI era. The first study was the LALA-94 trial that prospectively studied 154 patients with Ph+ ALL and

showed that among 103 patients eligible for HSCT, the presence of a sibling donor was independently predictive of remission duration.[47] The second trial, the previously mentioned UKALL XII/ECOG E2993 study, evaluated the outcome of 267 patients with Ph+ ALL and noted that those patients who had received a myeloablative sibling allogeneic or MUD transplantation had a better outcome than those who had received chemotherapy alone.[56]

There are no prospective randomized trials reported to date that use reduced intensity conditioning (RIC) in patients with Ph+ ALL. Investigators at the City of Hope Medical Center reported 24 adult patients with high-risk ALL treated with fludarabine and melphalan conditioning without T cell depletion with nearly half of the patients being over age 50. They found a 2-year OS and DFS of 62 percent with TRM of 22%.[57] There was another case series from the University of Minnesota Transplant program that reported a 3-year OS of 50% among 22 patients with a median age of 49 years, all with high-risk ALL treated with a RIC regimen of fludarabine, cyclophosphamide and low dose total body irradiation (TBI).[58] These studies show non-myeloablative regimens to be promising, but require careful prospective studies to define their role in Ph+ ALL. The UK National Cancer Research Institute, UKALL XIV, will assign all patients with ALL over the age of 40 to a non-myeloablative approach with fludarabine, melphalan and alemtuzumab in an attempt to decrease GVHD, which was seen in 86% of the City of Hope patients who did not undergo T cell depletion as part of their conditioning regimen.[49]

Prospective studies that randomize between allogeneic HSCT and continued chemotherapy introduce complexity in the analysis and interpretation of the trial data. Specifically the analysis might be biased by survivor treatment selection bias, also known as immortal time bias. Simply, patients with Ph+ ALL on a prospective study who undergo HSCT must have achieved, and remained in, a CR before transplant, resulting in a period of "immortal time." Patients dying of either disease or treatment-related causes within the immortal time window are never transplanted, resulting in an immortal time bias. This type of bias is present in studies of Ph+ ALL due to the lower rates of CR, short remission duration and toxicity of the initial treatment, as compared to Ph- patients.[49] The overall effect is to overestimate the effect of allogeneic HSCT as compared to chemotherapy when analyzed in an intent-to-treat fashion. The UKALL XII/ECOG E2993 trial is a good example of how the potential benefits of HSCT can be overestimated. Analysis by treatment received showed that those who received either a sibling or MUD HSCT had a much better 5-year OS (44% and 36%) than those who had received chemotherapy alone (19% at 5 years). All of these results, in addition to EFS and relapse free survival (RFS) were highly statistically significant. In contrast, when the analysis was repeated, adjusting for age, sex, presenting WBC and chemotherapy-treated patients who relapsed or died before median time to transplant were excluded; only RFS remained significantly superior in the transplanted group.[49]

Childhood ALL with t(9;22) remains an indication for HSCT. Due to the rarity of the disease, only 2% of cases, studies have been difficult to carry out. The Children's Oncology Group conducted a study using imatinib with intensive chemotherapy.[59] The study evaluated 92 patients ages 1-21 who were divided into 5 cohorts who received progressively increased exposure to imatinib from 42 days to 280 continuous days (cohort 5, n=50) before maintenance therapy. Patients with an HLA identical sibling underwent HSCT with imatinib given for 6 months following their transplant. This allowed for comparison between the group that did

not undergo transplantation and only received chemotherapy in combination, to the group that eventually went on to transplant. The concluding data was slightly confounded by the relatively high rate of off protocol use of MUD HSCT. Nevertheless, at 3 years, the outcomes were not significantly different for those treated with chemotherapy plus imatinib (n=25) compared to those treated with allogeneic HSCT (n=21). More than 85% of patients were alive and disease free at 3 years without allogeneic HSCT. This study was not powered to answer the question of whether imatinib plus chemotherapy could replace sibling allogeneic HSCT in Ph+ ALL, but the results encourage further investigation.

The UKALL XII/ECOG E2993 trial also reported in abstract form a large cohort of patients who were treated with imatinib and chemotherapy who did not undergo HSCT, in which the 3 year OS was 28%. By comparison, the 5 year OS of historical controls in the pre-TKI era was 19%.[60, 61]

A small series reported by Thomas et al added imatinib to hyper-CVAD induction chemotherapy and concluded superiority over historical controls treated with chemotherapy alone.[62] In older patients, for whom HSCT is not an option due to the presence of co-morbid conditions, the efficacy of imatinib alone can be studied more clearly. In a German study that included patients over 55 years of age (median 68 years), patients were randomized between co-administration of imatinib with induction chemotherapy or subsequent co-administration with consolidation chemotherapy.[61] The CR rates were 96% and 50%, respectively; however, there was no significant difference between the 2 cohorts in OS. Only 43% of the patients had undetectable *BCR-ABL* transcripts. Patients negative by reverse transcriptase polymerase chain retention assay (RT-PCR) for *BCR-ABL* had superior OS compared to those who remained positive.[2]

In other studies imatinib was given as monotherapy without subsequent HSCT, but the majority of those patients were older. These studies have shown similar impressive initial responses to that seen in the younger patients. CR rates of 90% to 100% have been documented, however relapse occurs quickly and long-term DFS remains low.[60, 61] A substantial number of patients treated with imatinib develop resistance which accounts for the high number of relapses. Second generation TKIs, such as dasatinib and nilotinib, have demonstrated promising efficacy in treatment of patients with imatinib resistance.[63-65] Long term survival however, remains elusive with monotherapy.

The CALGB has conducted a clinical trial (study 10001) to determine the activity and tolerability of imatinib used in initial treatment of Ph+ ALL. In that trial, imatinib is administered after sequential chemotherapy. Subsequently patients underwent autologous HSCT, allogeneic HSCT or consolidation chemotherapy with Etoposide and Cytarabine. All patients were given imatinib maintenance therapy beginning on day 30 post transplant or after consolidation chemotherapy and were continued on treatment for at least 1 year. Therapy was stopped before 1 year if the patient had 2 consecutive negative RT-PCR at least 3 months apart or until relapse. The final results of this study are not yet available and accrual closed April 2010 (https://www.clinicaltrials. gov ID:NCT00039377). Other trials compared alternating blocks of chemotherapy with single agent imatinib versus a concurrent treatment regimen. The simultaneous treatment schedule did induce greater reductions in the *BCR-ABL* transcripts than the alternating schedule (p = 0.01), however there was no significant improvement in overall survival.[66]

For patients with Ph+ ALL, myeloablative HSCT is still the treatment of choice if the patient is able to tolerate the procedure. There is a lack of prospective data showing TKIs alone or in

combination with chemotherapy, have increased survival in ALL. Whether the incorporation of TKIs into the treatment of Ph+ ALL will increase the efficacy of allogeneic HSCT remains an open question. If TKI therapeutics were to be administered early in the treatment of Ph+ ALL, this strategy might facilitate allogeneic HSCT if CR is improved and extended. The use of TKI therapy after allogeneic HSCT might provide sufficient post-transplant leukemia suppression to allow a GVL effect to develop. In those patients with persistent MRD after transplant the GVL might be more potent with TKI suppression of MRD.

8. Conditioning regimens

Conditioning regimens previously employed in the treatment of ALL range from the fully myeloablative TBI containing regimens to the RIC regimens. Novel methods of radiation administration such as tomotherapy and radioimmunoconjugates are under clinical investigation.

8.1 Myeloablative conditioning regimens

Although many different regimens have been developed for ALL, the one most commonly used is cyclophosphamide (Cy) plus TBI.[32] TBI has remained the backbone of conditioning regimens for ALL since the decade beginning 1970. It is prudent to understand the details of TBI with respect to DFS and TRM and how the patient population under treatment influences these statistics.

8.2 Role of TBI

Initially, TBI was intended for eradication of disease or to reduce the tumor burden.[67-69] After TBI was established as a myeloablative agent in the setting of autologous and allogeneic transplantation, several groups also recognized its potential role as an immunosuppressive agent.[70] TBI can be employed as an immunosuppressant, facilitating engraftment of donor cells and allowing for an immunotherapeutic effect of donor cells against ALL. In this role, TBI is not used for its myeloablative properties.

Early myeloablative regimens employed TBI as single doses of 8-10 Gray (Gy).[67-69] These large dosages of radiation resulted in significant morbidity and mortality, particularly from interstitial pneumonitis.[71, 72] In order to decrease toxicity and improve tolerability, fractionation and dose rate reduction were employed.[72-76] Studies in both rodents and humans indicated that rates less than 10-12 cGy/min were associated with reduced morbidity.[73, 77, 78] Other studies showed that fractionated TBI given daily or even up to four times daily improved the therapeutic ratio, thus allowing for higher doses of radiation to be delivered safely.[68, 77, 79, 80] These data support reduced dose-rate, fractionated TBI as standard and myeloablative regimens containing TBI commonly employ a schedule delivering 12 Gy TBI administered twice daily in six fractions over three days (200 cGy per fraction), in combination with chemotherapy. These regimens provide both immunosuppressive and cytotoxic activity. Dose escalation to 15-16 Gy in hopes of further reducing relapse rates has not been shown to improve overall survival. Although relapse rates did decrease, there was an increase in non-relapse mortality, thus offsetting any benefit from the higher dose of TBI.[79, 81, 82]

8.3 Cy/TBI versus BuCy

Investigators substituted Busulfan (Bu) for TBI creating the regimen BuCy as some centers did not have TBI available.[83, 84] These studies showed that combined alkylating agents could replace Cy/TBI as conditioning for HSCT in the treatment of ALL.

There is conflicting data on the superiority of one regimen over another and various studies have tried to answer this question. A retrospective analysis from the CIBMTR concluded that the Cy/TBI regimen was superior to the non-TBI-containing regimen of BuCy, with a 3-year survival of 55% versus 40% for BuCy (P = 0.003). The study also found that the risk for relapse was similar between the groups.[85] A more recent meta-analysis of seven randomized controlled trials involving 730 patients compared Cy/TBI to BuCy in patients with acute leukemia and found that Cy/TBI was associated with a modest but non-significant reduction in all cause mortality (RR = 0.82, 95%CI: 0.64-1.05; p = 0.12) and relapse of leukemia (RR = 0.89, 95%CI: 0.72-1.10; p = 0.28). Treatment related mortality was significantly less with Cy/TBI compared to BuCy (RR-0.53, 95%CI: 0.31-0.90; p = 0.02) but the cumulative incidence of major complications was not significantly different between the two regimens.[86]

8.4 Other regimens

Several centers have employed high-dose fractionated TBI in combination with high-dose Ara-C in patients receiving allogeneic HSCT from sibling donors, and have not shown any significant improvement in DFS, except for a small series of pediatric patients in one study.[87, 88] Another study looked at combining Busulfan, Fludarabine and 400 cGy of TBI as a myeloablative regimen and showed low transplant-related mortality of 3% and projected DFS of 65%.[89] Significant interest has also been shown in evaluating the role of etoposide as part of conditioning regimens including a phase I/II study that evaluated substituting etoposide for Cyclophosphamide in combination with fractionated TBI (13.2Gy). This study found DFS to be 57% with a 32% relapse rate suggesting that this regimen had significant activity in patients with advanced ALL.[90] A subsequent randomized controlled trial also confirmed these findings.[91] The UKALL XII/ECOG E2993 trial utilized Etoposide/TBI as their conditioning regimen for patients with ALL in CR1. Another study that compared Cy/TBI to Etoposide/TBI (60mg/kg) in 502 patients with ALL found that relapse rates, treatment failure and mortality were lower with etoposide/TBI, regardless of TBI dose (*P*=0.001).[92] However, in patients receiving Cy/TBI, OS was significantly improved with TBI doses less than 13 Gy (p = 0.0005).

We conclude that both the chemotherapeutic agents used, as well as the dose of radiation therapy, interact in altering the outcome of patients with ALL undergoing HSCT. There is still no conclusive evidence of one regimen's superiority over another but most centers are still inclined to include TBI as part of any regimen used for myeloablative conditioning in patients with ALL.

8.5 Role of reduced intensity conditioning

As mentioned previously, the UKALL XII/ECOG E2993 trial showed that allogeneic HSCT confers the greatest durable benefit for standard risk adult patients and is more effective than either chemotherapy or autologous HSCT.[10] However, the same trial also showed that in patients over 45 years of age and others with high-risk ALL, a high non-relapse mortality (NRM) of 36% would offset any potential survival advantage of a reduced relapse rate

conferred by myeloablative transplant. Thus, myeloablative regimens are often limited to patients who are less than 50 years of age and have an excellent performance status. RIC regimens have been developed over the last decade to allow engraftment with reduced regimen related toxicity. Once donor engraftment is achieved and immune reconstitution has started a GVL effect might be operative. Hence the benefit of allogeneic transplantation might be retained and with decreased regimen related toxicity this type of transplant could be offered to older patients with greater safety.

Investigation of RIC in ALL has somewhat lagged behind studies of other hematological malignancies such as AML, despite evidence of a GVL effect.[93] Gyurkocza and collaborators reported 247 patients with AML with a median age of 60 who underwent allogeneic HSCT from both related as well as unrelated donors.[94] The estimated OS at 5 years was 33% and the estimated 5-year relapse/progression rate and non-relapse mortality were 42% and 26%, respectively.

There have been several reports published with regards to using RIC in adult patients with ALL. One series of 24 patients, primarily with high risk ALL, who received Fludarabine and Melphalan conditioning, followed by matched related (33%) or unrelated (67%) HSCT.[57] Only 10 patients in the series were in CR1 and there was a median follow-up of 28.5 months for living patients. Both OS and DFS at 2 years was 62%, relapse incidence was 21% and non-relapse mortality was 22% at two years.

The European Group for Blood and Marrow Transplantation (EBMT) reported the outcome of 97 adult patients with ALL who received RIC allogeneic HSCT.[95] Only 29% of patients were in CR1 and the 2-year OS for this sub-group was 52%. Inclusive of all patients, the 2-year OS was 31% with a non-relapse mortality of 18%. Marks et al reported 93 adult patients with Philadelphia negative ALL receiving RIC allogeneic HSCT compared to 1428 patients receiving full-intensity allografts using sibling and unrelated donors in first or second CR.[96] Surprisingly, the RIC cohort had a similar OS to the full intensity cohort at 3 years (38% versus 43%, p = 0.39) despite a substantially older median age (45 versus 28, p < 0.01).

A retrospective study reported by the EBMT compared the outcome of 576 adult ALL patients aged 45 and over in CR who received RIC (n=127) or full intensity conditioning (n=449) followed by allogeneic HSCT from an HLA-identical sibling.[97] With a median follow-up of 16 months, the non-relapse mortality was significantly higher in the cohort of patients receiving the full intensity conditioning while rates of relapse were significantly higher in the RIC cohort. In a multivariate analysis, the type of conditioning regimen was not significantly associated with leukemia-free survival.

Ram et al evaluated the utility of RIC in patients with high-risk ALL.[98] Fifty-one patients, median age 56 years, underwent allogeneic HSCT from a sibling or MUD after fludarabine and 2 Gy TBI. Twenty-five patients were Ph+ ALL. Eighteen of these patients received post-grafting imatinib. With a median follow-up of 43 months, the 3-year overall survival was 34%. The 3-year relapse/progression and non-relapse mortality rates were 40% and 28%, respectively. Three-year OS for patients with Ph- ALL in CR1 and beyond was 52% and 8%, respectively. For patients with Ph+ ALL in CR1 who received post-grafting imatinib, the 3-year OS was 62%; for the subgroup without evidence of MRD at transplantation, the overall survival was 73%.

Data from the pediatric population also suggests that RIC might be a viable option. Verneris et al reported on 38 pediatric patients median age of 12 years who received a RIC allogeneic HSCT.[99] Only 13% of the patients were in CR1. A third of the patients received

MUD transplantation. At 3 years, the probability of TRM was 40%, relapse 37%, and DFS was 30%.

These results show consistently that OS is not decreased with RIC when compared to fully myeloablative regimens. The improved tolerability of RIC regimens, when compared to myeloablative regimens, makes RIC an option for older patients. RIC may also extend the option of an allogeneic HSCT to patients who would not otherwise be transplant candidates because of co-morbid conditions.

8.6 Novel conditioning regimens

Studies performed on patients with other hematological malignancies have suggested that with higher doses of TBI the rates of relapse are lower.[32] These findings suggest that methods that can selectively deliver radiation to sites of leukemia without increasing toxicity might be of benefit. Two such radiation delivery methods are currently being explored, one is helical tomotherapy and the other is utilization of tumor-reactive monoclonal antibody (MAB) conjugated with locally acting radionucleotides such as Iodine-131 or yttrium-90.

8.7 Radioimmunotherapy

A phase I trial of iodine-131 MAB plus Cy and TBI for advanced leukemia looked primarily at the biodistribution and toxicity of escalating doses of targeted radiation therapy combined with 120 mg/kg Cy and 12 Gy TBI followed by matched related or autologous HSCT.[100] A total of 44 patients were included in this study, 10 had ALL, 5 of which had ALL in relapse or refractory disease. Five of the patients were in CR2 or third CR. The study demonstrated that by utilizing iodine-131 anti-CD45 MAB, appreciable supplemental doses of radiation could be delivered to the marrow (approximately 24 Gy) and spleen when combined with conventional fractionated TBI.

Bethge et al reported a phase II study evaluating the utility of yttrium-90 as the radionucleotide.[101] Forty patients with advanced non-Hodgkin lymphoma were enrolled in this study combining radioimmunotherapy (RIT) using yttrium-90-ibritumomab-tiuxetan with RIC employing fludarabine and 2 Gy TBI followed by allogeneic HSCT from related (n = 13) or unrelated (n = 27) donors. Median age in the study was 55 years. All patients were high-risk with refractory disease or relapse after preceding autologous HSCT. No additional toxicity attributable to RIT was observed. Engraftment was rapid and sustained and estimated NRM was 45% at 2 years. Estimated 2-year OS was reported to be 51%.

These early results point the way to strategy that effectively increases the intensity of the conditioning regimen without increased toxicity. Further study is needed to assess the efficacy and safety of RIT in adult patients with ALL. Other radioconjugated MAB are needed to target ALL as the majority do not express CD20.

8.8 Helical tomotherapy

Helical tomotherapy is a newer method of delivering radiation therapy. With its ability to focus and intensify local radiation treatment, there is potential to augment the radiation to the marrow containing bones without increasing toxicity to other organs. This technology employs a megavoltage linear accelerator mounted on a computed tomography gantry that

allows the beam source to continually rotate around the patient. Simultaneously, the couch, or patient placement device, moves perpendicularly to the beam source. The beam moves in a spiral or helical pattern relative to the patient. The beam can be modulated with a multileaf collimator. During treatment planning, these qualities allow large volumes to be delineated and treated, while neighboring volumes are spared.[102]

Because conventional TBI can be associated with significant toxicity, there remains an interest in exploring helical tomotherapy as a means of delivering TBI because of its ability to deliver minimal radiation to sensitive organs such as the lungs and kidneys. Interstitial pneumonitis is an important toxicity seen with TBI and has been observed to occur in approximately 50% of patients receiving a single fraction of 8-10 Gy, with 50% of cases proving fatal.[71] Even when low-dose-rate, fractionated TBI is employed with concurrent chemotherapy, the rate of interstitial pneumonitis may approach 25%.[103] Important acute toxicity associated with TBI includes nausea, vomiting, parotitis, dry mouth and mucositis. These can be a source of significant morbidity for patients. TBI may also result in significant end-organ damage. Cataract formation is seen in 30-40% of patients, and gonadal failure, thyroid dysfunction, kidney dysfunction and decreased bone mineral density have all been documented.[102] Survivors are also at known risk for chronic oral and dental complications especially xerostomia which greatly affects quality of life. Other long term complications may also include the development of secondary neoplasms with a 3 to 7% increase in risk at 15 years following transplant.[104, 105] Thus, hypothetically, delivering TBI via helical tomotherapy might minimize these complications while allowing dose escalation of radiotherapy to the target tissues.

Zhuang et al reported a dosimetric comparison of TBI delivered via helical tomotherapy compared with the more traditional extended source to surface distance (SSD) approach.[106] Results from this study showed that the average dose delivered to the target volume was improved with tomotherapy while a lesser dose was delivered to the lungs, which were excluded from the target volume. Another similar study evaluated the use of tomotherapy to treat the marrow cavity (target region skeletal bone) as well as the major lymph node chains, spleen and sanctuary sites.[107] A 1.7 to 7.5-fold reduction in median organ dose was demonstrated and a dose-volume histogram analysis predicted that dose escalation up to 20 Gy was feasible and potentially safe with this technique.

Penagaricano et al reported the utility of TBI with helical tomotherapy in patients with AML.[108] Four patients with AML received TBI by tomotherapy as part of their conditioning regimen prior to allogeneic transplantation. They each received 12 Gy in six equal fractions at two fractions per day, over 3 days. TBI planning was set up so that the lungs and kidneys would receive minimal radiation. Analysis showed that although the delivered clinical target volume doses ranged from 11.9 to 12.3 Gy, the delivered lung doses ranged from 6.5 to 7.4 Gy and the delivered kidney doses ranged from 7.2 to 8.6 Gy. Overall toxicity was limited to grade I asymptomatic radiation dermatitis and grade I headache.

These studies have demonstrated the feasibility of helical tomotherapy to deliver TBI. Tomotherapy delivers an elegant and dosimetrically superior solution to the conventional technique of TBI. With tomotherapy, there is no need for blocks or compensators, low dose rates, extended source to skin distances, beam spoilers or uncomfortable patient positioning. Further investigation in this area might allow delivery of higher doses of radiation to sites of disease while limiting exposure to critical structures and thus reducing toxicity and long-term complications.

9. Conclusion

Allogeneic HSCT remains integral to the treatment of adult patients with ALL. Preliminary evidence supports the use of alternative donors in HSCT for ALL. As in other forms of hematological malignancy the use of fully matched unrelated donors shows similar outcome to matched related donor HSCT in patients with ALL. The use of UCB as the donor source appears feasible in children and also in adults. Whether the use of less well matched donors, such as haploidentical siblings, or unrelated multiple UCB units has utility in the treatment of ALL needs further study of efficacy but is certainly feasible.

The UKALL XII/ECOG E2993 trial confirmed the presence of GVL in allogeneic HSCT for ALL. It also showed that the benefit of allogeneic HSCT was operative in standard-risk ALL. Surprisingly, the benefit of allogeneic HSCT was not clearly demonstrated in patients with high-risk ALL, but was certainly not inferior to other therapy. Autologous HSCT proved inferior to allogeneic HSCT and chemotherapy only treatment. Despite these findings the trial has been the focus of much debate and alternative analyses have been presented that question the magnitude of the benefit from allogeneic HSCT. Nevertheless we conclude that allogeneic HSCT should be included as a therapeutic option for all patients with ALL eligible for HSCT.

The applicability of pediatric style chemotherapeutic regimens to adult patients is currently under investigation. If these regimens can be safely administered to adult patients and yield improved results particularly in the AYA population, then the benefit from GVL might be reduced negating the need for allogeneic HSCT in first remission.

Ph+ ALL presents a unique therapeutic opportunity with TKIs such as imatinib, nilotinib and dasatinib. The combination of TKIs and chemotherapy has been demonstrated to be feasible and they may also be effectively administered after both autologous and allogeneic HSCT. The utility of allogeneic transplantation will need to be tested again in Ph+ ALL, if recently conducted studies show superiority of TKIs in combination with chemotherapy over historical data.

Moreover, the expanded use of MRD monitoring and a better understanding of its utility might further refine selection of patients who would benefit from allogeneic HSCT.

Innovative approaches to conditioning regimens including RIC, radioimmunoconjugates and helical tomotherapy offer the possibility of reduced toxicity and thus wider applicability of HSCT. The more elderly patient with ALL might then become a candidate for allogeneic HSCT with consequent improvement in survival. In younger patients the ability to escalate the intensity of the conditioning regimen might improve disease control without adding to toxicity.

The treatment of adult ALL has improved but remains inferior to the results seen in the pediatric population. Further research into the biological diversity of ALL may help explain this difference and allow therapy to be tailored to individual circumstance. Ultimately only well designed and conducted clinical trials will allow us to address these questions and refine therapy. Given the relative rarity of this disease, international collaboration remains the most efficient way of obtaining timely answers to questions surrounding the treatment of adult ALL.

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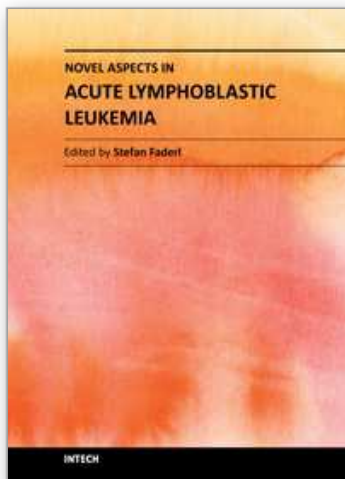
Novel Aspects in Acute Lymphoblastic Leukemia

Edited by Dr. Stefan Faderl

Acute lymphoblastic leukemia (ALL) has turned from a universally fatal to a highly curable disease in little more than four decades. Even though differences in outcome continue to exist between children and adults, intense efforts are under way to overcome this discrepancy and improve the prognosis of adult patients as well. This exemplary progress in ALL therapy has been possible by the combination of an increasingly better understanding of the biology of the disease, availability of a range of effective drugs, and astute designs and relentless executions of many clinical trials. ALL is a complex disease requiring complex therapy. Whereas this book cannot provide a comprehensive review of every one of its many facets, the chapters from many investigators from around the world nevertheless cover a number of relevant topics: aspects of the epidemiology of ALL in Hispanics, ophthalmologic manifestations of ALL, overviews of current therapy and drug-resistance mechanisms, novel biological pathways and targets, new drugs in development, and long-term consequences of CNS prophylaxis and therapy. The publishers and editor therefore hope that the prospective readers will find enough insight and information for their own endeavors.

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