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Pediatric-Like Therapy for Adults with ALL

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Abstract Ten years ago, the first studies comparing the results of adult versus pediatric protocols in adolescents with acute lymphoblastic leukemia (ALL) clearly showed that differences in ALL genetics and treatment tolerance could not be the only reasons for the worse outcome observed in adults with this disease as compared to children. It became evident that intensified pediatric chemotherapy regimens could be associated with better response rates and longer survival in adults as well. During the last decade, the use of pediatric-like or pediatric-inspired protocols in adults allowed markedly improving the outcome of young adult patients aged up from 40 years to 60 years, confirming this initial observation. Administration of pediatric-like therapy in adults is now associated with estimated 5-year overall survival comprised between 60 % and 70 %. In this new context, the risk factors and the place of stem cell transplantation need to be reassessed.

Keywords Acute lymphoblastic leukemia · Pediatric-like therapy · Stem cell transplantation · Ph-positive ALL

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Introduction

The concept of pediatric-like therapy for adult patients with acute lymphoblastic leukemia (ALL) was introduced approximately ten years ago, as opposed to most treatments previously used in adult patients. One may retrospectively wonder why pediatric and adult treatment strategies had diverged at that time in such a way they had to be opposed. This was due to two important factors. First, it became clear that ALL genomic landscape is not similar in adults and children with the disease, with more frequent genomic subgroups resistant to standard therapy in adults, like Philadelphia chromosome (Ph)-positive ALL [1, 2]. Similarly, a higher incidence of the newly-described bad-prognosis *BCR-ABL*-like B-cell precursor (BCP) ALL subset has been recently reported in adolescents and young adults (AYAs) as opposed to children [3]. Conversely, relatively favorable subsets, like ALL with a high hyperdiploid karyotype or ALL carrying an *ETV6-RUNX1* fusion gene, are rarely observed or even almost absent in adult patients. Secondly, tolerability of prolonged intensified chemotherapy is clearly better in children as compared to adults. Both factors have been responsible for the worse outcome observed in adult patients. While the progressive increase in chemotherapy intensity has been associated with a spectacular improvement in childhood ALL outcome during the last five decades, the results observed in adult ALL were desperately stagnant. Nonetheless, these differences in ALL subsets and treatment tolerability were not the only explanations for the progressive divergence in the outcome of children and adult patients. Maybe due to these stagnant poor results, maybe due to the benefits associated with allogeneic stem cell transplantation (SCT) in patients with acute myeloid leukemia (AML), most "adult" hematologists adopted "AML-like" treatment schedules based on induction and short intensive consolidation, followed as soon as possible by allogeneic or autologous SCT, probably without paying enough attention to advances

made in parallel in pediatric protocols. This resulted in amazing differences in treatment strategies. Two shocks came in the early 2000s. The first was the introduction of the tyrosine kinase inhibitor (TKI) imatinib to treat patients with Ph-positive ALL, which represents no less than 25 % of adult ALLs. The second was the brutal awareness of the errors made when the results associated with pediatric and adult strategies were compared in adolescents.

The Concept of Pediatric-Like Therapy

Adult Versus Pediatric Protocol Comparisons

Between 2003 and 2008, six studies aimed to compare the outcome of adolescents with ALL when treated with a protocol designed for adults or for children [4••, 5–9]. For this purpose, these studies focused on patients aged between 14 years old and 20 years old, taking advantage of the initial referral diversity of these patients. For many reasons, including hospital proximity and personal or familial reasons, these patients may actually be first admitted in a pediatric or adult unit and treated accordingly in a pediatric or adult trial. Table 1 summarizes the results of these six comparative studies. These results were impressive and surprisingly very reproducible from one country to another. At five years, gains in event-free survival (EFS) and overall survival (OS) observed in favor of the pediatric trial reached 16 % to 35 % and 15 % to 41 %, respectively.

In all these studies, despite a higher median age usually observed in cohorts of patients treated in adult trials, pediatric and adult cohorts were relatively well matched with respect to patient and ALL characteristics. As expected, the incidence of T-cell ALL (T-ALL) was slightly higher in this age range than in childhood and adult ALL populations in general, while the proportion of patients with Ph-positive ALL was low, ranging from 1 % to 8 %. The role of putative confounding factors, such as sexual maturity, was discussed, as sexual hormones might potentially interfere with anti-leukemic drug metabolism. It was, however, hard to imagine how such uncontrolled factors might explain the huge difference observed between pediatric and adult trial cohort outcomes. At the end, the two factors that appeared to be the most important were the protocols themselves and the adherence to planned therapies.

Pediatric protocols are using higher doses of non-myelotoxic drugs like vincristine, steroids and L-asparaginase. For a long time, they included one or two so-called late intensifications, which basically are delayed repetitions of induction-like treatment courses. They also included higher doses of methotrexate, a more continuous exposure to chemotherapy, and a more intensive, even if sometimes shorter, maintenance phase. Finally, indications for allogeneic SCT in first CR are less common in pediatric than in adult protocols. Conversely, adult protocols were using higher doses of anthracyclines, cytarabine, and often cyclophosphamide and etoposide, especially during "AML-like" consolidation courses. The use of high-dose cytarabine, combined with anthracyclines such as mitoxantrone in the HAM regimen, induced prolonged duration of neutropenia and thrombocytopenia, not allowing continuous exposure to post-remission chemotherapy. In addition, more patients were and are still receiving early SCT, possibly administered before an optimal reduction in minimal residual disease (MRD) level. In addition, the adherence to therapy, as planned by the protocol, was

Table 1 Characteristics and outcome of AYAs among pediatric and adult trials: six comparative studies.

Trial	Years	Age range (years)	Patients (N)	CR rate	EFS		OS		Reference
					(years)		(years)		
FRALLE-93	1993–1999	15–20	77	94 %	5	67 %	5	78 %	Boissel et al. (JCO 2003)
LALA-94	1994–2000	15–20	100	83 %	5	41 %	5	45 %	Boissel et al. (JCO 2003)
DCOG 6-9	1985–1999	15–18	47	98 %	5	69 %	5	79 %	De Bont et al. (Leukemia 2004)
HOVON 5/18	1985–1999	15–18	44	91 %	5	34 %	5	38 %	De Bont et al. (Leukemia 2004)
UKALL 97/99	1997–2002	15–17	61	98 %	5	65 %	5	71 %	Ramanujachar et al. (Ped. Blood & Cancer 2007)
UKALL XII/E2993	1997–2002	15–17	67	94 %	5	49 %	5	56 %	Ramanujachar et al. (Ped. Blood & Cancer 2007)
NOPHO 92	1992–2000	15–18	36	NA	5	74 %	NA	NA	Hallbook et al. (Cancer 2006)
Adult ALL Group	1994–2000	15–20	23	NA	5	39 %	NA	NA	Hallbook et al. (Cancer 2006)
CCG	1989–1995	16–20	197	90 %	7	63 %	7	67 %	Stock et al. (Blood 2008)
CALGB	1988–2001	16–20	124	90 %	7	34 %	7	46 %	Stock et al. (Blood 2008)
AEIOP 95/2000	1996–2003	14–18	150	94 %	NA	NA	2	80 %	Testi et al. (ASH 2004)
GIMEMA	1996–2003	14–18	95	89 %	NA	NA	2	71 %	Testi et al. (ASH 2004)

NA: not available.

probably not similar in adult versus pediatric units. As pointed out by Dr. Schiffer in 2003, "pediatricians administer these treatments with a military precision on the basis of a near-religious conviction about the necessity of maintaining prescribed dose and schedule come hell, high water, birthdays, Bastille Day, or Christmas" [10]. This level of precision was probably lower in adult units, due to delayed myeloid recovery after "AML-like" consolidation courses, infectious adverse events, less bed availability, or simply habits. Longer intervals between CR achievement and initiation of further chemotherapy phases, that could potentially impact on relapse incidence, have been actually reported in patients treated in adult hospitals.

Pediatric Versus Pediatric-Inspired Protocols in Adults

The use of intensive unmodified pediatric protocols in adult patients may be associated with some limitations, including myelosuppression, steroid-related toxicities like hypertension or hyperglycemia, higher incidence of L-asparaginase- or vincristine-induced toxicity, or late events like therapy-related myeloid disorders. Nonetheless, as tolerability remained partially unknown, some investigators decided to investigate whether and until which limit of age in pediatric protocols might be administered to an adult patient population. These initiatives are presented in Table 2A. First pioneer single-center experiences seemed to indicate that pediatric protocols might be used in selected adult patients up to 50 years to 55 years of age [11–13]. Patient outcomes appeared very promising, even if median follow-up was relatively short. Then, prospective studies evaluating pediatric protocols in adults focused on relatively young adults with maximum age limits ranging from 24 years to 40 years [14••, 15••, 16, 18–20]. Results remained excellent, even when reported with a longer follow-up, but median ages ranged here from 16 years to 26 years only. The largest prospective study was conducted by the US Intergroup (Alliance), which has treated 318 patients aged 16 to 39 years old with the Children's Oncology Group (COG) AALL0232/COG0232 protocol. To date, only safety results have been reported [21]. When compared to children similarly treated, these patients had higher rates of hypersensitivity to L-asparaginase and motor neuropathy. However, toxicities were manageable and the overall treatment-related mortality rate was low (3 %). It thus appears that unmodified pediatric treatment schedules might be safely administered to adult patients up to 40 years of age. Less is known on tolerability in older adults.

On the other hand, two large European adult ALL groups chose to develop their own "pediatric-inspired" protocols, designed to be administered to patients until the age of 55 years to 60 years old (Table 2B) [22, 23]. Basically, pediatric options were introduced and adapted for an adult patient population. This was possible due to advances achieved in supportive care and extensive use of granulocyte colony-

Table 2 Pediatric-like protocols in adult patients

2A. Pediatric protocols

Trial	Age range (years)	Patients (N)	Median age	CR rate	EFS (years)		OS (years)		Reference
DFCI 00-01	18–50	75	28 years	84 %	2	72 %	2	77 %	De Angelo et al. (ASH 2007)
USCH (A-BFM)	19–57	34	33 years	97 %	3	61 %	NA	NA	Douer et al. (ASH 2007)
PETHEMA ALL-96	15–30	81	20 years	98 %	6	61 %	6	69 %	Ribera et al. (JCO 2008)
HOVON (FRALLE 93)	17–40	54	26 years	91 %	2	66 %	2	72 %	Rijneveld et al. (Leukemia 2011)
FRALLE 93	18–55	40	33 years	90 %	3	DFS, 76 %	3	75 %	Haiat et al. (Leuk Res 2011)
FRALLE 2000	15–29	89	19 years	99 %	5	61 %	5	66 %	Cluzeau et al. (ASH 2012)
JACLS ALL-02-HR	16–24	138	19 years	97 %	4	DFS, 71 %	4	74 %	Sakura t al. (ASH 2012)
Saudi Arabia (A-BFM)	14–25	41	16 years	100 %	3	83 %	3	88 %	Rabi et al. (ASH 2012)
MDACC (A-BFM)	12–40	85	21 years	94 %	NA	NA	3	75 %	Rytting et al. (ASH 2013)
Alliance (AALL02132)	16–39	318	25 years	NR	NR	NR	NR	NR	Advani et al. (ASH 2013)

2B. Pediatric-inspired protocols

Trial	Age range (years)	Patients (N)	Median age	CR rate	EFS (at, years)		OS (at, years)		Reference
GMALL 07/03	15–55	713	34 years	89 %	NA	NA	5	54 %	Gökbuget et al. (ASH 2007)
GMALL 07/03	15–35	887	NA	91 %	NA	NA	5	65 %	Gökbuget et al. (ASH 2013)
GRAALL-2003	15–60	225	31 years	93.5 %	3.5	55 %	3.5	60 %	Huguet et al. (JCO 2009)
GRAALL-2003/2005 *	15–55	867	32 years	93.5 %	5	54 %	5	60 %	*GRAALL data on file*
	15–35	502	24 years	97 %	5	59 %	5	65 %	*GRAALL data on file*

NA: not available; NR: not reported; *: unpublished GRAALL data.

stimulating factor. The GMALL group did this progressively over the last decades, while the GRAALL group started from scratch in 2003. It should be mentioned that former "adult" indications for allogeneic SCT in first CR were retained by both groups, based on conventional high-risk ALL factors. Interestingly, these two groups achieved very similar results, even if using different protocols. The GMALL group has reported an 89 % CR rate and a 54 % estimated 5-year OS in a cohort of 713 adults with Ph-negative ALL aged 15 years to 55 years old and treated between 2003 and 2007 [22]. In a cohort of 867 similar patients treated between 2003 and 2011 in the GRAALL-2003/2005 trials, we observed a 93.5 % CR rate and a 5-year OS estimate at 60 % (unpublished GRAALL data on file). When GRAALL results were compared to the historical LALA-94 adult trial, the gain in survival was impressive. Very interestingly, similar OS gains were observed in patients aged 45 years to 55 years old (23 % to 49 % at five years) than in those aged 15 years to 44 years old (40 % to 63 % at five years), meaning that a pediatric-inspired protocol may benefit to adult patients at least until the age of 55 years (Fig. 1).

Finally, the Hyper-CVAD protocol used for a long time by the M.D. Anderson Cancer Center (MDACC) in Houston is a very original protocol developed to treat adult patients with ALL. This dose-dense protocol is based on alternating cycles of Hyper-CVAD (including sequential cyclophosphamide administration) and cycles comprising relatively high doses of methotrexate and cytarabine, followed by maintenance. The protocol does not strictly look like a pediatric-like protocol and does not include L-asparaginase, but it can be administered to adults up to 60 years of age. Of note, an augmented Hyper-CVAD regimen, including asparaginase, has been recently evaluated [17]. In a recent report, the MDACC group showed a similar, but not superior, outcome in a cohort of 85 patients aged 12 years to 40 years old (median, 21 years) treated with the pediatric augmented BFM protocol as compared to an historical cohort of 71 patients treated by this Hyper-CVAD protocol [18]. At three years, estimated OS was 75 % and 71 %, respectively. In younger adults aged 15 years to 35 years old, results achieved with the European pediatric-inspired protocols look also comparable to those achieved with unmodified pediatric protocols. The GMALL group has recently reported a 65 % 5-year OS in a large cohort of 887 patients aged 15 years to 35 years old [24]. Unpublished data from the GRAALL Intergroup show a similar 65 % OS in a cohort of 502 similar patients (Table 2B). We observed a similar 66 % 5-year OS in a French cohort of 89 patients treated with the pediatric FRALLE-2000 protocol in a multicenter setting [16]. To date, there is, thus, no strong evidence to support the idea that unmodified pediatric protocols should be preferred to pediatric-inspired protocols in younger adults with the

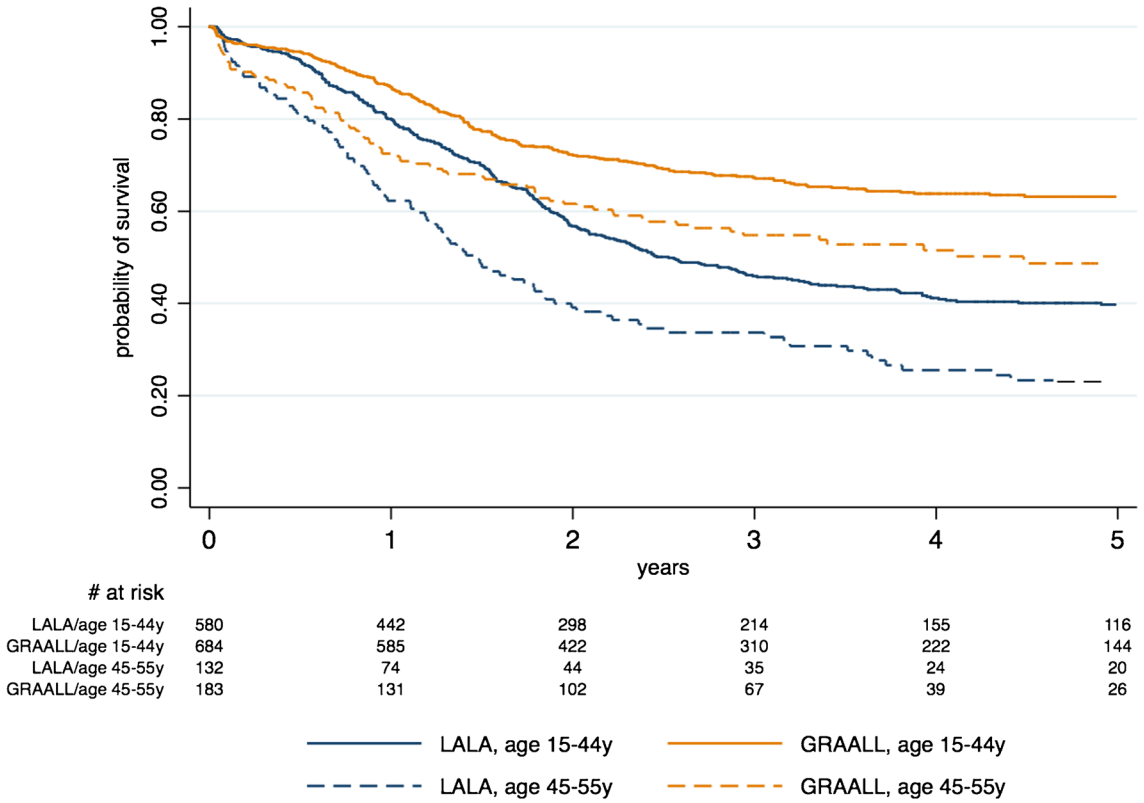

Fig. 1 Pediatric-inspired GRAALL versus former adult LALA trial: overall survival by age subgroup

disease. Only a randomized trial could eventually answer this question.

The Tolerability of Pediatric-Like Protocols in Adults

Figure 1 also illustrates the fact that advanced age is still a bad-prognosis factor in adults with Ph-negative ALL. In GRAALL patients, we observed it was only due to a higher incidence of treatment-related death during all the phases of therapy including allogeneic SCT, rather than to a higher incidence of refractory disease and relapse. During induction, the toxic death rate reached 12.5 % in patients aged 45–60 years old, while it was 2 % and 5 % in those aged 15–24 and 25–44 years old, respectively. Conversely, the incidences of primary refractory ALL and poor MRD response after induction did not increase with age. After CR achievement, 5-year cumulative incidence of non relapse-related mortality reached 19 % in patients aged 45–60 years old versus 8 % in younger patients. These percentages remained 19 % versus 3 % after censoring patients who received allogeneic SCT in first CR at SCT time. Main causes of non-ALL-related deaths were infection and graft-versus-host disease (GvHD) after allogeneic SCT. Less frequent causes include bleeding, thrombosis, cardiac events and secondary malignancies. Conversely, cumulative incidence of relapse was strictly comparable among these three age subgroups (32 % at five years, overall). This suggests that between the ages of 18 to 60 years and not considering Ph-positive ALL, the distribution of the various genetic ALL subsets among age subgroups does not seem to significantly influence disease resistance, at least when patients are treated with current intensive pediatric-inspired therapy.

The Hematopoietic SCT Issue

This major change in the results of adult Ph-negative ALL therapy described above must lead one to reconsider both current risk classifications and indications of SCT in first CR. Conventional risk factors that most European adult ALL groups have used for a long time to delimitate high-risk patients include initial white blood cell count (especially for BCP-ALL), immunophenotypic features (as immature CD10-negative BCP-ALL or non-cortical T-ALL), cytogenetic features (as translocation t[1;19], t[4;11] or other *MLL* gene abnormalities, low hypodiploidy/near triploidy, or complex karyotype), and early response to therapy (now preferentially evaluated by post-induction or post-consolidation MRD levels) [25]. Usually, the presence of one factor only is enough to classify a patient in a high-risk group and offer him allogeneic SCT in first CR if he has a donor. To our knowledge, no weighted risk score has been developed in this disease. More recently, some new oncogenetic markers have been reported as strongly influencing the outcome of children and potentially adults with Ph-negative ALL. In B-lineage ALL, this includes focal *IKZF1* gene deletions, *CRLF2* gene alterations or overexpression and *BCR-ABL*-like gene expression profile [26]. In T-ALL, this includes *NOTCH1/FBXW7* gene mutations, *N/K-RAS* gene mutation and *PTEN* gene anomalies [27, 28••]. In a recent study, we aimed to reassess the value of conventional factors and some of these new factors in a multivariable setting and found that oncogenetic events and early MRD response only independently governed the incidence of relapse in patients treated in the GRAALL-2003/2005 trials [29]. This study suggests that a number of conventional risk factors, including WBC, immunophenotype, most cytogenetic features and early steroid resistance could be simply abandoned as prognostic factors when using a pediatric-inspired protocol.

In this new setting, which factor(s) should be used to indicate allogeneic SCT in first CR remains an open issue. In the last large MRD study from the German GMALL group, it has been shown by landmark analysis that patients with poor early MRD response significantly benefit from allogeneic SCT in first CR [30••]. Using time-dependent analysis, we also identified poor early MRD response not only as a strong prognostic factor, but also as a strong predictive factor for a positive SCT effect. Conversely, none of the other conventional factors was associated with significant interaction predictive of a SCT effect [31]. Based on this finding, we will use MRD levels only to indicate or not indicate allogeneic SCT in first CR in the next GRAALL trial. This means that the proportion of patients considered eligible for allogeneic SCT in first CR will dramatically drop down from approximately 70 % to 35 % as compared to previous GRAALL-2003/2005 trials.

Using a totally different risk classification, essentially based on age (with a 35-year cutoff) and WBC, the UKALL-ECOG Intergroup demonstrated in the largest adult ALL study reported to date, that standard-risk patients (mostly the youngest) benefited from allogeneic SCT, while high-risk patients (mostly the oldest) did not [32]. This conclusion is debatable, as one could argue that a young adult with a good MRD response might do very well with chemotherapy alone, especially when treated in a more "pediatric-like" protocol than the UKALL-ECOG one. On the other hand, the introduction of reduced-intensity conditioning SCT for patients aged 40–45 years or more might allow reducing transplant-related mortality and using the graft-versus-leukemia effect as an anti-leukemic tool in patients with persistent MRD.

The Ph-Positive ALL Issue

Since the introduction of imatinib, no standard of care has been established to treat patients with Ph-positive ALL. All adult and pediatric groups are using combination regimens including imatinib and standard chemotherapy, but the

respective contribution of these two components may significantly differ. Generally, the pediatric strategy was to cautiously introduce imatinib without decreasing the intensity of associated chemotherapy. Some adult ALL groups, including the German GMALL or the MDACC, followed a similar "total therapy" strategy. On the other hand, other adult ALL groups investigated how imatinib, then second-generation TKIs, might allow significantly reducing the intensity of associated chemotherapy. The main reason for that was the median age of Ph-positive ALL patients, which is around 45 years. The idea was, thus, to reach CR, and eventually molecular CR, without exposing these older adults to excess toxicity associated with chemotherapy, prior to offering them SCT. The GRAALL Intergroup is following this TKI-based strategy through random omissions of Hyper-CVAD components, first with imatinib [33], and next with nilotinib. The Italian group went further, by using TKIs only to induce CR in Ph-positive ALL patients [34, 35].

Conclusion

Over the last decade, the use of pediatric or pediatric-inspired protocols has been associated with a dramatic improvement in the outcome of younger adults with ALL until the age of 55 to 60 years old. This improvement should allow a marked reduction in the proportion of patients who will really benefit from allogeneic SCT in first CR in this new context. In high-risk patients, who may be defined on the basis of MRD levels, further improvements might come from new therapies, including antibodies, immune-conjugates and chimeric antigen receptor (CAR) T-cells.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Hervé Dombret, Dr. Thomas Cluzeau, and Dr. Nicolas Boissel each declare no potential conflicts of interest relevant to this article.

Dr. Françoise Huguet has served on the ad boards for BMS, Novartis, Pfizer, Ariad, and Amgen.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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