







# Pediatric Autologous Hematopoietic Stem Cell Transplantation: Safety, Efficacy, and Patient Outcomes. Literature Review

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**Abstract:** Autologous stem cell transplantation (auto-HSCT) is a part of the therapeutic strategy for various oncohematological diseases. The auto-HSCT procedure enables hematological recovery after high-dose chemotherapy, otherwise not tolerable, by the infusion of autologous hematopoietic stem cells. Unlike allogeneic transplant (allo-HSCT), auto-HSCT has the advantage of lacking acute-graft-versus-host disease (GVHD) and prolonged immunosuppression, however, these advantages are counterbalanced by the absence of graft-versus-leukemia. Moreover, in hematological malignancies, the autologous hematopoietic stem cell source may be contaminated by neoplastic cells, leading to disease reappearance. In recent years, allogeneic transplant-related mortality (TRM) has progressively decreased, almost approaching auto-TRM, and many alternative donor sources are available for the majority of patients eligible for transplant procedures. In adults, the role of auto-HSCT compared to conventional chemotherapy (CT) in hematological malignancies has been well defined in many extended randomized trials; however, such trials are lacking in pediatric cohorts. Therefore, the role of auto-HSCT in pediatric oncohematology is limited, in both first- and second-line therapies and still remains to be defined. Nowadays, the accurate stratification in risk groups, according to the biological characteristics of the tumors and therapy response, and the introduction of new biological therapies, have to be taken into account in order to assign auto-HSCT a precise role in the therapeutic strategies, also considering that in the developmental age, auto-HSCT has a clear advantage over allo-HSCT, in terms of late sequelae, such as organ damage and second neoplasms. The purpose of this review is to report the results obtained with auto-HSCT in the different pediatric oncohematological diseases, focusing on the most significant literature data in the context of the various diseases and discussing this data in the light of the current therapeutic landscape.

**Keywords:** autologous stem cell transplant, pediatric age, acute leukemia, chronic myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma

## Acute Myeloid Leukemia (AML)

The current probability of event-free survival (EFS) and overall survival (OS), for children with acute myeloid leukemia (AML) ranges between 45–50% and 65–70%, at 3–10 years, respectively.<sup>1</sup> Improvement of prognosis in children, but also adults, is due to better patient stratification in risk groups, which has made it possible to adapt the treatment to the clinical-biological characteristics of the disease. Allo-HSCT has increasingly been used in high-risk (HR) patients, and the improvement of supportive therapy and the optimization of induction and consolidation strategies have decreased therapy-related toxicity. Currently, new target therapies are also beginning to be used in pediatric age.<sup>2</sup>

Over the past years, randomized studies have been carried out to clarify the role of auto-HSCT in AML patients in first remission (CR1) (Table 1).<sup>2</sup> Two previous meta-analyses showed that auto-HSCT, compared with standard consolidation CT, improved the EFS but not the OS.<sup>3–5</sup> In children with AML in CR1, auto-HSCT seemed to decrease the number of relapses and, consequently, improve disease-free survival (DFS) and OS.<sup>6</sup> Data from 13 studies of 12 randomized controlled trials (12 adult, 9 pediatric), including a total of 3027 patients (377 children), were collected.<sup>3,4</sup>

**Table 1** Results of Autologous Hematopoietic Stem Cell Transplant in Pediatric Acute Myeloid Leukemia in First Complete Remission

Author (Reference)	N. Pts	Median Age (Years) (Range)	Years	Purging	Conditioning Regimen	Outcome (Years)
Amadori (1993) <sup>7</sup>	35 +9	7 (0.3–14)	1984–1986	No	BAVC	Relapses 25; DFS 28% (5)
Ravindranath (1996) <sup>9</sup>	71	<21	1988–1993	4-HC	BU+CY	OS 40%; EFS 38% (3)
Stevens (1998) <sup>11</sup>	44	<15	1988–1995	No	TBI+CT/BU+CY	OS 70%; DFS 68% (7)
Woods (2001) <sup>8</sup>	137	<21	1989–1995	No	BU+CY	OS 48% (3)
Shaw (1994) <sup>10</sup>	21	6 (0.2–14.7)	1987–1992	No	BU+CY	LFS 60% (6)
Pession (2013) <sup>13</sup>	102	<18	2002–2011	Mafofamide	BU+CY+MEL	DFS 63% (8) TRM 7%
Sakaguchi (2019) <sup>14</sup>	220	8 (0.8–15)	1989–2002	No	BU+CY+MEL/TBI+CT	OS 62%; LFS 56% (5)
Alonzo (2005) <sup>15</sup>	217	< 21	1979–1996	4-HC	NR	OS 49%; DFS 41% (8)

**Abbreviations:** BAVC, carmustine, etoposide, cytarabine, cyclophosphamide; BU, busulfan; CT, chemotherapy; CY, cyclophosphamide; DFS, disease-free survival; EFS, event-free survival; LFS, leukemia-free survival; MEL, melfalan; NR, not reported; OS, overall survival; pts, patients; TBI, total body irradiation; TRM, therapy-related mortality; 4-HC, hydroperoxycyclophosphamide.

The conditioning regimen usually included Busulfan (BU) and Cyclophosphamide (CY), however, in one trial bone marrow cells were in vitro chemo-purged with 4-hydroperoxycyclophosphamide (4-HC). Auto-HSCT, in adult AML patients in CR1, improved DFS compared with CT (HR = 0.98; 95% CI = 0.80–0.98); in children, there were no statistical differences in relapse incidence, TRM, DFS and OS (Table 1).<sup>7–11</sup> The authors concluded that in children and adolescents with CR1 AML, auto-HSCT does not add benefit compared to CT. Furthermore, the late toxicity associated with the pre-auto-HSCT conditioning regimen has to be considered in young patients who have a longer life expectancy.<sup>12</sup>

Subsequently, Pession et al published data on 482 children with de novo AML treated with the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) 2002/2001 protocol from December 2002 to June 2011.<sup>13</sup> In this trial, the children were stratified into risk groups and the transplant procedures, either allo- or auto-HSCT, were reserved for those at HR. One hundred and forty-one children received allo-HSCT, and 102 were autotransplanted after induction and consolidation therapy. The 8-year DFS was 73% and 63% for allo- and auto-HSCT, respectively; the 8-year cumulative incidence (CI) of relapse was 17% versus 28% and no difference in the CI of TRM was observed (7% in both cohorts) (Table 1).

In the attempt to identify the optimal conditioning regimen before auto-HSCT in children with AML in CR1, the Pediatric AML Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) analyzed 220 children autotransplanted between 1989 and 2022.<sup>14</sup> Different conditioning regimens were employed and included: BU+melfalan (MEL), BU+CY±etoposide (ETP), BU+Cytarabine (CA)+ETP, BU+CY+CA, and BU+MEL+ETP or total-body irradiation (TBI). The 5-year OS was 62% and 61% for children receiving CT and TBI, respectively. However, more favorable results were obtained by patients receiving BU+MEL and BU+CY+ETP compared to those treated with TBI, or other BU-based regimens: the OS rates were 74%, 49% and 61%, respectively. A higher relapse rate was observed in the other BU-based regimens, and the non-relapse mortality (NRM) was higher after TBI (Table 1). Also in this paper, the authors argue in favor of conditioning regimens that do not include TBI, responsible for major short- and long-term toxicity.

In the same years, other published papers reported the results of several trials comparing consolidation CT with auto-HSCT in children with CR1 AML; all of them agreed that auto-HSCT offered no benefit over CT.<sup>12,15–18</sup> In these studies, the high NRM associated with auto-HSCT was probably due to the use of bone marrow (BM) stem cells source and TBI in the conditioning regimen.

Over the last three decades, the introduction of peripheral blood stem cells (PBSC) leading to a faster hematologic recovery and the improvement in supportive care, with better management of infections, lowered the TRM of auto-HSCT. Moreover, due to recent advances in understanding the leukemogenesis mechanisms that have led to new prognostic risk stratification, and to the highly sensitive techniques for minimal residual disease (MRD) monitoring, auto-HSCT has gained a place in selected categories of adult patients. On the contrary, at least in the major childhood AML study groups, where the genomic landscape of the disease drives the modern therapeutic strategies, auto-HSCT is no longer used as post-remission AML therapy. Currently, children with favorable risk AML are supposed to receive intensive consolidation CT without transplant, while patients with HR genetic features are directed to allo-HCT in CR1.

Treatment of AML is quickly changing in adults, yet advances in pediatrics are slower to evolve. Tailored drugs, such as gemtuzumab-ozogamicin (GO) and FLT3 inhibitors, have only recently been incorporated into pediatric trials, and the optimal way to include them in therapy is still under investigation.<sup>2</sup> In the future, the role of auto-HSCT could be re-defined, as a consequence of the implementation of new drugs in the initial treatment phases, even in pediatric age.

## Take Home Messages

- Several pediatric studies have reported that auto-HSCT during CR1 in patients not HR had no major advantage over CT alone; allo-HSCT is recommended for those at HR
- In most pediatric AML study groups, auto-HSCT is no longer used in consolidation therapy
- The role of auto-HSCT could be re-defined as a consequence of the implementation of new drugs in the initial treatment phases, even in children

## Acute Promyelocytic Leukemia (APL)

The current combination of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) with, or without low dose CT, achieves cure rate in more than 90% of children and adults with acute promyelocytic leukemia (APL), and disease recurrence has become a very rare event. HSCT is no longer part of first-line therapy in these patients. HSCT, either allogeneic or autologous, has been successfully used as consolidation for patients in second remission (CR2) and appears to offer better results than CT.<sup>19–21</sup> The Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) reported the results of 341 and 228 patients with APL in CR2 consolidated with auto- and allo-HSCT, respectively.<sup>21,22</sup> The probability of EFS was significantly higher in autotransplanted patients compared to those who underwent allo-HSCT (5-year EFS: 75% vs 55%). Similar results have been reported in other large patient series and all confirm the best OS in autotransplant patients.<sup>20–23</sup> Peripheral blood was the preferred stem cell source in most of these studies.

Most of the data refers to adult patients with relapsed/refractory APL. Small pediatric series were reported: 5 children in molecular CR2, after ATO salvage therapy, underwent auto-HSCT and all of them were in continuous CR2 at the time of the analysis;<sup>24</sup> another 9 children were salvaged with ATO followed by consolidation auto-HSCT that allowed long-term survival in 5 of them.<sup>24</sup> Dvorak et al described 32 pediatric cases with relapsed/refractory APL; the 5-year EFS and OS for the 11 children consolidated with auto-HSCT were 82% and 76% and the incidence of TRM and CI of relapse were 0% and 19% (Table 2).<sup>25</sup>

A large number of patients (294 cases; 79 of them aged <20 years) with APL in CR2 receiving allo-HSCT (232), or auto-HSCT (62) as consolidation, were retrospectively analyzed.<sup>22</sup> The 5-year OS and DFS favoured autologous transplant compared to allo-HSCT (75% vs 54% and 63% vs 50%, respectively). The use of ATO pre-HSCT and molecular or cytogenetically positive grafts were not associated with an increased risk of relapse and overall mortality (Table 2). The largest pediatric APL series (95 children treated between 1990 and 2014) was reported by the Japan Society of Hematopoietic Cell Transplantation (JSHCT); 40 children underwent transplant in CR1, 41 in CR2, 3 in CR3 and 11 with persistent disease.<sup>26</sup> Both auto- and allo-HSCT were effective in children transplanted in CR2 (5-year OS 85% vs 78%; DFS 76% vs 75%). Data on salvage induction therapy and pre-transplant molecular response were not reported in this study.

This data has been confirmed by the 25-year Italian experience on relapsed/refractory children and adolescents with APL.<sup>27</sup> Eight patients in CR2 were consolidated with auto-HSCT and 17 with allo-HSCT. No significant differences

**Table 2** Results of Autologous Hematopoietic Stem Cell Transplant in Pediatric Acute Promyelocytic Leukemia in Second Complete Remission

Author (Reference)	N. Patients	Median Age (Years) (Range)	Years	Outcome (Years)
Termuhlen (2008) <sup>24</sup>	5	13 (3–18)	2004–2006	OS 100% and EFS 100% (median FU 20 mos); TRM 0%; RI 0%
Dvorak (2008) <sup>25</sup>	11	12 (2–18)	1992–2007	OS 82% and EFS 73% (5); TRM 0%; RI 27%
Baidil'dina (2010)	7	<18	Before 2010	6 CCR; 1 death (FU: 23–40 mos)
Chakrabarty (2014) <sup>22</sup>	9 70	<20 <20	1995–2006 1995–2006	OS 75%; DFS 63% (5); TRM 7%; RI 30% OS 54%; DFS 50% (5); TRM 31%; RI 18%
Yamamoto (2020) <sup>26</sup>	13	<19	1990–2014	OS 85%; DFS 78% (5)
Testi (2021) <sup>27</sup>	8	13.9 (2.4–24.9)	1994–2017	OS 87.5%; EFS 73% (10) TRM 0%

**Abbreviations:** CCR, continuous complete remission; DFS, disease-free survival; EFS, event-free survival; FU, follow-up; mos, months; OS, overall survival; RI, relapse index; TRM, therapy-related mortality.

between the two transplant procedures have been observed; the 10-year OS and EFS were 87.5% vs 76% and 72.9% vs 70.6%, respectively (Table 2).

Members of the North American Childrens' Oncology Group (COG) and International Berlin-Frankfurt-Munster Study Group (I-BFM-SG) reported recommendations on pediatric APL salvage therapy.<sup>23</sup> According to previous publications and personal experiences, the following characteristics have been considered unfavourable for patient outcomes: short time to relapse, previous ATO treatment and failure to clean *PML-RARA* transcript. Consolidation auto-HSCT is recommended for children not previously treated with ATO, an early relapse, and a molecular CR2. Auto-HSCT is also included in consolidation phase for pediatric patients previously treated with ATO, a late relapse and a molecular CR2 after consolidation. Recommended conditioning regimens do not include TBI, but BU + CY ± MEL.

The best management of children with APL and an extramedullary relapse remains to be determined.<sup>23</sup> The European LeukemiaNet, in 2009, suggested HSCT for patients with central nervous system (CNS) relapse.<sup>19</sup>

In these patients, HD-CA followed by auto-HSCT had been previously employed successfully.<sup>28</sup> More recently, the use of ATO, which can reach therapeutic levels in the CNS, would seem to be of greater benefit in localization of the disease in the CNS.

## Take Home Messages

- The current treatment with ATRA/ATO, in combination, or not, with CT, has significantly improved the prognosis of children and adults with APL, and auto-HSCT is no longer indicated as first-line treatment consolidation
- For patients in CR2, consolidation with auto-HSCT has resulted in better outcomes than non-transplant strategies
- The outcome of patients autotransplanted in CR2 is particularly favourable, if molecularly negative cells are collected
- No impact of ATO-containing versus no-ATO salvage regimens pre-auto-HSCT on the relapse risk after transplant was observed
- The role of auto-HSCT in children with extramedullary relapse is still controversial, although it was recommended by the European LeukemiaNET in 2009

## Acute Lymphoblastic Leukemia (ALL)

Currently, allo-HSCT is considered the best consolidation treatment for adults and children with very HR (VHR) acute lymphoblastic leukemia (ALL) in CR1, and for those in second or subsequent remission. Auto-HSCT has been reserved for patients who were ineligible for allo-HSCT, or for those who did not have a matched related or unrelated donor. In an attempt to eliminate pathological cells from the marrow taken from patients, specific drugs such as mafosfamide (4-HC), or monoclonal antibodies (MoAbs), directed against leukemia cell antigens have been used in vitro, with similar results.<sup>29,30</sup> Pre-HSCT conditioning regimens frequently included TBI (80% of patients); the 3-year DFS ranged from 25% to 35% and TRM from 5% to 21%, but most patients had disease recurrence. Unsatisfactory results were obtained mainly in children undergoing auto-HSCT after early relapses or in third/subsequent remissions (Table 3).<sup>29,30</sup> For late relapses (>2 years from diagnosis) of B precursor ALL, the prognosis after auto-HSCT consolidation appeared better with 3-year EFS of more than 50%. The Spanish Pediatric BM Transplant Units reported data of 55 children with ALL in CR2, undergoing auto-HSCT with in vitro BM stem cells purged (MoAbs and complement, or magnetic microsphere).<sup>31</sup> Pre-transplant conditioning regimens included CT associated, or not, to TBI; the 6-year EFS probability was 46%; first CR duration statistically influenced the patients' outcome (Table 3). TBI included conditioning regimen resulted in better results.

In 10 Italian pediatric centres, 154 children with ALL in second, or subsequent remission, underwent auto-HSCT. Indications to autologous transplant were as follows: relapse within 30 months from diagnosis, HR criteria at diagnosis, lack of any suitable donor, and third or subsequent CR. TRM occurred in 9.7% of patients and the 8-year EFS was 34.6% for children transplanted in CR2, and 10.6% for those in subsequent CR. As in the previous Spanish reports, better results were obtained in children receiving TBI including conditioning regimen (8-year EFS 48% vs 15.4%;  $p = 0.0023$ ), and in those with extramedullary relapse, compared with patients with BM relapse (8-year EFS 68% vs 18%) (Table 3).<sup>32</sup>

Treatment results for children who underwent auto-HSCT, and for those who had CT in CR2, were retrospectively compared (BFM).<sup>33</sup> Eight hundred and eighty-nine patients (age <18 years), with first ALL relapse were enrolled in the BFM multicenter trials; 682 received conventional CT-radiotherapy, 207 underwent HSCT (66 auto-, 141 allo-HSCT). Patients with early BM relapse, or with T-cell ALL, lacking a matched donor, were submitted to auto-HSCT. After a median follow-up of 55 months, the 9-year EFS rates were 32% and 26% for patients receiving CT and auto-HSCT, respectively. Similar results were achieved in the 38 patients treated with late relapse: the 9-year EFS were 55% and 41%

**Table 3** Results of Autologous Hematopoietic Stem Cell Transplant in Pediatric Acute Lymphoblastic Leukemia in CR2 and VHR CR1

Author (Reference)	N. Pts	Median Age (Years) (Range)	Years	Purging	Conditioning Regimen	Outcome (Years)
Billet (1993) <sup>29</sup>	66 CR1, CR2	8 (3–18)	1980–1990	MoAbs	ETP+CA+CY+ TBI	EFS 47% (3)
Billet (1993) <sup>30</sup>	51 CR2	9 (3–18)	1980–1991	MoAbs	ETP+CA+CY+TBI	EFS 53% (NR)
Messina (1998) <sup>32</sup>	154 CR2; >CR2	10 (3–21)	1984–1994	ASTA-Z	TBI+CY; BU+CY	EFS-CR2 34.6%; EFS >CR2 10.6% (8)
Maldonado (1998) <sup>31</sup>	55 CR2	8 (3–17)	1987–1994	MoAbs	TBI+CY	EFS 46% (6)
Borgmann (1995) <sup>33</sup>	66 CR2	6.3 (2–18)	1983–1994	MoAbs/ASTA-Z	ETP+TBI±CY/ETP+CY+BU or Thiotepa	EFS 26% (9)
Balduzzi (2001–2011) <sup>35</sup>	30 CR2	9 (5–16)	1997–1999	MoAbs	TBI+CY+ETP	OS 86.5%; EFS 73.3% (5)
Houtenbos (2001) <sup>36</sup>	24 CR2; >CR2	(0->10)	1990–1996	VCR+ETP+Verapamil	TBI+verapamil+ETP+CY	OS 54%; DFS 42% (2)
Ribera (2007) <sup>37</sup>	38 VHR-CR1	(1–17)	1993–2002	No	TBI+CY; BU+CY	OS 45%; DFS 44% (5)
Hong (2018) <sup>38</sup>	10 VHR-CR1	4.3 (0.3–10.7)	1997–2012	No	BCVAC	OS 70%; EFS 70% (NR)
Capria (2018) <sup>39</sup>	28 VHR-CR1; CR2	31 (10–68)	1996–2015	No	BU+CY/ETP/Thiotepa/MEL	OS 46%; DFS 44% (10)

**Abbreviations:** ASTA-Z, mafosfamide; BCVAC, carmustine, etoposide, cytarabine, cyclophosphamide; BU, busulfan; CA, cytarabine; CR1, first complete remission; CR2, second complete remission; CY, cyclophosphamide; DFS, disease-free survival; EFS, event-free survival; ETP, etoposide; MEL, melfalan; MoAbs, monoclonal antibodies; NR, not reported; OS, overall survival; pts, patients; TBI, total body irradiation; VCR, vincristine; VHR, very high risk.

and TRM 2% and 4%, respectively for CT and auto-HSCT. However, aside from acute procedure-related toxicity, the authors expressed their concerns regarding the late sequelae in transplant survivors (infertility, growth retardation, endocrine defects, or marrow function), less likely to occur after conventional CT.<sup>33</sup>

The results of children with ALL who underwent auto-HSCT with in vitro purified leukoapheretic products were subsequently reported. In an Italian center, BM collected cells treated with MoAbs were utilized in 11 children with late relapse of B precursor ALL, in CR2.<sup>34</sup> The efficacy of in vitro leukemia eradication was assessed by polymerase-chain reaction (PCR) and children rescued with PCR negative cells had 2-year EFS of 89%. These results were confirmed in 30 Italian children with B-cell precursor ALL, in CR2 after isolated extramedullary relapse and/or late relapse.<sup>35</sup>

Subsequently, 103 children treated in the same period with CT (BFM best salvage chemotherapeutic schema) were compared to the 30 autotransplanted patients. The 103 control cases matched the 30 autografted patients, according to site of relapse, CR1 duration, time elapsed in CR2 and period of relapse. The 5-year EFS and OS were 73.3% and 86.5% for autotransplanted cases, and 40% and 62.5% for CT-treated controls. The final analysis showed an advantage of purified auto-HSCT, compared with CT in low-risk relapsed ALL, possibly explained by the single-centre effect, the myeloablation of TBI, and the stem cell isolation procedure (Table 3).<sup>35</sup>

In the USA, in the attempt to reduce the relapse rate associated with auto-HSCT, five children with HR ALL in CR1, and 19 in second, or subsequent CR, lacking matched family allogeneic donors underwent auto-HSCT with chemopurged BM, utilizing verapamil, vincristine (VCR) and ETP. Conditioning regimen included TBI, verapamil bolus, ETP and CY.<sup>36</sup> Additionally, based on previous adult experiences demonstrating that post-transplant immune-CT may reduce the risk of relapse, seven children received cyclosporine A (CsA) and alpha-interferon ( $\alpha$ IFN), 13 patients CsA, and six alternating cycles of  $\alpha$ IFN and CT, plus six additional CT cycles (VCR, ETP, CA, prednisone) and, the last four patients, CsA, alone. The 2-year DFS and OS were 42% and 54%, respectively. Patients receiving post-transplant immune-CT compared with those receiving immunotherapy alone, had a better 2-year DFS and OS (69% versus 13% and 85% versus 25%, respectively). Chemopurged auto-HSCT, combining with post-transplant immune-CT, usually well tolerated, represented an alternative approach in the treatment of a subset of children with HR ALL in CR1, CR2 and subsequent CR, lacking allogeneic donor. The immune-CT after transplant may be a method to eradicate residual leukemic disease and consequently, to decrease the high relapse rate associated with auto-HSCT.<sup>36</sup>

In the past years, auto-HSCT was part of the consolidation therapy for children in CR1 with VHR ALL. The Programa Espanol de Tratamientos en Hematologia (PETHEMA) ALL-93 trial compared intensive CT, allo-HSCT and auto-HSCT for ALL children with the following characteristics: age <1 year, B-lineage ALL with initial WBC  $\geq 300.0 \times 10^9/L$ , T-lineage ALL with diagnostic WBC  $\geq 100.0 \times 10^9/L$ , t(9;22), t(4;11) or other 11q23 rearrangements.<sup>37</sup> Patients in CR with an HLA-identical sibling received allo-HSCT, whereas the remaining patients were randomly assigned to auto-HSCT, or delayed intensification CT and maintenance. The three groups were comparable in the main pre-treatment ALL characteristics. No differences for donor versus no donor in the 5-year DFS (45%), as well as for auto-HSCT versus CT comparison (5-year DFS: 44% vs 46%), were found (Table 3); similar outcomes were observed within the different ALL subgroups (Table 3). However, the overall results obtained in this trial confirmed the poor prognosis of these VHR-ALL children.

The Japanese Society of Hematology reported the results achieved in children with VHR ALL lacking HLA-matched allogeneic donors and treated with HD-CT, auto-HSCT followed by maintenance CT.<sup>38</sup> Between 1997 and 2012, patients in CR1 received HD-CA and ETP, and G-CSF for peripheral blood stem cells mobilization; BAVC (carmustine, ETP, CA and CY) was used as pre-transplant conditioning regimen. The OS and EFS for the 10 treated children were 70% (median follow-up 7.4 years) (Table 3). No severe adverse events were observed during treatment.

In more recent years, the ALL therapeutic protocols, first for children and then also for adults, have included the evaluation of MRD assessed by flow cytometry (MFC) and/or PCR in the early phases of treatment (at the end of induction and consolidation). This has allowed a more precise classification of patients into risk categories, and a better identification of patients who need to undergo allo-HSCT.<sup>39</sup> In addition, the improvement of MRD detection strategies may help to identify a specific subgroup of ALL cases, MRD-negative and ineligible for allogeneic transplantation that could be considered for auto-HSCT. In our centre, 28 ALL patients (adults and children; 20 in CR1 and 8 in CR2) were treated with HD-CT and auto-HSCT, followed by standard maintenance and intrathecal CT for 1 year. Pre-transplant

MRD was tested in BM by MFC (11 cases), and PCR-based assay in 17 cases (Table 3).<sup>39</sup> Twenty-two patients were MRD negative and six were positive. MRD was also investigated in the apheretic product in 22 patients and proved negative in 20 of them. The 10-year DFS was 59% for patients MRD negative compared to 0% for MRD positive ones (all patients MRD positive relapsed). Moreover, the DFS was 83% for patients MRD negative by PCR.

Patients with isolated extramedullary relapse appeared to benefit from HD-CT and auto-HSCT. Despite the relatively small number of patients, these results confirmed the role of molecular negativity at the time of transplant and corroborated the concept that patients with isolated extramedullary relapse may have an excellent likelihood of achieving long-term DFS with consolidation auto-HSCT.

## Take Home Messages

- Allo-HSCT is currently the standard of care for HR ALL children in CR1, or subsequent CR
- Different techniques, either pharmacologic or immunologic, to purge stem cell collection, have been used, and comparable results have been reported
- Patients with isolated extramedullary relapse achieve long-term DFS with auto-HSCT, if they present a molecular negative disease at the time of transplant
- In the future, the improvement of MRD detection strategies may help to identify a specific ALL subgroup that may be considered for auto-HSCT, if lacking an allogeneic donor, or are not eligible for allo-HSCT

## Chronic Myeloid Leukemia (CML)

Chronic myeloid leukemia (CML) is a rare pathology in childhood and represents 2–3% of all leukemias in children and adolescents.<sup>40,41</sup> It occurs more frequently in adolescents than in younger children and, at onset, shows more aggressive clinical features (elevated WBC, significant splenomegaly, advanced phase) than adult CML.<sup>40–43</sup> The history of the disease has changed completely with the advent of tyrosine kinase inhibitors (TKIs), a class medication that inhibits the *BCR-ABL1* oncoprotein. In adults, the use of these orally administered drugs has significantly improved the expectation and quality of life which is currently comparable to that of the healthy population.<sup>44,45</sup> Imatinib was the first TKI used in the treatment of CML. This was followed by second-generation TKIs, such as dasatinib, nilotinib, recently approved as first-line therapy and designed to be active in imatinib-resistant or intolerant patients.<sup>40–42,46,47</sup> Successful experiences in adults have also been transferred to children, where TKIs have confirmed their effectiveness. In children, however, the prolonged use of these drugs has led to the appearance of some side effects, such as growth disturbances, which were not evident in adulthood.<sup>48–50</sup>

In adult patients who showed a prolonged and profound molecular response with TKIs therapy, it was possible to discontinue the treatment. Even in pediatric age, some positive experiences of therapy discontinuation have been reported which are sometimes due to an attempt to reduce therapy-related side effects.<sup>51–53</sup>

Before the development of TKIs, standard treatment of CML involved CT, particularly hydroxyurea,  $\alpha$ IFN and allo-HSCT. In the 1990s, in Europe, auto-HSCT was used in patients with chronic CML phase and preliminary results suggested that, in some patients, it was possible to obtain a cytogenetic response and to prolong survival.<sup>54–57</sup> Subsequently, several centres reported their experience of auto-HSCT in CML using in vivo or in vitro manipulation of BM designed to increase the overall response rate.<sup>58,59</sup> During the chronic phase, HD-CT was used to mobilize negative BCR-ABL cells; the cryopreserved cells were reinfused into the patient in chronic or accelerated phase, or frank blast crisis. In addition to in vivo purging approaches, in vitro manipulations such as cultures with cytotoxic agents, use of MoAbs directed against the BCR-ABL fusion protein, antisense oligonucleotides directed against the BCR-ABL oncogene, or the *Myb* gene were performed.<sup>58,59</sup> The results, mainly reported in adults, were controversial.

After the advent of TKIs, some adult patients in cytogenetic remission (CCyR), treated with imatinib, have had attempts made at stem cell harvesting. Fifty-eight patients in CCyR received G-CSF during imatinib treatment; 84% of them had a BCR-ABL negative collection.<sup>60</sup> These results, reported by the United Kingdom (UK) CML Working Party, were confirmed by the German and Italian CML groups with an identical strategy.<sup>61,62</sup> None of these studies included pediatric patients alone.

In the era of TKIs, the role of HSCT, both allogeneic and autologous, has been considerably limited; allo-HSCT is currently reserved for patients, both children and adults, resistant or intolerant to TKIs; auto-HSCT, with collected *BCR-ABL* negative stem cells, in CCyR patients could represent a further therapeutic option.

## Take Home Messages

- The advent of TKIs has dramatically improved the outcome of patients with CML
- The majority of TKI responders can have a *BCR-ABL* negative stem cell collection
- Auto-HSCT with *BCR-ABL* negative stem cells, collected in CCyR, may represent a therapeutic option for some pediatric patients showing TKIs toxicity or disease resistance

## Non-Hodgkin Lymphoma (NHL)

In pediatric non-Hodgkin lymphoma (NHL), the cure rates range from 75% to more than 90% according to histological subtypes.<sup>63,64</sup> With the current protocols, HSCT, either autologous or allogeneic, is reserved for refractory/relapsed cases. The results of the largest study analyzing international strategies on re-induction treatment, and the employment of HSCT in pediatric relapsed/refractory NHL, were recently published.<sup>65</sup> Of the 639 evaluable patients, 23% underwent auto-HSCT, 39% allo-HSCT, and 37% were not transplanted. The 8-year OS from relapse was 34% for the entire population, 55% for autotransplanted, 47% for allotransplanted and only 8% for not transplanted patients. The remission status at HSCT was highly associated with the outcome, and no clear advantage for allo- versus auto-HSCT was observed. Significant differences were found in the different histological subtypes, with OS ranging from 57% for primary mediastinal large B-cell NHL (PMBCL) to 28% for Burkitt lymphoma (BL)/B-cell acute leukemia (BAL) and 27% for T-lymphoblastic lymphoma (T-LBL).

## Aggressive B-Cell NHL

Children and adolescents with B-cell NHL account for about 60% of pediatric NHL. Currently, short intensive CTs, modulated according to the extent of the disease, associated to anti-CD20 (rituximab) in HR patients, provide an EFS rate of 90%, at 3–4 years.<sup>64,66,67</sup> Very few patients experience a relapsed/refractory disease. However, the prognosis of these patients is still poor, with survival rates less than 50% in most reports. The outcome is particularly poor for those children with primary refractory to first-line therapy, or those not responding to salvage schemas.

Auto-HSCT and allo-HSCT are considered the best options for patients responding to salvage therapies. However, in the reported pediatric experiences, the proportion of patients treated with different salvage regimens which could be submitted to an HSCT ranged from 21% to 63%.<sup>68–74</sup> Most of the data is limited to retrospective analyses or single/few-centre experiences, mostly including patients with B- and with T-cell NHL submitted to auto- or allo-HSCT with heterogeneous conditioning regimens. The EFS rates ranged from 27% to 59% and the OS from 27% to 58%, at 4–5-year (Table 4). No clear differences between auto or allografted patients were reported and the disease remission at HSCT was the only predictive factor for better survival.<sup>68–75</sup> The outcome of BL/BAL patients treated with strategies including HSCT was recently analyzed by Woessmann for the BFM group.<sup>76</sup> Seventy-one patients, who relapsed after 2001, were included; the 3-year OS was 25% for 20 autotransplanted patients compared with 58% for 26 allotransplanted patients ( $p = 0.026$ ). Twenty-five patients were unable to receive an HSCT because of disease progression and all of them died. No conclusions regarding the efficacy of auto-HSCT versus allo-HSCT were drawn by the authors<sup>76</sup> (Table 4).

Larger series of relapsed/refractory pediatric NHL from HSCT registries have been published.<sup>77–79</sup> The European Bone Marrow Transplantation Registry (EBMTR) reported 89 patients who received an auto-HSCT between 1979 and 1991; the 5-year EFS was 39.4% and was significantly associated with the degree of response prior to transplant.<sup>77</sup> Gross reported the outcome of pediatric patients with relapsed/refractory NHL transplanted between 1990 and 2005, with data obtained from the Centre for International Blood and Marrow Transplant Research (CIBMTR).<sup>78</sup> The 5-year EFS was 27% after auto- and 31% after allo-HSCT for 41 patients with BL, and 50% after auto- and 52% after allo-HSCT for the 52 patients with diffuse large B-cell NHL (DLBCL) (Table 4).

In the recent international study on pediatric relapsed/refractory NHL, the 8-year OS was 28% for the 254 patients with BL/BAL. HD-CT followed by HSCT was planned for all patients; however, 38% of them could not reach HSCT.



**Table 4** Results of Autologous Hematopoietic Stem Cell Transplant in Pediatric Relapsed/Refractory Aggressive B-Cell Lymphoma

Author (Reference)	N. Patients	Age (Years)	Years	Disease Status Before HSCT	Outcome (Years)
Loiseau (1991) <sup>68</sup>	24 auto (B-NHL 16)	< 18	NR	NR	OS 33% (NR)
Bureo (1995) <sup>69</sup>	46 (auto 32, allo 14) (B-NHL 25)	< 18	NR	NR	EFS 58% (NR)
Philip (1993) <sup>72</sup>	15 (auto 14, allo 1)	< 18	1984–1987	NR	EFS 27% (4)
Landestein (1997) <sup>77</sup>	89 auto	< 18	1979–1991	CR 24, PR 51, Res 14	EFS 39.4% (5)
Won (2006) <sup>70</sup>	12 auto (BL 6, DLBCL 6)	< 18	1997–2004	CR, no CR	EFS BL 66%; DLBCL 55% (2)
Gross (2010) <sup>78</sup>	93 (auto 52, allo 41) <b>BL/BAL</b> 41 (auto 17, allo 24) <b>DLBCL</b> 52 (auto 35, allo 17)	< 18	1990–2005	NR	<b>BL/BAL</b> : EFS auto 27%; allo 31% (5) <b>DLBCL</b> : EFS auto 50%; allo 52% (5)
Harris (2011) <sup>73</sup>	10 auto (B-NHL)	< 21	-	NR	EFS 70% (3)
Giulino-Roth (2013) <sup>71</sup>	36 (auto 15, allo 21) (B-NHL 9)	< 18	1982–2004	NR	DFS 53% auto and allo (10)
Jourdain (2015) <sup>74</sup>	41 (auto 33, allo 8)	< 20	1989–2007	CR 35, no CR 6	OS 46.3% (auto 48.5%; allo 37.5%) (5)
Hazar (2018) <sup>79</sup>	22 (auto 15, allo 7)	< 18	2006–2014	CR 13, PR 3, Res 6	EFS auto 53%; allo 86% (NR)
Rigaud (2019) <sup>75</sup>	21 (auto 13, allo 8)	< 18	2001–2011	CR 12, no CR 9	OS 54% (auto 54%; allo 50%) (5)
Burkhardt (2021) <sup>65</sup>	<b>BL/BAL</b> 254 (auto 64, allo 87) <b>DLBCL</b> 98 (auto 47, allo 25)	< 18	2000 - NR	CR, PR, SD, PD	<b>BL/BAL</b> : OS 28%; auto 44% allo 46% (8) <b>DLBCL</b> : OS 50%, (auto 68%; allo 55%) (8)
Woessman (2020) <sup>76</sup>	71 BL/BAL (auto 20, allo 26)	< 18	1986–2016	CR	OS auto 25%; allo 58% (3)
Satwani (2015) <sup>80</sup>	5 tandem auto-allo	7–33	2001–2011	CR 2, PR 3	5/5 alive
Gardenswartz (2018) <sup>81</sup>	13 tandem auto-allo	7–33	NR	Chemosensitive disease	EFS 91% (NR)

**Abbreviations:** Allo, allogeneic transplant; auto, autologous transplant; BAL, B acute leukemia; BL, Burkitt lymphoma; EFS, event free survival; CR, complete remission; DFS, disease free survival; DLBCL, diffuse large B-cell lymphoma; HSCT, hematopoietic stem cell transplant; NHL, non-Hodgkin lymphoma; NR, not reported; OS, overall survival; PD, progressive disease; PR, partial remission; Res, resistant; SD, stable disease.

The survival rate for the 103 BL/BAL patients not transplanted was 3% compared with 44% for the 64 autotransplanted, and 46% for 87 patients submitted to allo-HSCT.<sup>65</sup> The 8-year OS was 50% for the 98 relapsed/refractory DLBCL and, in particular, 13%, for 26 not transplanted, 68% for 47 autotransplanted, and 55% for the last 25 patients who received allo-HSCT.<sup>65</sup>

In order to improve the prognosis in these patients, a multicenter prospective study of myeloablative conditioning (MAC) and auto-HSCT, followed by a reduced intensity conditioning (RIC) and allo-HSCT in children, adolescents, and young adults with poor risk refractory, or recurrent NHL, was designed.<sup>80,81</sup> Conditioning for MAC consisted of carmustine/ETP/CY; RIC included BU/fludarabine. Thirty patients, 16 Hodgkin lymphoma (HL) and 14 NHL, with a median age of 16 years and median follow-up of 5 years were enrolled. Twenty-three patients completed both MAC auto-HSCT and RIC allo-HSCT. Allogeneic donor sources included unrelated cord blood (n = 9), unrelated donor (n = 8), and matched siblings (n = 6). The incidence of TRM following RIC allo-HSCT was 12%. In patients with NHL, the 10-year EFS was 70% (Table 4). The approach was safe and encouraging for young patients with poor prognostic characteristics.

Numerous novel therapies are currently being tested in adults with relapsed/refractory B-NHL with promising results, but for several reasons, new agents are difficult to test in the pediatric population. However, in children and adolescents, some selected new agents (new targets, next-generation MoAbs and novel approaches in cellular therapy) are starting to be used. The creation of an international working group to develop clinical trial strategies in refractory/relapsed B-cell NHL is recommended.

## Lymphoblastic Lymphoma (LBL)

Lymphoblastic lymphoma (LBL) is the second most common type of NHL in childhood and adolescents, accounting for 25–35% of all cases. The majority (70–80%) is of T-lymphoblastic origin, while 20–25% arise from B-lymphoblasts.<sup>82,83</sup>

The application of ALL-like treatment regimens, including hyper-CVAD (fractionated CY, VCR, doxorubicin and dexamethasone) and BFM protocols, has led to a significant improvement of the outcome, with OS rates exceeding 80% of pediatric T-cell LBL.<sup>82,83</sup> The role of HSCT consolidation remains unclear, especially in the modern ALL-like regimens setting. However, the cure rates for patients with relapsed/refractory disease remain dismal with survival rates of 10–30%.<sup>83,84</sup> According to the limited data available in literature, only patients receiving HD-treatment followed by auto- or allo-HSCT, have a chance of cure. In a Japanese cohort of patients with relapsed/refractory LBL, 19 underwent allo-HSCT. At 3 years, ten survived in CR, six relapsed, and three died of TRM. Six patients received auto-HSCT: four relapsed and two survived<sup>85</sup> (Table 5).

The role of HSCT was analyzed by the CIBMTR of North America: 53 pediatric LBL received allo-HSCT (39 children) or auto-HSCT (14 children) between 1990 and 2005.<sup>78</sup> The 5-year EFS for 39 allotransplanted patients was 40% compared with 4% in the 14 autotransplanted patients. In Korea, 14 children with relapsed/refractory LBL received consolidation auto-HSCT and the 2-year EFS was 50%.<sup>70</sup>

The NHL-BFM group reported 12/34 patients with relapsed LBL who received allo-HSCT. Five survived, six died after relapse, and two of TRM. Two other patients underwent auto-HSCT and both died due to disease progression.<sup>86</sup> Similar results were reported by Michaux with 5/12 patients alive after allo-HSCT and neither of the two autotransplanted patients (Table 5).<sup>87</sup>

Recent results published by the International Study of relapsed/refractory pediatric NHL show an 8-year OS of 27%, for the 177 T-cell LBL. A high proportion of patients (43%) could not receive any HSCT, due to disease progression before transplant procedure. The 8-year OS for not-transplanted patients was significantly lower compared to the 12 patients treated with auto-HSCT (OS 6% and 33%; respectively) (Table 5).<sup>65</sup>

Concerning the discussion on whether allo- or auto-HSCT is superior, there is a trend for higher TRM, but also a higher probability of DFS after allo-HSCT compared to auto-HSCT. Auto-HSCT does not seem to have a major role in the treatment of relapsed/refractory LBL. However, the total number of cases in literature is too small to draw definitive conclusions.

## Anaplastic Large Cell Lymphoma (ALCL)

Anaplastic large cell lymphoma (ALCL) accounts for about 15% of pediatric NHL. Currently, with different intensive multiagent CT regimens, EFS rates, vary between 65% and 75%, and OS rates between 70% and 90%, at 3–8 years.<sup>88–91</sup> A second disease response is obtained in most relapsed patients. Consolidation strategies based on auto- or allo-HSCT have been analyzed in some retrospective studies. The French Group reported the outcome of 41 ALCL relapse. DFS was 45% for 15 ALCL patients who received HSCT (14 auto-HSCT, 1 allo-HSCT) in CR2.<sup>92</sup> An initial Japanese study on 26 relapsed ALCL patients reported better results in those patients in CR2 consolidated with allo-HSCT (6 cases), compared to auto-HSCT (8 cases).<sup>93</sup> A second study, also from Japan, described the outcome of 47 ALCL relapsed patients receiving HSCT: 23 auto-HSCT, 24 allo-HSCT. The 5-year EFS was 38% and 50%, respectively, for auto- and allo-

**Table 5** Results of Autologous Hematopoietic Stem Cell Transplant in Pediatric Relapsed/Refractory Lymphoblastic Lymphoma

Author (Reference)	N. Patients	Age (Years)	Years	Disease Status Before HSCT	Outcome (Years)
Won (2006) <sup>70</sup>	14 auto	< 18	1997–2004	CR, no CR	EFS 50% (2)
Mitsui (2009) <sup>85</sup>	33 (auto 7, allo 26)	< 15	1996–2004	CR, PR, PD	OS 43.2% (3)
Gross (2010) <sup>78</sup>	53 (auto 14, allo 39)	< 18	1990–2005	NR	EFS 4% auto; 40% allo (5)
Burkhardt (2009) <sup>86</sup>	14 (auto 2, allo 12)	< 18	1990–2003	CR, PR	CCR 0 auto; 5/12 allo
Michaux (2016) <sup>87</sup>	10 (auto 2, allo 8)	< 18	1997–2008	CR, PR, PD	2/2 deaths auto; 2/8 alive allo
Burkhardt (2021) <sup>65</sup>	T-LBL 177 (auto 12, allo 89) B-LBL 34	< 18	2000 - NR	CR, PR	T-LBL: OS 33% auto; 44% allo (8) B-LBL: OS 52% (8)

**Abbreviations:** Allo, allogeneic transplant; auto, autologous transplant; EFS, event free survival; CCR, continuous complete remission; CR, complete remission; HSCT, hematopoietic stem cell transplant; LBL, lymphoblastic lymphoma; NR, not reported; OS, overall survival; PD, progressive disease; PR, partial remission.

HSCT.<sup>94</sup> The analysis of 36 relapsed/refractory ALCL patients from CIBMTR showed a 5-year RFS of 35% for 24 patients who were consolidated with auto-HSCT, compared to 46% 5-year EFS for 12 allotransplanted patients.<sup>78</sup> The BFM group reported a large retrospective cohort of 74 children with first relapse of ALCL after front-line BFM-NHL therapy. CT followed by auto-HSCT was planned for all patients; the 5-year EFS and OS for the 39 children who were autotransplanted were 59% and 77%, respectively (Table 6). The results were strongly influenced by the time to relapse and the CD3 positivity.<sup>95</sup>

The role of auto- and allo-HSCT in relapsed/refractory ALCL was more recently analyzed in the International prospective ALCL-relapse trial (NCT00317408) for children and adolescents with relapsed ALCL.<sup>96</sup> The trial was based on different strategies for 4 risk groups, defined as VHR, HR, intermediate and low risk, according to time to relapse, CD3 expression, and prior vinblastine treatment. Low-risk patients received vinblastine alone; all the other risk groups were treated with CT followed by allo-HSCT for those at VHR and HR, and auto-HSCT for the intermediate risk group, or HR patients without an available donor. Allo-HSCT, performed in 36 patients, confirmed its efficacy as consolidation therapy for HR relapsed ALCL, the 5-year OS and EFS were 83% and 81%, respectively. Auto-HSCT was performed in 22 patients. The 5-year OS and EFS rates were 82% and 41% (Table 6).

The high rate of events in patients scheduled for auto-HSCT led to the abandonment of this procedure in 2012, and the authors concluded that auto-HSCT is not indicated as consolidation therapy for children with relapsed/refractory ALCL.

## Nonanaplastic Peripheral T-Cell Lymphomas (PTCL)

Nonanaplastic peripheral T-cell lymphomas (PTCLs) are very rare in children and adolescents comprising 0.9% of NHL.<sup>97</sup> The literature available on PTCL in children and adolescents shows that survival rates with conventional CT and HSCT are still poor compared to other NHL subentities, but also that treatment results vary among different PTCL subgroups. Five-year EFS and OS were 45% and 56%, respectively, for the 143 patients of the BFM study.<sup>98</sup> Outcomes varied among the histopathological subgroups, suggesting that a subtype-specific treatment approach might be indicated. However, solid basic therapy principles based on prospective randomized trials are completely lacking in children and adolescents, so treatment recommendations are merely based on adult experience and retrospective pediatric series. There is no standardized treatment for pediatric PTCL-Not-otherwise-specified-(NOS) that receive block-like mature B-cell NHL- or ALCL-type therapy ± maintenance, or T-cell ALL treatment. No difference in EFS and OS among the different groups of treatments has been found (5-year OS 56%–75%; EFS 47%–55%, respectively).<sup>98</sup> While consolidation therapy with auto- or allo-HSCT in CR1 is recommended in adults, its role in children and adolescents with PTCL is still a matter of debate. Few experiences reported small numbers of children transplanted in CR1, or CR2, or with disease progression; most of them received allo-HSCT and the OS rate was almost 50%. While the indication for allo-HSCT in CR1 seems to be clear, auto-HSCT does not seem to have a role in CR1 and CR2.

**Table 6** Results of Autologous Hematopoietic Stem Cell Transplant in Pediatric Relapsed/Refractory Anaplastic Large Cell Lymphoma

Author (Reference)	N. Patients	Age (Years)	Years	Disease Status Before HSCT	Outcome (Years)
Brugieres (2000) <sup>92</sup>	15 auto	< 18	1975–1997	CR	DFS 45% (3)
Mori (2006) <sup>93</sup>	Auto 8, allo 6	< 18	1989–2003	CR	RFS 33% auto; 100% allo (3)
Won (2006) <sup>70</sup>	7 auto	< 18	1997–2004	CR, no CR	EFS 100% (2)
Gross (2010) <sup>78</sup>	Auto 24, allo 12	< 18	1990–2005	NR	EFS 35% auto; 46% allo (5)
Woessmann (2011) <sup>95</sup>	39 auto	< 18	1990–2003	CR	EFS 59%; OS 77% (5)
Fukano (2015) <sup>94</sup>	Auto 23, allo 24	< 18	1990–2010	CR 16/23 auto, CR 8/24 allo	EFS 38% auto; 50% allo (5)
Knorr (2020) <sup>96</sup>	Auto 22, allo 36	< 21	2004–2014	CR 21/22 auto, NR allo	EFS 41% auto; 81% allo (5)

**Abbreviations:** Allo, allogeneic transplant; auto, autologous transplant; EFS, event free survival; CR, complete remission; DFS, disease free survival; HSCT, hematopoietic stem cell transplant; NR, not reported; OS, overall survival; RFS, relapse free survival.

## Take Home Messages

- Currently, excellent results are achieved in children and adolescents with B-cell NHL combining CT and rituximab
- International trials have reported better results in pediatric patients with relapsed/refractory B-cell NHL consolidated with both auto- or allo-HSCT compared to non-transplanted patients
- The remission status at HSCT has been highly associated with the outcome and no clear advantage of allo- versus auto-HSCT was observed
- A new approach with myeloablative conditioning and auto-HSCT, followed by a reduced intensity conditioning and allo-HSCT, in relapsed/refractory children and adolescents with very poor prognostic characteristics has demonstrated to be safe, with encouraging results in this poor category of patients
- Auto-HSCT does not seem to have a major role in the treatment of relapsed/refractory LBL and ALCL.

## Hodgkin Lymphoma (HL)

The prognosis of children and adolescents with Hodgkin Lymphoma (HL) has progressively improved, reaching an OS of more than 90%, at 5–10 years. In children and adolescents, the first-line strategies have changed over the past decades with the aim of reducing the serious late effects and maintaining their high efficacy. Use of radiotherapy (RT) was progressively reduced in terms of doses and irradiation fields and is reserved for patients with an inadequate early or late response assessment by metabolic imaging (fluorodeoxyglucose positron emission computed tomography-FDG-PET scans). However, despite the improvements in outcomes, up to 15% of patients present relapse or refractory disease. Cure may be achieved also in these settings, but in children and adolescents, there is still no defined salvage treatment, and randomized trials comparing standard-dose CT (SD-CT) to HD-CT and auto-HSCT are lacking. However, HD-CT followed by auto-HSCT, which represents the standard of care for adults with relapsed/refractory disease, is largely employed also in pediatric age.<sup>99–102</sup> Two adult randomized studies compared SD-CT with HD-CT in patients with HL first relapse.<sup>101,103</sup> The British National Lymphoma Investigation (BNLI) trial randomized HD-BEAM (carmustine, ETP, CA, MEL) and auto-HSCT or mini-BEAM and CT in 40 adult patients not responding to conventional CT. The German Hodgkin's Lymphoma Study Group (GHSG) and the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (EBMT)-HDR1 trial compared BEAM and auto-HSCT with Dexamethasone-BEAM in 117 adults with CT-sensitive relapse. Both studies showed superior progression-free survival (PFS) for salvage regimen including auto-HSCT versus CT.<sup>101,103,104</sup>

In pediatric relapsed/refractory HL, in the absence of randomized studies to evaluate the role of auto-HSCT, data on the outcome and potential prognostic factors can be inferred from the literature in one prospective and some retrospective studies.

Older series have included both children and adults (Table 7). The impact of auto-HSCT was evaluated in 81 pediatric patients (<16 years at diagnosis) and 81 adults (16–50 years). There was no significant difference in the outcome between the two groups in terms of PFS (39% vs 48%;  $p = 0.64$ , at a median follow-up of 37 months) and relapse rate (52% vs 40%;  $p = 0.65$ ).<sup>105</sup> Several other studies reported retrospective series of pediatric patients; the 5-year EFS were 45–65% and the 5-year OS 55%–74%.<sup>106–112</sup> The prospective multicenter German-Austrian pediatric nonrandomized salvage therapy (ST-HD-86 trial) reported a 10-year OS of 51% in 53 children treated with auto-HSCT out of 176 relapsed/refractory HL.<sup>113</sup> A more recent review of the CIBMTR reported a lower 10-year PFS of 41% in auto-transplanted pediatric and young adults HL owing to late relapses and late toxicity.<sup>114</sup> The Memorial Sloan Kettering Cancer Center (MSKCC) retrospectively analyzed 36 consecutive pediatric patients with relapsed or refractory HL, auto-transplanted between 1989 and 2013.<sup>115</sup> All patients underwent a disease evaluation before auto-HSCT. The majority of them were transplanted in CR (61%) or partial response (14%). The 10-year OS was 74.1% and EFS 67.1%. Univariate analysis showed that sensitive disease at HSCT (EFS and OS: HR 0.18,  $p = 0.0039$  and 0.22,  $p = 0.0219$ , respectively) and the absence of B symptoms (EFS and OS: HR 0.12,  $p = 0.0015$  and 0.18,  $p = 0.0170$ , respectively) were associated with improved outcome. In this paper, patients were divided between those who underwent auto-HSCT before 1997, and those transplanted from 1998; this last cohort of patients had a superior outcome for both EFS and OS (85.8% and 91.7%, respectively, compared to 48.8% and 59.1%) (Table 7). Other retrospective series of children and adolescents with HL have reported potential factors associated with a poor outcome. All concluded that prognostic factors for risk of further

**Table 7** Results of Autologous Hematopoietic Stem Cell Transplant in Pediatric Relapsed/Refractory Hodgkin Lymphoma

Author (Reference)	N. Patients	Median Age (Years) (Range)	Years	Disease Evaluation Before HSCT	Outcome (Years)
Williams (1993) <sup>105</sup>	81	16.9 (5.2–32.6)	< 1992	NR	PFS 39% (3)
Brice (1997) <sup>99</sup>	280	30 (5–59)	1982–1993	NR	OS 66%; PFS 60% (4)
Baker (1999) <sup>106</sup>	53	< 21	1984–1996	NR	OS 43%; EFS 31% (5)
Verdeguer (2000) <sup>109</sup>	20	10.5 (5–18)	1986–1997	NR	OS 95%; EFS 62% (5)
Stoneham (2004) <sup>107</sup>	51	12 (3–16)	1982–2000	RX/CT	34 patients alive (median FU 4.5 years)
Frankovich (2001) <sup>108</sup>	34	17 (7–21)	1989–1998	RX/CT	OS 79%; DFS 67% (5)
Lieskovsky (2004) <sup>110</sup>	41	18 (7–20)	1989–2001	RX/CT	OS 68%; EFS 53% (5)
Claviez (2008) <sup>111</sup>	74	14 (8–18)	NR	NR	OS 59%; PFS 50% (5)
Schellong (2005) <sup>113</sup>	53	14.7 (4.3–24.5)	1986–2003	RX/TC	OS 75%; EFS 57% (10)
Metzger (2010) <sup>118</sup>	50	16.1 (14.9–22)	1990–2006	CT/FDG-PET	OS 58% (5)
Gorde-Crosjean (2011) <sup>119</sup>	50	15 (4–20)	1990–2006	CT/FDG-PET	OS 66%; DFS 64% (median FU 40 mos)
Harris (2011) <sup>73</sup>	28	< 21	2000–2010	NR	OS 63%; EFS 65% (3)
Sumaili (2014) <sup>117</sup>	29	9.8 (3.6–16.7)	1995–2012	NR	OS 61.9%; EFS 60.4% (5)
Garfin (2015) <sup>112</sup>	89	17.8 (8–21)	1989–2012	CT/FDG-PET	OS 71%; EFS 65% (5)
Satwani (2015) <sup>114</sup>	606	23 (3–29)	1995–2010	NR	OS 58%; PFS 47% (5)
Hazar (2015) <sup>79</sup>	66	15 (7–20)	1993–2013	NR	OS 63%; EFS 54% (median FU 43 mos)
Giulino-Roth (2018) <sup>115</sup>	36	17.7 (9.7–21)	1989–2013	CT/FDG-PET	OS 74.1%; EFS 67.1% (10)

**Abbreviations:** CT, computed tomography; DFS, disease free survival; EFS, event free survival; FDG/PET, fluorodeoxyglucose positron emission computed tomography; FU, follow-up; HSCT, hematopoietic stem cell transplant; mos, months; NR, not reported; OS, overall survival; PFS, progression free survival; RX, radiography.

relapse were chemo-refractory disease, both primary or after salvage treatment, and short remission duration.<sup>110,116,117</sup> Other poor prognostic factors emerged from various studies, such as extra-nodal disease, mediastinal bulk, B symptoms, anemia, elevated erythrocyte sedimentation rate, elevated lactate dehydrogenase at relapse.<sup>110,113,116–119</sup> The Childhood Hodgkin Lymphoma International Prognostic score (CHIPS), developed by COG to stratify patients in risk categories at diagnosis, was also predictive for children at relapse, with a better OS for patients with a lower R-CHIPS.<sup>115</sup> The stratification of pediatric patients with refractory/relapsed HL will help to select the patients that may benefit of SD-CT plus RT, or are candidate to auto-HSCT, or need alternative therapies. In fact, in the past years, in children with relapsed HL, some studies showed that non-transplant salvage therapy with SD-CT plus RT is effective for a good risk subset of patients that do not require HD-CT and auto-HSCT. The prospective pediatric ST-HD-86 relapse trial reported 10-year DFS of 86% with SD-CT and RT in patients with late relapse (>12 months).<sup>113</sup> These results were confirmed by other studies, such as the UK HD3 trial, and the United States (US) St. Jude study, that reported 5-year 74% DFS and 10-year 80% DFS in late relapse, and 5-year 100% DFS in children responding to first salvage CT (Table 7).<sup>118,120</sup> A survival benefit with HD-CT followed by auto-HSCT was instead observed in children with primary refractory and multiple relapsed disease.<sup>109,121</sup> In order to standardized recommendations for salvage therapy in children with relapsed/refractory HL, a risk stratification at the time of relapse, was published by the European (EuroNet) Pediatric Hodgkin Lymphoma Group.<sup>104</sup> Patients were divided into 3 risk-groups, based on time to relapse, prior first-line CT treatment, and disease stage at relapse: low-risk (late relapse), HR (primary resistant) and intermediate-risk (all the others). HD-CT and auto-HSCT should be reserved for the intermediate-group still PDG/PET positive after the first 2 courses of salvage CT, or to low-risk and intermediate-risk patients achieving a complete metabolic response only after 4 courses of SD-CT. For HR children, the best salvage treatment remains undefined, and could include HD-CT and auto- or allo-HSCT, or new drugs.

Recently, the efficacy of new target immune therapies, like brentuximab vedotin (BV) and checkpoint inhibitors, has been demonstrated both for adults and children with relapsed/refractory HL.<sup>122,123</sup> BV has been approved, not only as first-part of salvage treatment, but also as consolidation after auto-HSCT, with the role of reducing the further disease progression.<sup>122–125</sup> Checkpoint inhibitors, such as pembrolizumab, are currently under evaluation as maintenance therapy after auto-HSCT, in children and adolescents with HL (NCT02362997).

All these new agents, along with auto-HSCT will soon be part of the strategies for pediatric refractory/relapsed HL, adapted according to the correct evaluation of the childhood risk category.

## Take Home Messages

- HD-CT followed by auto-HSCT is the standard of care of adults with relapsed/refractory HL. Optimal salvage strategy has still to be defined in pediatric age
- The European Pediatric Hodgkin Lymphoma Group has recently published recommendations for salvage therapy in children and adolescents, dividing patients into risk-groups according to time of relapse, prior therapy, and disease stage at time of relapse. Auto-HSCT should be reserved for those children at intermediate-risk still PDG/PET positive after two courses of salvage CT, or those at low or intermediate-risk, with a complete metabolic response only after 4 courses
- Recent target therapies are currently in evaluation as maintenance therapy after auto-HSCT, with the role of reducing the further disease progression

## Comments

Since the first patient received auto-HSCT, 60 years ago, progress in this procedure has been remarkable. Mobilized peripheral blood cells have replaced bone marrow as stem cell source, the pre-HSCT conditioning regimens have been adapted to the different pathologies, and the support therapy has considerably improved, thus allowing the use of this procedure, not only in oncological diseases, but also in autoimmune conditions. Moreover, the improvements of MRD detection strategies in acute leukemias, and of methods for disease response evaluation in lymphomas, have helped to identify better selected categories of patients that could benefit from auto-HSCT. However, with the recent identification of extremely effective and less toxic target therapies in the pediatric age, the use of auto-HSCT in first- and second-line therapies is limited. This is essentially due to the need to reduce the long-term side effects in a growing population, which, even if minor compared to allogeneic transplantation, are to be attributed to conditioning therapies. Replacing toxic therapies with precisely targeted therapies promises to improve not only the cure rate but also the quality of life of patients.

## Abbreviations

4-HC, 4-hydroperoxycyclophosphamide;  $\alpha$ IFN, alpha interferon; AIEOP, associazione italiana Ematologia Oncologia Pediatrica; ALCL, Anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; Allo-HSCT, allogeneic hematopoietic stem cell transplant; ALWP, Acute Leukemia Working Party; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; Auto-HSCT, autologous hematopoietic stem cell transplant; BAL, B-cell acute leukemia; BCR-ABL1, breakpoint cluster region-Abelson 1; BL, Burkitt Lymphoma; BM, bone marrow; BU, Busulfan; CA, cytarabine; CCyR, cytogenetic complete remission; CI, Cumulative Incidence; CIBMTR, Center for International Blood and Marrow Transplant Research; CML, Chronic myeloid leukemia; CNS, central nervous system; COG, Childrens' Oncology Group; CR, complete remission; CR2, second-complete remission; CsA, cyclosporine A; CT, Chemotherapy; CT scan, computed tomography; CY, Cyclophosphamide; DFS, disease-free survival; DLBCL, diffuse large B-cell NHL; DP, disease progression; EBMT, European Blood Bone Marrow Transplantation; EBMT, European Bone Marrow Transplantation Registry; EFS, event-free survival; ETP, Etoposide; G-CSF, granulocyte-colony stimulating factor; GHSG, German Hodgkin's Lymphoma Study Group; GO, gemtuzumab ozogamicin; GVL, graft-versus-leukemia; HD, high dose; HL, Hodgkin Lymphoma; I-BFM-SG, International Berlin-Frankfurt-Munster Study Group; JSHCT, Japan Society for Hematopoietic Cell Transplantation; LBL, Lymphoblastic lymphoma; MAC, myeloablative conditioning; MEL, Melphalan; MFC, multi-parametric flow cytometry; MoAbs, monoclonal antibodies; MRD, minimal residual disease; MSKCC, Memorial Sloan

Kettering Cancer Center; NHL, non-Hodgkin lymphoma; NRM, Non-relapse Mortality; OS, overall survival; PBSC, peripheral blood stem cells; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell NHL; PML-RARA, Promyelocytic Leukemia-Retinoic acid receptor; PR, partial remission; PRC, polymerase-chain reaction; PTCL, Nonanaplastic peripheral T-cell lymphomas; RIC, reduced intensity conditioning; SD, stable disease; SD-CT, standard-dose chemotherapy; TBI, total body irradiation; TKIs, tyrosine kinase inhibitors; T-LBL, T-lymphoblastic lymphoma; TRM, transplant-related mortality; VCR, Vincristine; VHR, very-high risk.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting and in critically reviewing the article. All authors gave final approval of the version to be published. The authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work. Our main text and Tables have been edited and revised by a native English teacher.

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