We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 10

Autologous Stem Cell Transplantation for Acute Myeloid Leukemia

Pier Paolo Piccaluga, Stefania Paolini, Giovanna Meloni, Giuseppe Visani and Felicetto Ferrara

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54280

1. Introduction

In the majority of patients, the therapy of acute myeloid leukemia (AML) has a curative intent and includes two phases, i.e. induction and consolidation. The former aims at complete remission (CR) achievement, the latter at the eradication of residual leukemic cells, which are undetectable at morphologic examination of bone marrow after induction therapy in patients in CR. Current induction regimens, conventionally based on the combination of daunorubicin and cytarabine result in CR rates of 60 – 70% of AML patients younger than 65 years; in order to improve both CR rate and quality, different studies tested alternative anthracyclines [1]-[5], higher schedules of Ara-C[6]-[10], the addition of a third cytotoxic drug [11]-[16] and, more recently, the combination with new agents. Overall, results have been disappointing even though the addition of gemtuzumab ozogamycin (GO), an antiCD33 monoclonal antibody conjugated with the cytotoxic agents chalicheamycin, has been reported to confer a significant advantage in selected patients with AML [17]-[21]. Notwithstanding, in absence of intensive post-induction therapy virtually all patients will ultimately relapse, therefore consolidation therapy is strictly needed. At present, after CR achievement all patients receive a consolidation chemotherapy based on intermediate or high dose ARA-C and then in young adult patients three options can be considered, i.e. allogeneic stem cell transplantation (allo-SCT), autologous SCT (ASCT) or repetitive intensive consolidation chemotherapy cycles (ICC) with high or intermediate dose ARA-C [22]-[37], depending on age, disease risk and donor availability. In particular, it is widely accepted that ICC and ASCT would be limited to patients with favorable risk, such as AML with t(8;21), AML with inv(16) or t(16;16) and AML with normal karyotype with NPM1 mutation in absence of mu-

tations of FLT3/ITD gene [38], [39]. In the remaining patient population, allo-SCT must be considered when age and performance status result in an acceptable risk/benefit ratio. In this regard, it should be considered that in the last years morbidity and mortality from allo-SCT have been considerably reduced; in addition, the introduction into daily practice of reduced intensity conditioning (RIC) has allowed to offer the procedure to selected old and/or previously not eligible patient population.

Currently, even in patients with favourable prognostic factors at diagnosis, the role of ASCT remains unclear although most studies that have compared ASCT with ICC demonstrated a significantly lower rate of relapse following ASCT (5,6). Results in terms of survival were, however, less encouraging because of transplant-related deaths and the low rate of second CR in patients who relapsed after ASCT, therefore in the last year ASCT has become less popular, mainly in USA. Notwithstanding, different considerations should be made: first, both the occurrence of toxicity and mortality related to ASCT have greatly decreased since use of peripheral-blood stem cells was introduced, even in older patients. Second, reduction of relapse rate would represent a main therapeutic objective in the therapy of AML, just as it is any malignant disorder. Finally, consolidation therapy based on repeated courses of high-dose or intermediate-dose cytarabine is probably more toxic and costly than ASCT and is poorly feasible in patients aged over 55-60 years. In elderly patients, particularly, the dose intensification by either ASCT or ICC has failed so far to induce a significant benefit [40]-[42]. Therefore, novel more rational targeted agents are particularly warranted in this setting. On the other hand, two important conditions are necessary in order to perform ASCT: CR achievement and collection of an adequate number of $CD34^+$ cells ($> 2 \times 10^6$/Kg). As the latter aspect is concerned, it should be mentioned that a previous history of myeloid disorder (especially myelodysplastic syndrome), advanced age and the use of certain drugs during the induction and consolidation phases (e.g. fludarabine [43]) can significantly impair the possibility to collect an adequate number of cells.

Overall, data from the literature are controversial, but it has been definitively demonstrated that ASCT provides better results in patients with favorable risk diseases and low amount of minimal residual disease after induction/consolidation therapy. In the last years, a few complete meta-analyses and extensive reviews tried to draw some conclusions but were not able to indicate definite guidelines [44]-[46].

In this chapter, the authors review the current knowledge on the use of SCT in post-consolidation therapy of AML, based on their own experience and the most recent literature data, by mainly focusing on randomized clinical trials (RCT).

2. Randomized clinical trials comparing autologous stem cell transplantation and chemotherapy or no further therapy

In 1995 Zittoun et al. for the EORTC-GIMEMA groups reported on 941 AML patients treated with one or two cycles of standard Daunorubicine/Cytarabine schedule (3/7). Patients obtaining CR were submitted to one consolidation cycle including high-dose cytar-

abine (HD-AC) and Amsacrine. Subsequently, patients with HLA identical donor were allo-transplanted, whereas patients without HLA identical donor were randomized to receive ASCT or a second consolidation (ICC) with daunorubicine and HD-AC. The CR rate after induction therapy was 66%. The relapse rate were 40% in the two arms (ASCT) and 57% (ICC), respectively; DFS was longer for patients submitted to ASCT compared to patients submitted to ICC (48% vs 30%; p=0.05). However the OS was not significantly superior in the ASCT group, due to the greater ability of ASCT to rescue relapsed patients in the ICC arm [24].

In 1997 Harousseau and Colleagues reported data on 517 eligible patients (15-50 years of age) affected by previously untreated AML. Patients received 3 - 4 courses of conventional induction treatment (Ara-C: 200 mg/sqm/day for 7 consecutive days with either idarubicin administered intravenously on days 1 - 5 at a daily dose of 8 mg/sqm or rubidazone administered intravenously on days 1 - 4 at a daily dose of 200 mg/sqm). Patients aged 40 year or younger, in CR after induction therapy, were assigned to SCT if an HLA identical donor was available. All other patients received a first course of HD-Ara-C (3 gr/sqm) administered every 12 hours along 4 days (ICC) and then were randomized to receive either a second course of ICC or an ASCT. Eighty-eight patients out of 517 received an SCT, while 164 out of 517 were eligible for randomization (75 received ASCT, 71 received ICC). No differences in terms of OS and DFS were observed between the two arms: the 4 years DFS was 44 +/- 5.5% in ASCT group and 40.5 +/- 5.5% in ICC group (p value 0.41); the 4 years OS was 50 +/- 6% in ASCT group and 54.5 +/- 6% in ICC group (p value 0.72). The retrospective analysis of DFS and OS based on the cytogenetic risk could not detect any differences between the ASCT group and the ICC group [28].

In 1998 Cassileth et al. reported on 740 AML patients treated with standard 3/7 – 3/5 induction – consolidation chemotherapy cycles. Patients without an HLA identical donor were randomized between ASCT and HD-AC. The overall CR rate was 70%; the 4-years-DFS was 35% in both groups; the 4 years OS was 43% in ASCT group and 52% in ICC group respectively (p= 0.05) [25].

The first report on the MRC AML 10 trial was published in 1998 [29]. Patients were firstly randomly assigned to different induction chemotherapy regimens (DAT vs. ADE); all patients achieving CR after two induction courses received a third consolidation chemotherapy course (MACE). Patients who lacked an HLA-matched sibling donor were randomized to receive one more chemotherapy course (MidAC) followed by either ASCT or no further therapy; patients with an HLA-matched sibling donor were assigned to receive an SCT. Basis on the intention to treat analysis the number of relapses was significantly lower in the ASCT group than in the group assigned no further treatment (37% vs. 58%; p= 0.0007), resulting in superior DFS at 7 years (53% vs. 40%; p=0.04). No difference in terms of OS was observed. Of note, however, in this trial only 38% of patients available for randomization were randomized [29].

Tsimberidou et al. then reported data on 120 patients with de novo AML in 2003. All patients were treated with standard 3/7 regimen (2 courses) and if in CR underwent a first HD-AC course. All patients aged less than 50 years and with an HLA compatible donor received

an SCT; patient aged more than 50 years or without an HLA-matched sibling donor were randomly assigned to receive a second HD-Ara course or an ASCT. With a median follow-up of 43 months the 3-year failure free survival rates was 42% for patients receiving ASCT and 33% for patients receiving conventional chemotherapy [33].

Subsequently, Breems et al in 2005 reported data on 646 patients enrolled in the HOVO/SAKK AML4 trial. After two cycle of induction therapy combining cytarabine with daunorubicine (first course) and amsacrine (second course), CR patients (75%) were addressed to a consolidation therapy with mitoxantrone and VP16. Eighty-one patients received SCT. Patients non eligible for SCT were randomized between ASCT (66 patients) and no further therapy (46 patients). After a median follow up of 154 months, there were no statistically significant differences concerning DFS, OS and relapse rate within the two randomization arms. There was a trend towards a better OS of the non-autografted patients. This was associated with a higher, though non significant, incidence of death in CR within the auto-transplanted group with respect to the no treatment group. The 5 years OS after relapse for patients previously auto-grafted was significantly shorter with respect to patients who received no further treatment [34].

A large European intergroup trial [47] later evaluated HD-AC induction and escalation of post-remission therapy in a 2-stage RCT. Patients under the age of 60 years were randomized to 1 of 2 induction courses (double HD-AC vs. standard cytarabine/HD-AC). Patients in remission received a third cycle of chemotherapy followed by a second randomization to ASCT or maintenance chemotherapy. Fifty-one percent assigned to maintenance received the assigned therapy, while only 24% received the assigned ASCT. Three-year remission duration was 50% versus 44%, 3-year relapse-free survival was 48% versus 43% for maintenance and ASCT, respectively, and there was no significant difference between the 2 arms when stratified according to cytogenetic risk profile [47].

An update of the AML10 study was then reported in 2006 [35]. Briefly, The overall survival of patients allocated to autologous transplantation was better than for those in the no-further-therapy arm (53% vs. 45%) at 10 years, with 165 patients at risk at that time point. Of note, although this difference was not statistically significant on a log-rank analysis (P=.09), the Kaplan-Meier plots clearly diverged after the first 3 years, the difference becoming significant. This was related to a highly significant reduction in relapse risk in the autograft arm (40% vs. 58%; P=.0005), with consequent improved DFS in the ASCT arm (50% vs. 39%; P=.03), a data which was partially obscured by a higher risk of death in remission (16% vs. 6%; P=.02). Overall, the study suggested a survival benefit with ASCT in patients in the good- and standard-risk groups but not in the poor-risk group. Conversely, it was unclear if any specific age group benefited [35].

Based on these studies, a couple of systematic meta-analyses and reviews, tried to delineate some possible indications. However, many data were conflicting a definitive recommendations appeared difficult. Particularly, Nathan and Colleagues performed a comprehensive meta-analysis on consolidation therapy for AML. In particular, they analyzed 6 studies including 1044 patients randomly assigned t receive ASCT vs. ICC (5 studies), or ASCT vs. no further treatment (1 study). Patients receiving ASCT had a better disease free but not differ-

http://dx.doi.org/10.5772/54280

ent overall survival. Thus, they did not recommend ASCT as routine options for AML patients in first CR [45]. Thereafter, Visani and Colleagues, based on evidence based medicine (EBM) criteria, considered 6 RCT evaluating the role of ASCT and concluded that due to the heterogeneity of AML biology (i.e. molecular genetics), further studies specifically dedicated to the different entities were probably necessary to build robust recommendation according to EBM rules [46].

More recently, the HOVON Group reported the results of a prospective, randomized phase 3 trial evaluating ASCT vs. ICC in newly diagnosed AML patients in first CR (CR1) [48]. Patients with AML (16-60 years) in CR1 after 2 cycles of intensive chemotherapy and not eligible for allogeneic SCT were randomized between ICC (including etoposide and mitoxantrone) or ASCT (Bu/Cy). More than 90% of randomized patients received their assigned treatment (ICC, n = 259; ASCT, n = 258),. The 2 groups were comparable with regard to prognostic factors. The ASCT group showed a markedly reduced relapse rate (58% vs. 70%, P = 0.02) and better relapse-free survival at 5 years (38% vs. 29%,P =0.065) with non-relapse mortality of 4% vs. 1% in the chemotherapy arm (P =0.02). OS was similar (44% vs. 41% at 5 years, P =0.86), possibly because of more opportunities for salvage with second-line chemotherapy and SCT in patients relapsing on the chemotherapy arm. [48].

Finally, Pfirman et al reported the results of the AML96 trial [49], aiming to differentiate groups of patients according to the treatments that would provide them optimum benefit. Five hundred eighty six AML patients (aged below 60 years) - excluding those with t(8;21) – in CR1 after double induction treatment were consolidated with SCT or ASCT, or ICC containing HD-AC, in a priority-based and risk-adapted manner. The association between potentially prognostic variables and OS was assessed and a post-remission treatment (PRT) score was developed in 452 patients with a complete dataset. This score was then validated in additional 407 patients from the AML2003 trial. Age, percentage of CD34-positive blasts, FLT3-ITD mutant-to-wild-type ratio, cytogenetic risk, and de-novo or secondary AML were identified as independent prognostic factors, and included in the PRT score. Accordingly, patients were separated into three groups: favorable (N=190; 3-year survival 68%), intermediate (N=198; 49%), and unfavorable (n=64; 20%). These results were confirmed in the AML2003 trial dataset: 3-year survival for the favorable group (n=265) was 69%, for the intermediate group (n=114) it was 61%, and for the unfavorable group (n=28) it was 46%. Therefore, the 3 groups presented with significantly different survival probabilities (p=0.015). Additionally, the Authors found that in the favorable group, patients who received SCT (n=60) had higher survival probabilities (82%) than did those given chemotherapy (n=56, 55%; p=0.0012) or ASCT (n=74, 66%; p=0.044). In the intermediate PRT score group, patients receiving ASCT (n=69) had the best survival probabilities (62%) compared with those given chemotherapy (n=72, 41%; p=0.0006) or SCT (n=57, 44%; p=0.0045).

Overall, the study thus supported the use of autologous HSCT in patients aged 60 years or younger with an intermediate PRT score.

Results of the above mentioned studies on ASCT are summarized in Table 1.

Author	Population – Study design	Outcome		*Pvalues*
		Auto-SCT	**Chemotherapy/no further therapy**	
Zittoun et al	990 patients (< 59 y) previously untreated AML. (941 evaluable)	4 yrs DFS: 48 ± 5%	4 yrs DFS: 30 ± 5%	0.05
	Study design:	4 yrs OS : 56 ± 5%	4 yrs OS : 56 ± 5%	NS
	- Induction: cytarabine + doxorubicine			
	If PR: 2nd course of induction therapy Consolidation: HDAC+amsacrine			
	If CR, age<45 yrs and HLA compatible donor: allo-SCT (N= 144)			
	- If > 45 yrs and/or no HLA compatible donor: randomization (auto-SCT, N= 95 vs. 2nd course of intensive therapy, N=104)			
Harousseau et al	517 previously untreated AML patients (15-50 yrs)	4 yrs DFS: 44 ± 5.5%	4 y DFS: 40.5 ± 5.5%	NS
	Study design:	4 yrs OS: 50 ± 6%	4 y OS: 54.5 ± 6%	
	- Induction: cytarabine and idarubicine or rubidazone. If no CR: 2nd cycle	*Low risk group*		
	- Consolidation: HD-AC + Idarubicine or Rubidazone	4 yrs DFS: 50 ± 9%	4 yrs DFS : 56 ± 11%	NS
	If CR, age <40 yrs and HLA compatible donor: allo-SCT (N=88)	4 yrs OS: 59 ± 9%	4 yrs OS: 71 ± 8%	NS
	- If > 40 yrs and/or no HLA compatible donor: randomization (auto-SCT, N= 75 vs. ICC, N=71)			
		Intermediate risk group		
		- 4 yrs DFS: 38.5 ± 9%	- 4 yrs DFS: 31 ± 8.5%	NS
		- 4 yrs OS: 42.5 ± 9%	- 4 yrs OS: 55 ± 9%	NS
		High risk group		
		- 4 yrs DFS: 38 ± 10%	- 4 yrs DFS: 28.5 ± 10%	NS
		- 4 yrs OS: 46.5 ± 11%	- 4 yrs OS: 40 ± 11.5%	NS
Cassileth et al	772 previously untreated AML patients (16-55 yrs)	4 yrs DFS: 35±9 %	4 yrs DFS: 35±9 %	NS
	Study design:	4 yrs OS: 43±9 %	4 yrs OS: 52±9 %	P=0.05

http://dx.doi.org/10.5772/54280

Author	Population – Study design	Outcome		*Pvalues*
		Auto-SCT	**Chemotherapy/no further therapy**	
	Induction: 2 cycles of idarubicine and cytarabine Consolidation: idarubicine and cytarabine - If CR and HLA compatible donor: allo-SCT (N=113) - If not HLA compatible donor: randomization auto-SCT (N =116) vs. HD-Cytarabine (N = 117)			
Burnett et al	1509 previously untreated AML patients aged less than < 56 yrs *Study design:* - 2 Induction: Daunorubicine, Cytarabine, Thioguanine vs Daunorubicine, Cytarabine, VP-16 - 1st Consolidation: Amsacrine, Cytarabine, VP-16 - Pts with HLA identical donor: 2nd consolidation (Mitoxantrone, Cytarabine) and allo-SCT - Pts lacking HLA identical donor: 2nd consolidation (Mitozantrone, Cytarabine) and randomization to auto-SCT (N =190) vs. no further therapy (N =191)	10 yrs DFS: 50% 10 yrs OS: 53% Relapse rate at 10 yrs: 40%	10 yrs DFS: 39% 10 yrs OS : 45% Relapse rate at 10 yrs: 58%	0.03 0.009 0.0005
Tsimberidou et al	120 previously untreated AML patients (<60 yrs) *Study design:* - 2 Induction: Idarubicine, Cytarabine (3+7) - Consolidation: HD-AC - If < 50 y and HLA compatible donor : allo-SCT (N = 21) - If > 50 y and/or no HLA compatible donor: randomization (auto-SCT, N = 19 vs. 2nd HD-AC, N= 15)	3 yrs OS: 58% 3 yrs FFS: 42%	3 yrs OS: 46% 3 yrs FFS: 33%	NS NS
Breems et al	646 previously untreated AML patients (< 60 years) *Study design:* - Induction 1: Daunorubicine, Cytarabine (3+7)	5 yrs DFS: about 35% 5 yrs OS : about 45%	5 yrs DFS: about 37% 5 yrs OS : about 55%	NS NS

Author	Population – Study design	Outcome		*Pvalues*
		Auto-SCT	**Chemotherapy/no further therapy**	
	- Induction 2: Amsacrine, Cytarabine	7 pts died in CR within 9 months	1 pts died in CR within 9 months	NS
	- Consolidation: Mitoxantrone, VP16			
	- If eligible and compatible donor : allo-SCT (N = 81)	5 yrs OS after relapse: about 5%	5 yrs OS after relapse: about 25%	0.003
	- If non eligible: randomization (auto-SCT, N =66 vs. no therapy, N = 64)			
Buchner et al.	840 AML/high-risk MDS patients (age ≤ 60 years)	3 yrs DFS: 48%	3 yrs DFS: 46%	0.65
	Study design:			
	1st Randomization at induction: TAM-HAM vs. HAM-HAM	3 yrs OS : 43%	3 yrs OS : 41%	0.52
	TAD: thioguanine, cytarabine, and daunorubicin			
	HAM: cytarabine and mitoxantrone			
	Consolidation: TAD			
	2nd Randomization (auto-SCT, N=429 vs. mantei-nance, N = 411)			
	If eligible and compatible donor : allo-SCT (N= 128)			
Vellenga 2011	2,017 AML patients (age ≤ 60 years)			
	Induction 1: cytarabine and idarubicinInduction 2: cytarabine and amsacrine	5 yrs DFS: 38%	5 yrs DFS: 29%	0.065
	Consolidation: etoposide and mitoxantrone	5 yrs OS: 44%	5 yrs OS : 41%	0.86
	Randomization to ASCT (N=258) vs. Chemothera-py (N=259)	Relapse rate: 58%	Relapse rate: 70%	0.02
Pfirman 2012	1,151 AML patients (age ≤ 60 years)	*Favorable PRT:*		
	Assigment to ASCT (N=191) vs. Chemotherapy (N=223)	3 yrs OS: 66%	3 yrs OS : 55%	
	Assigment to SCT (N=172)	*Intermediate PRT:*		
		3 yrs OS: 62%	3 yrs OS : 41%	0.0006
		Adverse PRT:		
		3 yrs OS: 7%	3 yrs OS : 19%	

Table 1. Summary of the most relevant randomized clinical trials evaluating the role of ASCT in AML

http://dx.doi.org/10.5772/54280

3. Discussion and perspectives

Current intensive induction chemotherapy for patients with AML produces CR rates higher than 60-65 %; however, less than 30% of patients still survive for more 5 years free of disease. In this context, the aim of post-remission treatment is to eradicate clonogenic leukemic cells, which persists after induction and are ultimately able to induce disease relapse. Nonetheless, the optimal form of treatment is still under debate. As discussed, three main strategies are used to prevent relapse in patients with AML in first CR, including intensive chemotherapy based on intermediate-dose or high-dose cytarabine, and allogeneic and autologous hemopoietic stem cell transplantation. The choice among these approaches for an individual patient relies on two main factors, namely the expected risk of relapse as determined by biological features of leukemic cells and expected morbidity and mortality associated with a specific option, according to age and comorbidities [50].

Intensive chemotherapy (ICC) proved to be useful for improving AML patients outcome [17], [19]-[21], [51]-[55].

On the other hand, allogeneic SCT was demonstrated to be the most effective strategy to reduce the relapse risk [24], [25], [28], [29]. However, it is associated with a high-risk of treatment-related morbidity and mortality (TRM), and it is conventionally offered to younger patients with a HLA-matched sibling or unrelated donor. Of note, in the last years several evidences emerged that allogeneic SCT should not be offered as first option to patients with relatively favorable biological characteristics. The latter include a few genetic abnormalities – t(8;21)(q23;q22), inv(16)(p13q22), and t(15;17)(q22;q21) – as well as the presence of somatic mutations of *NMP1* and/or *CEBPA* genes in absence of other abnormalities. Therefore, for these patients, with the exception of M3 patients that can benefit from specific targeted agents, once achieved CR, the most suitable therapeutic options remain intensive chemotherapy and ASCT.

ASCT is an alternative approach to deliver an effective anti-leukemic myeloablative therapy to AML patients in CR, when a donor is not available. It has been demonstrated that ASCT is feasible and effective in AML, provided that an adequate induction/consolidation treatment has previously determined an effective in vivo purging. In fact, the results obtained with ASCT can be significantly affected by other relevant factors, including intensity of induction and consolidation chemotherapy as well as conditioning regimens, which strongly influencing the MRD burden before the procedure is performed [50]. Bearing this in mind, it is not surprising that the several RCT trying to define the role of ASCT as post-remission therapy in AML ended up with discrepant result. In particular, the nine largest studies, though considering 2,894 patients assigned to either ASCT or chemotherapy/no further therapy (among more than 8,000 enrolled ones) did not reach definitive conclusions (Table 1). In fact, although a reduced relapse risk was often recorded, only one study provided evidences of survival advantages for patients receiving ASCT, considering the whole population [35], while one assessed a significant advantage only in

patients with an intermediate prognostic score [49]. Indeed, in most instances, the reduced leukemia recurrence was balanced by an increase TRM. In this regard, however, it should be mentioned that in the last years the mortality of ASCT has definitely declined, possibly challenging some of the results published so far. Moreover, reduction of the relapse rate is a pivotal objective in the treatment of AML, as the only way toward the cure. In addition, the continuous and very fast improvement in our knowledge of the biology of the disease on one hand clearly established that AML is not a unique disease, providing the basis for future more rationale therapies based on the specific molecular features, while on the other hand made more difficult to be interpreted results from most clinical trials, that were initiated when a comprehensive molecular characterization was not available. Accordingly, a modern view of the problem should consider these new elements and rather than debating whether ASCT is superior to SCT or ICC in AML, it would be more useful to identify those patients who would more benefit from the procedure.

Of note, one study (actually the most recently published) tried to identify the optimal post-remission strategy according to both clinical and biological features of the single case, recognizing three different groups based on an original post-remission treatment (PRT) score. Indeed, ASCT turned out to be the treatment of choice for the intermediate class, the outcome being quite favourable (Table 1). Therefore, although the proposed scoring systems will be probably modified/updated in the future, following, for example, the knowledge derived fro the most recent massive parallel sequencing studies [56] and the introduction of novel anti-leukemic compounds, an interesting scenario has probably (re)opened for ASCT. Finally, future research should focus on designing better ways to do autografts rather than conducting more trials comparing chemotherapy with the same autograft procedures currently in use, including the adoption of immunotherapy, the selection of patients based on the absence of a minimal residual disease [57] and/or of new biologic molecularly targeted compounds in the post-ASCT phase.

In conclusion, although evidence based indication cannot be offered for ASCT in AML, it is reasonable to consider it as a valid therapeutic option for AML patients at low-intermediate risk in CR1. Indeed, a main goal should be having optimal frontline genetic characterization, as well as MRD evaluation on the harvested cells. For high risk patients, unfortunately, SCT can be an option, if they achieve a good quality CR; otherwise, experimental procedures are mandatory.

Acknowledgements

Supported by BolognAIL, AIRC (IG4987; 5xMille 10007; IG10519), RFO (Prof. Piccaluga), Fondazione Cassa di Risparmio in Bologna, Fondazione della Banca del Monte e Ravenna, Progetto Strategico di Ateneo 2006 (Prof. Piccaluga).

http://dx.doi.org/10.5772/54280

Author details

Pier Paolo Piccaluga[1*], Stefania Paolini[1], Giovanna Meloni[2], Giuseppe Visani[3] and Felicetto Ferrara[4]

*Address all correspondence to: pierpaolo.piccaluga@unibo.it

1 Hematopathology and Hematology Sections, Department of Hematology and Oncology "L. and A. Seràgnoli", S. Orsola-Malpighi Hospital, University of Bologna, Italy

2 Hematology, Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy

3 Haematology and Haematopoietic Stem Cell Transplant Center - San Salvatore Hospital – Pesaro, Italy

4 Division of Haematology and Stem Cell Transplantation Unit, Cardarelli General Hospital, Naples, Italy

References

[1] Yates J, Glidewell O, Wiernik P, et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. Blood 1982;60(2):454-62.

[2] Arlin Z, Case DC, Jr., Moore J, et al. Randomized multicenter trial of cytosine arabinoside with mitoxantrone or daunorubicin in previously untreated adult patients with acute nonlymphocytic leukemia (ANLL). Lederle Cooperative Group. Leukemia 1990;4(3):177-83.

[3] Vogler WR, Velez-Garcia E, Weiner RS, et al. A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: a Southeastern Cancer Study Group Study. J Clin Oncol 1992;10(7):1103-11.

[4] Lowenberg B, Suciu S, Archimbaud E, et al. Mitoxantrone versus daunorubicin in induction-consolidation chemotherapy--the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group. J Clin Oncol 1998;16(3):872-81.

[5] Visani G, Bernasconi P, Boni M, et al. The prognostic value of cytogenetics is reinforced by the kind of induction/consolidation therapy in influencing the outcome of acute myeloid leukemia--analysis of 848 patients. Leukemia 2001;15(6):903-9.

[6] Dillman RO, Davis RB, Green MR, et al. A comparative study of two different doses of cytarabine for acute myeloid leukemia: a phase III trial of Cancer and Leukemia Group B. Blood 1991;78(10):2520-6.

[7] Bishop JF, Matthews JP, Young GA, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood 1996;87(5):1710-7.

[8] Buchner T, Hiddemann W, Wormann B, et al. Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. Blood 1999;93(12):4116-24.

[9] Cahn JY, Labopin M, Sierra J, et al. No impact of high-dose cytarabine on the outcome of patients transplanted for acute myeloblastic leukaemia in first remission. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). British journal of haematology 2000;110(2):308-14.

[10] Bradstock KF, Matthews JP, Lowenthal RM, et al. A randomized trial of high-versus conventional-dose cytarabine in consolidation chemotherapy for adult de novo acute myeloid leukemia in first remission after induction therapy containing high-dose cytarabine. Blood 2005;105(2):481-8.

[11] Bishop JF, Lowenthal RM, Joshua D, et al. Etoposide in acute nonlymphocytic leukemia. Australian Leukemia Study Group. Blood 1990;75(1):27-32.

[12] Berman E, Arlin ZA, Gaynor J, et al. Comparative trial of cytarabine and thioguanine in combination with amsacrine or daunorubicin in patients with untreated acute nonlymphocytic leukemia: results of the L-16M protocol. Leukemia 1989;3(2):115-21.

[13] Rowe JM, Tallman MS. Intensifying induction therapy in acute myeloid leukemia: has a new standard of care emerged? Blood 1997;90(6):2121-6.

[14] Russo D, Pricolo G, Michieli M, et al. Fludarabine, arabinosyl cytosine and idarubicin (FLAI) for remission induction in poor-risk acute myeloid leukemia. Leukemia & lymphoma 2001;40(3-4):335-43.

[15] Robak T. Purine nucleoside analogues in the treatment of myleoid leukemias. Leukemia & lymphoma 2003;44(3):391-409.

[16] Holowiecki J, Grosicki S, Robak T, et al. Addition of cladribine to daunorubicin and cytarabine increases complete remission rate after a single course of induction treatment in acute myeloid leukemia. Multicenter, phase III study. Leukemia 2004;18(5): 989-97.

[17] Piccaluga PP, Martinelli G, Rondoni M, et al. Low dose gemtuzumab ozogamicin for relapsed acute myeloid leukaemia in elderly. Haematologica 2003;88(12):ECR37.

[18] Piccaluga PP, Martinelli G, Rondoni M, et al. Gemtuzumab ozogamicin for relapsed and refractory acute myeloid leukemia and myeloid sarcomas. Leukemia & lymphoma 2004;45(9):1791-5.

[19] Piccaluga PP, Martinelli G, Rondoni M, et al. First experience with gemtuzumab ozogamicin plus cytarabine as continuous infusion for elderly acute myeloid leukaemia patients. Leukemia research 2004;28(9):987-90.

[20] Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012;379(9825):1508-16.

[21] Burnett AK, Russell NH, Hills RK, et al. Addition of Gemtuzumab Ozogamicin to Induction Chemotherapy Improves Survival in Older Patients With Acute Myeloid Leukemia. J Clin Oncol 2012.

[22] Reiffers J, Gaspard MH, Maraninchi D, et al. Comparison of allogeneic or autologous bone marrow transplantation and chemotherapy in patients with acute myeloid leukaemia in first remission: a prospective controlled trial. British journal of haematology 1989;72(1):57-63.

[23] Ferrant A, Doyen C, Delannoy A, et al. Allogeneic or autologous bone marrow transplantation for acute non-lymphocytic leukemia in first remission. Bone marrow transplantation 1991;7(4):303-9.

[24] Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. The New England journal of medicine 1995;332(4):217-23.

[25] Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. The New England journal of medicine 1998;339(23):1649-56.

[26] Gale RP, Buchner T, Zhang MJ, et al. HLA-identical sibling bone marrow transplants vs chemotherapy for acute myelogenous leukemia in first remission. Leukemia 1996;10(11):1687-91.

[27] Isidori A, Bonifazi F, Visani G, Gherlinzoni F, Baccarani M, Lemoli RM. Autologous stem cell transplantation for acute myeloid leukemia patients in first complete remission: a 10-year follow-up study of 118 patients. Haematologica 2005;90(1):139-41.

[28] Harousseau JL, Cahn JY, Pignon B, et al. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia. The Groupe Ouest Est Leucemies Aigues Myeloblastiques (GOELAM). Blood 1997;90(8):2978-86.

[29] Burnett AK, Goldstone AH, Stevens RM, et al. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Re-

search Council Adult and Children's Leukaemia Working Parties. Lancet 1998;351(9104):700-8.

[30] Burnett AK, Wheatley K, Goldstone AH, et al. The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 10 trial. British journal of haematology 2002;118(2): 385-400.

[31] Gratwohl A, Baldomero H, Passweg J, et al. Hematopoietic stem cell transplantation for hematological malignancies in Europe. Leukemia 2003;17(5):941-59.

[32] Suciu S, Mandelli F, de Witte T, et al. Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMAAML-10 trial. Blood 2003;102(4):1232-40.

[33] Tsimberidou AM, Stavroyianni N, Viniou N, et al. Comparison of allogeneic stem cell transplantation, high-dose cytarabine, and autologous peripheral stem cell transplantation as postremission treatment in patients with de novo acute myelogenous leukemia. Cancer 2003;97(7):1721-31.

[34] Breems DA, Boogaerts MA, Dekker AW, et al. Autologous bone marrow transplantation as consolidation therapy in the treatment of adult patients under 60 years with acute myeloid leukaemia in first complete remission: a prospective randomized Dutch-Belgian Haemato-Oncology Co-operative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) trial. British journal of haematology 2005;128(1): 59-65.

[35] Burnett AK, Wheatley K, Goldstone AH, Stevens R, Hann I, Hills RK. Long-term results of the MRC AML10 trial. Clin Adv Hematol Oncol 2006;4(6):445-51.

[36] Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. Jama 2009;301(22):2349-61.

[37] Lioure B, Bene MC, Pigneux A, et al. Early matched sibling hematopoietic cell transplantation for adult AML in first remission using an age-adapted strategy: long-term results of a prospective GOELAMS study. Blood 2012;119(12):2943-8.

[38] Rosenblat TL, Jurcic JG. Induction and postremission strategies in acute myeloid leukemia: state of the art and future directions. Hematology/oncology clinics of North America 2011;25(6):1189-213.

[39] Rollig C, Bornhauser M, Thiede C, et al. Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system. J Clin Oncol 2011;29(20):2758-65.

[40] Thomas X, Suciu S, Rio B, et al. Autologous stem cell transplantation after complete remission and first consolidation in acute myeloid leukemia patients aged 61-70

years: results of the prospective EORTC-GIMEMA AML-13 study. Haematologica 2007;92(3):389-96.

[41] Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood 2007;109(12):5129-35.

[42] Hengeveld M, Suciu S, Karrasch M, et al. Intensive consolidation therapy compared with standard consolidation and maintenance therapy for adults with acute myeloid leukaemia aged between 46 and 60 years: final results of the randomized phase III study (AML 8B) of the European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. Annals of hematology 2012;91(6):825-35.

[43] Visani G, Lemoli RM, Tosi P, et al. Fludarabine-containing regimens severely impair peripheral blood stem cells mobilization and collection in acute myeloid leukaemia patients. British journal of haematology 1999;105(3):775-9.

[44] Reiffers J, Stoppa AM, Attal M, et al. Allogeneic vs autologous stem cell transplantation vs chemotherapy in patients with acute myeloid leukemia in first remission: the BGMT 87 study. Leukemia 1996;10(12):1874-82.

[45] Nathan PC, Sung L, Crump M, Beyene J. Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a meta-analysis. Journal of the National Cancer Institute 2004;96(1):38-45.

[46] Visani G, Olivieri A, Malagola M, et al. Consolidation therapy for adult acute myeloid leukemia: a systematic analysis according to evidence based medicine. Leukemia & lymphoma 2006;47(6):1091-102.

[47] Buchner T, Berdel WE, Schoch C, et al. Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia. J Clin Oncol 2006;24(16):2480-9.

[48] Vellenga E, van Putten W, Ossenkoppele GJ, et al. Autologous peripheral blood stem cell transplantation for acute myeloid leukemia. Blood 2011;118(23):6037-42.

[49] Pfirrmann M, Ehninger G, Thiede C, et al. Prediction of post-remission survival in acute myeloid leukaemia: a post-hoc analysis of the AML96 trial. The lancet oncology 2012;13(2):207-14.

[50] Ferrara F. Renaissance of autologous stem cell transplantation for AML? The lancet oncology 2012;13(2):121-3.

[51] Rees JK, Gray RG, Wheatley K. Dose intensification in acute myeloid leukaemia: greater effectiveness at lower cost. Principal report of the Medical Research Council's AML9 study. MRC Leukaemia in Adults Working Party. British journal of haematology 1996;94(1):89-98.

[52] Hann IM, Stevens RF, Goldstone AH, et al. Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia. Results of the Medical Research Council's 10th AML trial (MRC AML10). Adult and Childhood Leukaemia Working Parties of the Medical Research Council. Blood 1997;89(7):2311-8.

[53] Mandelli F, Petti MC, Lo Coco F. Therapy of acute myeloid leukemia: towards a patient-oriented, risk-adapted approach. Haematologica 1998;83(11):1015-23.

[54] Stein EM, Tallman MS. Remission induction in acute myeloid leukemia. International journal of hematology 2012;96(2):164-70.

[55] Candoni A, Martinelli G, Toffoletti E, et al. Gemtuzumab-ozogamicin in combination with fludarabine, cytarabine, idarubicin (FLAI-GO) as induction therapy in CD33-positive AML patients younger than 65 years. Leukemia research 2008;32(12):1800-8.

[56] Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. The New England journal of medicine 2012;366(12):1079-89.

[57] Inaba H, Coustan-Smith E, Cao X, et al. Comparative Analysis of Different Approaches to Measure Treatment Response in Acute Myeloid Leukemia. J Clin Oncol 2012.