Optimal acute myeloid leukemia therapy in 2012

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A B S T R A C T

Treatment of acute myeloid leukemia (AML) still relies on chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HSCT), at least in patients whose relapse risk is high enough to warrant the risk of the procedure. As some patients will not require HSCT because of their anticipated low relapse risk, and others will not be eligible and/or will not have a donor, approximately 40% of younger patients but only 15% of those aged more than 60 years will be subjected to this chemotherapy/HSCT sequence. Relapse risk prediction is still evolving due to descriptions of new gene mutations that may affect prognosis, also increasing the opportunity to assess individual minimal residual disease. Even if not widely recognized, results associated with chemotherapy alone are also improving, due to anthracycline/cytarabine dose escalation or adjunction of third agents. Even for older patients, new treatment options are opening, including hypomethylating agents, low-dose clofarabine, reduced-intensity conditioning HSCT, and immunotherapeutic approaches. Thus, the concept of personalized therapy has already become a fact, even if agents designed to target AML pathogenic events have not yet entered everyday clinical practice. It means that individual treatment decision-making should be based on both evidence and experience and involve biologists and clinicians within multidisciplinary teams.

Introduction

Two years ago, on behalf of the European LeukemiaNet (ELN), an international expert panel published recommendations for the diagnosis and management of adult patients with acute myeloid leukemia (AML) in Blood.[1] These recommendations covered states of the art in AML diagnosis procedures, prognostic factors and classification, clinical endpoints, AML therapy in younger and older adults, and supportive care. Hopefully, AML diagnosis and management is a constantly evolving field and some important new findings have been reported during the last 2 years, notably in AML genetics, but also in optimal patient management. Starting from these 2010 recommendations (reminded in italics in the text below), the aim of this review is to discuss the new aspects of front-line AML therapy, acute promyelocytic leukemia excluded.

Standard AML therapy

Induction therapy

Three days of an anthracycline (eg, daunorubicin, at least 60 mg/m^2 [higher doses are being explored], idarubicin, 10-12 mg/m^2, or the anthracenedione mitoxantrone, 10-12 mg/m^2) and 7 days of cytarabine (100-200 mg/m^2 continuous IV) ("3+7") currently remains the standard for induction therapy (2010 ELN recommendations).

Antracycline type and doses

Two studies exploring higher doses of daunorubicin were published in September 2009 in the New England Journal of Medicine.[2,3] The Eastern Cooperative Oncology Group (ECOG) trial included 657 younger patients aged 60 years old or less (median, 48 years) with either primary or therapy-related AML. The European trial from the Netherlands, Belgium, Germany, and Switzerland included 813 older patients aged 60 years of age or more (median, 67 years) with primary or secondary AML or high-risk myelodysplastic syndrome. Both studies compared a "standard" daily dose of 45 mg/m^2 *versus* a doubled dose of 90 mg/m^2 for three days as part of 3+7 induction therapy. In the ECOG study, patients in complete remission (CR) were eligible for autologous or allogeneic hematopoietic stem cell transplantation (HSCT) according to their disease risk. In the European study, they received a single but intensive additional course of intermediate-dose cytarabine. Higher daunorubicin dose was associated with higher CR rates, without delaying hematologic recovery or affecting the feasibility of planned post-remission therapies. This translated into prolonged overall survival (OS) in the younger trial,[2] subgroup analyses suggesting that the survival benefit was restricted to patients with favorable- or intermediate-risk cytogenetics and to those under the age of 50 years. Patients with *FLT3* or *MLL* internal tandem duplications did not seem to benefit from dose intensification. In the older AML European trial,[3] a benefit in OS

was observed only in patients aged less than 65 years old and in the small subgroup of patients with core-binding factor (CBF) leukemia. These important results confirm the role of increased dosage of daunorubicin in AML, which is not associated with increased toxicity. They demonstrate that the 45 mg/m^2 daily dose is definitely suboptimal until the age of 65 years. They do not, however, demonstrate that the 90 mg/m^2 daily dose should be preferred to the 60 mg/m^2 daily dose, which has been used in Europe for years and the international panel endorsed as the minimal dose to be administered to younger patients.

Paradoxically, the Acute Leukemia French Association (ALFA), which was using a high daunorubicin daily dose of 80 mg/m^2 until 65-70 years of age since the early nineties, decided to go back to the 60 mg/m^2 daily dose in patients aged from 50 to 70 years old when designing the gemtuzumab ozogamicin (GO) ALFA-0701 study in 2007 (see below). This was due to concerns about safety of the GO-chemotherapy combination, but also to results of the previous ALFA-9801 study, which did not demonstrate any superiority of high 3×80 mg/m^2 doses of daunorubicin compared with standard 3×12 mg/m^2 doses of idarubin in a series of patients aged 50 to 70 years old.[4] Similar results came from the Japan Acute Leukemia Study Group AML201 study, which compared 5×50 mg/m^2 daunorubicin to 3×12 mg/m^2 idarubicin.[5] Of note, ALFA experience also does not support the hypothesis that the higher 80 mg/m^2 might be superior to the more standard 60 mg/m^2 daunorubicin in patients aged 50 to 70 years old. Retrospective comparison between the 156 patients from the high 80 mg/m^2 daunorubicin arm of the ALFA-9801 study and the 139 patients from the 60 mg/m^2 daunorubicin control arm of the ALFA-0701 study, which did not differ in post-remission therapy, showed similar CR rate after one (60.9% *vs.* 60.4%; *P*=0.99) or eventually two (70.5% *vs.* 71.2%; *P*=0.90) induction courses, similar event-free survival (illustrated in Figure 1), and similar overall survival.

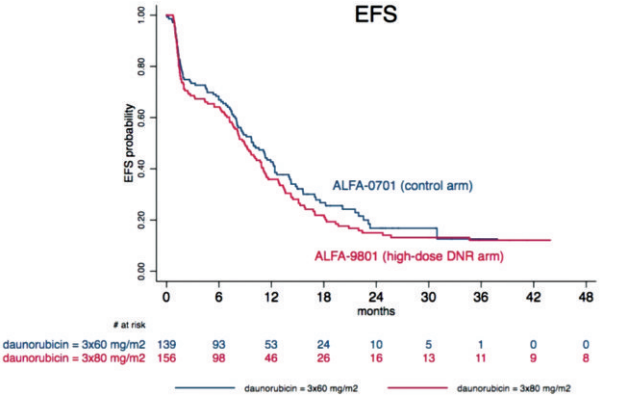

Figure 1. Historical comparison of 80 *versus* 60 mg/m^2/day daunorubicin during induction in patients aged 50 to 70 years old (ALFA-9801 *vs.* ALFA-0701 studies). The 80 mg/m^2 daunorubicin arm of the ALFA-9801 study was compared retrospectively with the control 60 mg/m^2 daunorubicin arm of the ALFA-0701 study. Both treatment arms only differed by the induction daunorubicin dose. As shown, no difference in event-free survival was apparent.

Cytarabine dose

It is not generally recommended that high-dose cytarabine (HiDAC) be included in induction regimens outside clinical trials (2010 ELN recommendations).

To increase the cumulative dose of cytarabine during first induction safely is probably more problematic. Historical randomized studies from the Southwest Oncology Group (SWOG) and the Australian Leukemia Study Group (ALSG) failed to demonstrate clinically relevant gains in efficacy, but both demonstrated increased toxicity.[6,7] Two recent studies reinvestigated higher than standard cytarabine doses during the initial therapy of younger adults with AML. The first study, conducted by the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and the Swiss Group for Clinical Cancer Research (SAKK), enrolled 860 patients aged 18 to 60 years old (median, 49 years). They were randomized between a so-called intermediate-dose cytarabine (IDAC) arm, comprising standard cytarabine dose at 200 mg/m^2/d CIV for 7 days during the first course followed by intermediate doses at 1000 mg/m^2/12h for 6 days during the second course, or a so-called HiDAC arm with 1000 mg/m^2/12h cytarabine for 5 days during the first course and 2000 mg/m^2/12h on day 1, 2, 4, and 6 during the second course.[8] This two-course induction was followed by one additional course of chemotherapy or autologous or allogeneic HSCT, according to the disease risk. Results were disappointing with similar CR rate, event-free, and overall survival observed in both randomization arms, and more toxicity observed in the HiDAC arm. The second study, conducted by the EORTC and GIMEMA Leukemia Groups, enrolled 1,942 patients aged 15 to 60 years old (median, 45 years). They were randomized to either receive standard doses of cytarabine at 100 mg/m^2/d CIV for 10 days or HiDAC at 3000 mg/m^2/12h on day 1, 3, 5, and 7 during the first induction course.[9] This first course was followed by one IDAC-containing course, similar for all patients, then allogeneic or autologous HSCT. A higher CR rate was observed in the HiDAC arm, with a trend for a longer overall survival that reached statistical significance in the subset of patients aged less than 46 years old. Discrepancy between the two studies might be explained by differences in the control arm.

Another attempt to increase induction dose intensity relies on systematic administration of a second sequence of chemotherapy starting earlier after the completion of the first one, generally between at day 7 and day 14. This sequential or dose-dense concept was initially developed by the Johns Hopkins group in Baltimore,[10] then evaluated prospectively by the ALFA group, without incorporating HiDAC.[11] After having investigated double induction containing one or two HiDAC sequences (TAD-HAM or HAM-HAM),[12] the German AML Cooperative Group (AMLCG) conducted a Phase 2 trial recently investigating dose-dense sequential HAM.[13] However, there is no evidence to date that dose-dense induction might be superior to standard 3+7 induction, especially when high doses of daunorubicin are used.

Finally, one has to keep in mind that results associated with any change in the early phase of AML therapy should be interpreted in the context of the whole treatment plan. The benefit that may be theoretically anticipat-

ed with dose escalation may be partially offset by further HiDAC consolidation cycles, or autologous or allogeneic HSCT. Potential redundancy in the number and timing of HiDAC administrations has been demonstrated by an Australian study that, in the converse way, evaluated HiDAC *versus* standard-dose cytarabine during consolidation after front-line HiDAC-based induction and concluded no significant difference.[14]

Allogeneic HSCT in first CR

The value of allogeneic HSCT needs to be reassessed based on the identification of AML-related genetic changes that profoundly impact on prognosis, on the availability of different transplant sources […] and in the light of the use of reduced-intensity conditioning (RIC) regimens. […] It is important to consider transplant-related mortality (TRM) that may vary between less than 15% and up to 50%. It is essential to assess whether the benefit of the reduced relapse rate outweighs TRM or will be offset by a high TRM (2010 ELN recommendations).

A beneficial effect of allogeneic HSCT has been shown in younger patients with intermediate/adverse-risk AML in first CR. This has mainly been demonstrated through so-called donor *versus* no-donor studies, which basically consider the biological donor *versus* no-donor allocation at time of CR achievement to be a random process.[15,16] One should, nevertheless, keep in mind that these studies were conducted before the recent refinements in AML genetics and focused on sibling donor myeloablative conditioning (MAC) transplantation only. Furthermore, the benefit associated with HSCT was only demonstrated for patients aged less than 35 to 40 years old at that time. Based on these studies, patients with favorable-risk core binding factor (CBF) AML are generally not considered candidates for allogeneic HSCT in first CR.[15,16] Patients with cytogenetically normal (CN) AML and a favorable genotype (defined as *NPM1* mutation without *FLT3-ITD* or CEPBA mutation) have been added recently to this favorable subset of patients. This was based on their relatively good outcome when treated with chemotherapy alone, with an overall relapse risk less than 30 to 40% that competed equally with TRM in donor *versus* no-donor analysis.[17] All other patients are still considered candidates for allogeneic HSCT in first CR, including those with *FLT3*-ITD AML. Within this newly defined favorable-risk subset, the identification of "favorable" patients at higher risk of relapse is an important clinical issue. Discrimination could be based on the presence of additional poor-prognosis gene mutations, such as *KIT* or *FLT3* mutations in CBF-AML,[18,19] or *ASXL1, IDH1*, or *DNMT3A* mutations in CN-AML.[20-25] Assessment of minimal residual disease (MRD) levels after CR achievement and consolidation therapy also represents an interesting tool to stratify therapy in these patients further, including reintroduction of allogeneic HSCT.[26-31]

Intent-to-treat donor *versus* no-donor comparisons, starting at the date of CR achievement, are not well suited to evaluate the real effect of HSCT in very high-risk patients, such as those with induction failure and/or adverse karyotype. As a significant proportion of these patients will never be transplanted in first CR despite an identified donor, transplant *versus* no-transplant comparisons should be preferred. Using either landmark comparison or evaluation of HSCT as a time-dependent covariate, two studies recently have confirmed the superiority of allogeneic HSCT over chemotherapy in these very high-risk patients, even if overall results remain disappointing.[32,33]

In 2012, besides the age and AML-risk issues, HSCT decision-making should probably also take into account the newly described gene mutations of prognostic significance, the newly available stem cell sources, and the possibility of reduced-intensity conditioning (RIC) in a personalized and sometimes difficult benefit-risk evaluation. We definitely need validated multivariate scores to guide this decision, but they do not exist in AML at the present time. It is thus more than ever essential to continue to "assess whether the benefit of the reduced relapse rate outweighs TRM or will be offset by a high TRM" within the various AML subsets and age categories. Awaiting such scores, individual decision-making will remain more experience-based than evidence-based.

Of particular interest are the recent results of studies evaluating the value of RIC transplantation in middle-aged patients enrolled and treated in prospective protocols. First results came from a Mantel-Byar analysis of the MRC AML15 trial, which showed longer relapse-free and some evidence for longer overall survival associated with RIC transplantation in patients aged over 45 years, those with both a sibling donor and intermediate cytogenetics being those who most likely benefited from this procedure.[34] Long-term results of the GOELAMS 2001 trial reveal a similar outcome for patients aged 50 to 60 years old receiving a RIC transplantation than for those aged less than 50 years receiving a MAC transplantation in first CR.[35] Finally, a retrospective analysis of allogeneic HSCT in 1,105 patients aged 40 to 60 years old treated in the HOVON/SAKK H29, H42, H42A, and H92 trials suggests that, due to lower TRM, RIC might yield longer survival than MAC transplantation in this age range.[36]

Chemotherapy in first CR

HiDAC consolidation

Post-remission therapy with repetitive cycles of HiDAC (3 g/m2 per q12h on days 1, 3, and 5) is considered a reasonable choice for younger adult patients with CBF AML, and also for AML with mutated NPM1 without FLT3-ITD and with mutated CEBPA. […] Outcome results similar to those after HiDAC consolidation may be obtained using other intense chemotherapy regimens. However, use of prolonged intensive consolidation, or of multiagent chemotherapy does not appear to be superior to HiDAC alone (2010 ELN recommendations).

For patients with favorable-risk AML, or for those with no suitable HSC donor or contra-indication to HSCT, optimal post-remission chemotherapy remains to be determined. Administration of several HiDAC consolidation courses using cytarabine at the 3 g/m^2 dosage twice the day on day 1, 3, and 5 (for a total of 6 bolus infusion) is a frequent option since the landmark Cancer and Leukemia Group B (CALGB) publication in 1994.[37] One should, nevertheless, keep in mind that in this study: i) comparative arms appear now to be suboptimal, almost 20 years later; ii) subsequent therapy with four less intensive courses comprising an anthracycline followed the four planned HiDAC courses. To date, if several studies have shown equivalent results when using multi-agent courses with cytarabine at lower doses,[38-41] no consolida-

tion regimen has been shown as superior to this CALGB HiDAC schedule. Some groups (SWOG, ALFA…) have simplified this historical CALGB post-remission therapy, by reducing the number of HiDAC courses at three and omitting the last four less intensive courses.

Autologous HSCT

Outcome after autologous HSCT is at least as good as after the use of post-remission chemotherapy; however, there has been no evidence of an improvement in outcome. Autologous HSCT may offer an advantage in specific subsets of AML (2010 ELN recommendations).

Before the HiDAC-based consolidation era, autologous bone marrow HSCT in first CR was associated with prolonged disease-free survival in some prospective studies, but never with prolonged OS.[42] That is why some groups are using autologous transplantation in patients who may not receive allogeneic transplantation, while other groups are using chemotherapy alone. Autologous transplantation is associated with a shorter duration of active therapy, but also with some non-hematological toxicity, such as decreased fertility. Given the advances made in AML biology and MRD evaluation, the time might have come to reassess the role of autologous HSCT in specific patient subsets. For instance, the German Study Alliance Leukaemia (SAL) has recently developed a post-remission treatment (PRT) score, including age CD34-positive blast percentage, *FLT3*-ITD ratio, cytogenetics, and *de novo versus* secondary AML, which separated AML patients in favorable, intermediate, and unfavorable subgroups.[43] Interestingly, autologous HSCT yielded better survival than allogeneic HSCT or chemotherapy in intermediate-risk patients.

New options in AML therapy

Growth factor priming

Priming with growth factors remains an active field of clinical investigation; it cannot be recommended in routine practice (2010 ELN recommendations).

During the last 15 years, numerous studies have evaluated the addition of a growth factor to AML induction and consolidation chemotherapy, either granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF). Some of these studies specifically evaluated their priming effect on leukemic blasts when administered during, but not after, chemotherapy. Beneficial effects have been reported in two studies, one with G-CSF and the other with GM-CSF.[44,45] Which AML subsets may benefit from such an approach remains, however, to be determined.[46] More recently, plerixafor, a CXCR4 antagonist blocking the CXCR4/SDF-1 interaction, has been developed as an agent capable to mobilize hematopoietic progenitors from the hematopoietic niche to the peripheral blood. Studies evaluating its safety and potential when used alone or combined with G-CSF as a chemo-sensitizing agent in AML patients are ongoing.[47]

Gemtuzumab ozogamicin

*GO is a humanized anti-CD33 antibody chemically linked to the cytotoxic agent calicheamicin that inhibits DNA synthesis and induces apoptosis. GO is approved for relapsed AML (currently in the United States and Japan, but not in Europe) in older patients who are not considered candidates for other cytotoxic therapies. […] Randomized trials evaluating the addition of GO to conventional chemotherapy have been completed (eg, MRC AML 15 trial; final results are pending) or are ongoing (*e.g.*, SWOG Protocol S0106).*

Table 1. Prospective randomized studies of gemtuzumab ozogamicin (GO) combined to conventional chemotherapy in adults with newly-diagnosed AML.

Study	Age	Patients (N)	GO dose and schedule	Results
SWOG S0106[48]	18-60 y	456	6 mg/m^2 d4 cycle 1	Similar response rate Higher induction mortality Similar RFS Similar OS
MRC AML15[49]	18-60 y	1,113	3 mg/m^2 d1 cycle 1	Similar response rate Similar RFS and OS Longer OS in favourable AML
MRC AML16[50]	60 y+	1,115	3 mg/m^2 d1 cycle 1	Similar response rate Longer RFS, OS from CR and OS
ALFA-0701[51]	50-70 y	278	3 mg/m^2 d1/4/7 cycle 1 d1 conso 1 d1 conso 2	Similar response rate Longer EFS, RFS, and OS
GOELAMS 2006-IR*[52]	18-60 y	254	6 mg/m^2 d4 cycle 1 d4 conso 1	Similar response rate Similar EFS and OS Longer EFS in non allo-HSCT patients

*:patients with intermediate-risk karyotype only; CR: complete remission; RFS: relapse-free survival; EFS: event-free survival; OS: overall survival.

Since the ELN guidelines publication, the Food and Drug Administration decided to no longer approve GO in the US, due to safety concerns. This decision was based on negative results from the younger AML SWOG S0106 trial, which was prematurely closed due to no benefit and a significantly higher incidence of fatal induction adverse events when 6 mg/m^2 GO was added on day 4 of a 3+7 induction, despite reduced 45 mg/m^2/day daunorubicin dose in the GO arm.[48] Conversely, three recent randomized studies, two from the British Medical Research Council (MRC) and one from the ALFA group, reported significant improvement in patient outcome when GO was combined to induction or induction and consolidation chemotherapy (Table 1).[49-51] Gemtuzumab ozogamicin, even if not exceeding 3 mg/m^2 per dosing, remained, however, associated with higher liver toxicity and more frequent persistent thrombocytopenia in these studies. Interestingly, positive results seem to be particularly marked in older patients, especially when using repeated low GO doses as developed by the ALFA group.[50,51] Subset analyses suggest that significant benefit of added GO is observed in patients of favorable and intermediate ELN risk, including those with internal tandem duplication of the *FLT3* gene, while not in those with an adverse karyotype.[49-51] Results of the GOELAMS 2006-IR study, which tested a 6 mg/m^2 dosing and was prematurely closed due to excess non AML-related toxicity, also suggest a benefit in event-free survival for younger patients with intermediate-risk cytogenetics, but restricted to those who do not receive further allogeneic HSCT.[52]

Purine analogues and other non-targeted agents

Among non-targeted agents, one should mentioned purine analogues (fludarabine, cladribine, clofarabine). In a subset analysis of a larger randomized study by the Polish Acute Leukemia Group (PALG), the addition of fludarabine or cladribine to a standard 3+7 treatment was associated with prolonged overall survival.[53] Even if clofarabine failed to show significant benefit when added to intermediate-dose cytarabine in patients with relapsed/refractory AML,[54] results of other randomized trials evaluating clofarabine in newly diagnosed patients are pending or will be available soon. Among other non-targeted agents, laromustine was not associated with interesting safety/efficacy profile, while amonafide combined with cytarabine failed to yield benefit compared with 3+7 in a secondary AML study. Vosaroxin, a replication-dependent DNA-damaging agent, is currently evaluated in combination with intermediate-dose cytarabine in relapsed/refractory AML patients.

Targeted agents

Progress has been made in deciphering the molecular pathogenesis of AML, and in a few instances this has led to the development of molecularly targeted approaches.

The German AML Study Group (AMLSG) group reported their randomized HD98B AML trial in older AML in 2004, in which all-trans retinoic acid (ATRA) administration after chemotherapy was shown to increase both CR and OS.[55] Patients with isolated *NPM1* mutation were those who derived OS benefit from use of ATRA.[56] In a preliminary report of a similar study, but in younger AML patients, an overall OS improvement was again seen in the ATRA arm, with both increased CR rate and EFS in *NPM1* mutated patients only.[57] However, no benefit of ATRA was evidenced in another large study from the British AML group.[58] These results should thus be confirmed independently before their general application. Targeted inhibition of constitutively activated *FLT3* receptors remains a subject of intense investigations. Currently, lestaurtinib in relapsed AML patients and sorafenib in newly diagnosed older AML have failed to demonstrate significant benefit when combined to intensive chemotherapy.[59,60] A large similar phase III randomized study of midostaurin restricted to *FLT3* mutated patients younger than 60 years is ongoing. Phase II study of quizartinib or AC220, the most selective *FLT3* inhibitor available, in relapsed AML have confirmed that clonal responses could be observed with monotherapy.[61] Interestingly, clonal escapes were associated with resistance mutations in the FLT3 gene.[62] Similar observations have been made *in vitro* under sorafenib selective pressure.[63] Finally, exon 8/17 *KIT* mutations, associated with unfavorable prognosis in CBF-AML, may be targeted with dasatinib. A frontline study of dasatinib combined to intensive chemotherapy is ongoing by the AMLSG. In the setting of molecular residual disease or early molecular relapse, however, no responses were observed with dasatinib alone in the French DASA-CBF study.[64]

Standard therapy in older AML patients

Older age per se, however, should not be a reason to withhold intensive therapy. Studies suggest that remission induction chemotherapy provides better quality of life and longer survival than supportive care only. Thus, these patients often deserve being offered the option of standard chemotherapy.

In 2009, the Swedish Acute Leukemia Registry demonstrated convincingly that an intensive chemotherapy remains the best currently available option, as it showed that older AML patients treated intensively in various Swedish regions always had a better outcome and lower early death rates than patients non intensively treated.[65,66] Intensive chemotherapy should thus remain the standard in patients capable to tolerate it. In those patients, the 3+7 remains the most frequently used chemotherapy induction regimen. As mentioned above, investigators of the HOVON/SAKK/AMLSG groups showed that high-dose daunorubicin improves outcome without increased toxicity until 65 years of age.[3] In patients who attained CR, what defines an optimal post-remission therapy remains unclear. At least in those with favorable cytogenetics or genotype, intensive post-remission chemotherapy may be of benefit, as a prolonged overall survival may be achieved in 40% of them. Use of repeated less intensive post-remission courses is another option, more convenient for the majority of patients, and consuming less hospital resources.[67] Allogeneic RIC-HSCT from a sibling or an unrelated donor might, however, be the best option. A prospective randomized RIC-HSCT study is currently running in Europe. At this time, we do not know if use of any of the new drugs under investigation, alone or in combination, will improve results over intensive chemotherapy in older patients aged more than 65-70 years old. Results of clofarabine monotherapy have been reported in two independent Phase II trials, with response

rate and survival comparable to 3+7 results, including in patients with adverse characteristics.[68,69] An ongoing Phase III ECOG trial compares upfront administration of clofarabine courses to 3+7 followed by intensive cytarabine-based consolidations.

Which approach should be offered to patients deemed unlikely to tolerate intensive therapy or unlikely to benefit from it is even less clear. In the UK non-intensive AML14 trial, low-dose cytarabine (LDAC) was found to be of benefit, at least in patients with non-adverse cytogenetics, when compared with best supportive care (BSC) including use of hydroxyurea.[70] In the "pick-a-winner" AML16 trial, clofarabine and LDAC + GO were compared with LDAC, using short-term response/survival as an endpoint for phase III trial extension. Despite improved CR rate, the addition of GO to LDAC failed to improve OS.[71] Results of the clofarabine *versus* LDAC comparison remain awaited. Hypomethylating agents, azacitidine and decitabine, have shown a significant survival benefit in high-risk MDS, including in patients with 20 to 30% marrow blasts, compared with conventional care including LDAC.[72] Phase II data in AML are also available for decitabine, showing significant response rate. Results of an international AML phase III trial, comparing decitabine to conventional care, either BSC or LDAC, have been reported in abstracts. The primary endpoint, increased overall survival was not met at time of pre-specified analysis, with a median OS of 7.7 months *versus* 5 months in the decitabine and control arm, respectively.[73] This study is used to support filing of decitabine in the indication of elderly AML non-eligible for intensive therapy and responses of the FDA and EMA agencies are awaited this year. Although azacitidine has also shown interesting results in retrospective AML studies, a large prospective study that will clarify its role in older AML therapy is ongoing, comparing azacitidine with conventional care including intensive therapy.

Conclusion

In conclusion, front-line AML therapy in 2012 relies on intensive chemotherapy incorporating adequate anthracycline and cytarabine doses if patients are capable of tolerating it. Allogeneic HSCT in first remission is indicated for the majority of patients with non favorable-risk AML with a suitable related or unrelated donor, conditioning being adapted to patient's age and health status. Inclusion in clinical trials should be encouraged whenever possible, especially to evaluate the benefits and risks associated with HSCT in subsets defined by patient/disease characteristics and transplant procedures. Among most promising third agents are GO and purine analogues. Older patients with favorable or standard prognosis features should receive intensive therapy, including RIC-HSCT, if eligible. If non-eligible for intensive treatments, they should be offered in priority participation to clinical trials with new drugs, instead of supportive care only or low-intensity therapy.

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