An update of current treatments for adult acute myeloid leukemia

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Abstract

Recent advances in acute myeloid leukemia (AML) biology and its genetic landscape should ultimately lead to more subset-specific AML therapies, ideally tailored to each patient's disease. Although a growing number of distinct AML subsets have been increasingly characterized, patient management has remained disappointingly uniform. If one excludes acute promyelocytic leukemia, current AML management still relies largely on intensive chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT), at least in younger patients who can tolerate such intensive treatments. Nevertheless, progress has been made, notably in terms of standard drug dose intensification and safer allogeneic HSCT procedures, allowing a larger proportion of patients to achieve durable remission. In addition, improved identification of patients at relatively low risk of relapse should limit their undue exposure to the risks of HSCT in first remission. The role of new effective agents, such as purine analogs or gemtuzumab ozogamicin, is still under investigation, while promising new targeted agents are under clinical development. In contrast, minimal advances have been made for patients unable to tolerate intensive treatment, mostly representing older patients. The availability of hypomethylating agents likely represents an encouraging first step for this latter population, and will hopefully allow for more efficient combinations with novel agents.
1. Introduction

Long-term cure of patients with acute promyelocytic leukemia (APL) using retinoic acid and arsenic trioxide (ATO) therapy represents the only dramatic therapeutic advance over the last two decades in acute myeloid leukemia (AML). Although increasingly refined knowledge of AML biology has led to the development of new targeted agents such as the mutated FLT3 or IDH inhibitors, current advances in non-APL patients lack innovation, relying instead on modifications to doses and schedules of standard cytotoxic drugs or progress in hematopoietic stem cell transplantation (HSCT) techniques. In younger patients, complete remission (CR) rates of 80% or more may be reached, with 5-year overall survival (OS) around 40%. In older patients, the use of hypomethylating agents has improved median and short-term OS but has not translated into improved cure rates, which remain disappointingly very low. Guidelines for AML management are widely available. This review aims to provide a balanced perspective of available data supporting AML treatment used in routine practice today. We have focused on data from randomized clinical trials using approved drugs. Early results with new investigational drugs will be discussed in depth in another article of this Review Series.

2. Front-line induction therapy

Induction therapy with cytarabine and an anthracycline remains a standard of care in AML. The standard combination is the 7+3, with a 7-day continuous infusion of cytarabine at the dosage of 100 or 200 mg/m²/day, days 1 to 7 and daunorubicin at 60 mg/m²/day, days 1 to 3. Recent randomized studies have investigated higher doses of anthracyclines or cytarabine or the addition of a third agent during induction. However it is very difficult to compare these studies, as they differ significantly in several key parameters, notably the number of induction courses, doses in the control arm, and subsequent therapies offered to responders or to patients with persistent marrow blasts after the first induction course. Differences in study results may thus be due to differences in the design of either experimental or control arms.
Anthracyclines

Recently reported randomized studies exploring daunorubicin or idarubicin doses during induction courses are summarized in Table 1. Four studies have evaluated higher daunorubicin doses.\textsuperscript{2-5} The Eastern Cooperative Oncology Group (ECOG) trial included patients aged 60 years old or less,\textsuperscript{2} while the European trial from a Dutch, Belgian, German, and Swiss consortium included patients aged 60 years of age or more.\textsuperscript{3} Both studies compared a daily dose of 45 mg/m\textsuperscript{2} versus a doubled dose of 90 mg/m\textsuperscript{2} for three days as part of 7+3 induction therapy. The higher daunorubicin dose was associated with higher CR rates, without delaying hematologic recovery or affecting the feasibility of planned post-remission therapies. In the younger population ECOG trial, OS was significantly prolonged in the 90 mg/m\textsuperscript{2} arm.\textsuperscript{2} The OS benefit was observed in all cytogenetic groups and in patients with internal tandem duplication (ITD) of the \textit{FLT3} gene, as well as in those with \textit{NPM1} and \textit{DNMT3A} gene mutations.\textsuperscript{6} In the older population trial, the OS benefit was restricted to patients between the age of 60 and 65 years and to the few patients with core-binding factor (CBF) AML.\textsuperscript{3}

These results demonstrate that the 45 mg/m\textsuperscript{2} daunorubicin daily dose is suboptimal up until the age of 65 years. They do not, however, establish that the 90 mg/m\textsuperscript{2} daily dose should be preferred over the 60 mg/m\textsuperscript{2} daily dose endorsed by the international 2010 guidelines.\textsuperscript{7} The recent UK NCRI AML17 trial addressed this question in an upfront comparison of the 60 and 90 mg/m\textsuperscript{2} doses in the first course.\textsuperscript{5} All favorable- and intermediate-risk patients went on to receive a second course with a 50 mg/m\textsuperscript{2} dose. In an interim analysis, a significant increase in day 60 mortality was observed in the 90 mg/m\textsuperscript{2} arm, leading to premature trial termination. No OS benefit was observed in this analysis, although evidence of a survival benefit in subgroups may require longer follow-up.

The Acute Leukemia French Association (ALFA) 9801 study comparing daunorubicin \textit{versus} idarubicin, failed to demonstrate superiority of 80 mg/m\textsuperscript{2} daunorubicin over a standard 12 mg/m\textsuperscript{2} idarubicin dose.\textsuperscript{8} A similar outcome was reported in the Japan
Acute Leukemia Study Group (JALSG) AML201 study which compared two courses of 50 mg/m² daunorubicin for 5 days with 12 mg/m² idarubicin for 3 days.\(^9\)

Anti-leukemic activity of 60 and 90 mg/m² daunorubicin or 12 mg/m² idarubicin daily doses thus appears to be similar, as are the toxicity profiles, at least in cases when a second anthracycline-containing cycle is not given systematically to responders.

**Cytarabine**

Randomized studies exploring cytarabine dose and schedule during induction are summarized in [Table 2](#). Historical studies from the Southwest Oncology Group (SWOG) and the Australian Leukemia Study Group (ALSG) failed to demonstrate clinically relevant gains in efficacy with higher cytarabine doses with alternative administration regimens, while both reported increased toxicity.\(^{10,11}\) Two recent studies further addressed this question, one in the context of idarubicin or amsacrine and the other using lower etoposide doses and alternative administration schedules.

In the study conducted by the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and the Swiss Group for Clinical Cancer Research (SAKK), patients were randomized between an IDAC arm, comprising 200 mg/m²/day cytarabine during the first course and 1,000 mg/m²/12h for 6 days during the second course, or a high-dose (HiDAC) arm with 1,000 mg/m²/12h for 5 days during the first course and 2,000 mg/m²/12h on day 1, 2, 4, and 6 during the second course.\(^{12}\) Similar rates of CR, event-free survival (EFS), and OS were observed in the two arms, with more toxicity associated with the HiDAC arm.

In the second study, conducted by the EORTC and GIMEMA Leukemia Groups, patients were randomized to receive either standard doses at 100 mg/m²/day cytarabine for 10 days or HiDAC at 3,000 mg/m²/12h on day 1, 3, 5, and 7 during the first course.\(^{13}\) A higher CR rate was observed in the HiDAC arm, with a trend for a longer OS that reached statistical significance in the subset of patients aged 45 years and younger. Finally, in the randomized German Intergroup study that included
a double induction as a “common” arm or an IDAC or HiDAC sequence during induction in at least three study arms, no difference in OS was observed.\textsuperscript{14} It thus remains unclear if increasing the cytarabine dose during induction may benefit patients planned to receive IDAC or HiDAC during post-remission therapy.

"Dose-dense" regimens

Another approach to increasing induction intensity relies on systematic administration of a second sequence of chemotherapy starting earlier than normal after the completion of the first sequence (generally between day 7 and day 14). This timed-sequential concept was initially developed by the John Hopkins group in Baltimore,\textsuperscript{15} then prospectively evaluated by the ALFA group without incorporating HiDAC.\textsuperscript{16} After investigating double induction containing one or two HiDAC sequences (TAD-HAM or HAM-HAM),\textsuperscript{17} the German AML Cooperative Group (AMLCG) recently conducted a phase 2 trial investigating a sequential S-HAM.\textsuperscript{18} However, none of these studies provide evidence that a dose-dense regimen is superior to the standard 7+3 regimen, especially when high doses of daunorubicin are used.

Addition of a third drug

Gemtuzumab ozogamicin (GO)

Randomized studies exploring the addition of GO to intensive chemotherapy (ICT) are summarized in Table 3. Six studies evaluating the addition of 3 or 6 mg/m\textsuperscript{2} GO during induction have been performed.\textsuperscript{19-24} The first of them, SWOG S0106, was negative and closed prematurely due to a higher early mortality rate despite a reduced 45 mg/m\textsuperscript{2}/day daunorubicin dose in the GO arm, leading to GO withdrawal by the Food and Drug Administration in the United States.\textsuperscript{19} Conversely, four studies reported significant improvements when GO was combined with induction or induction and consolidation chemotherapy.\textsuperscript{20-23} This finding was confirmed in a
recent meta-analysis. Nonetheless, the addition of GO was associated with more frequent severe liver toxicity and persistent thrombocytopenia. The benefit/risk ratio appeared to be at least as good with 3 mg/m$^2$ per dosing, a dose that can be administered to older patients, and ultimately be repeated as successfully developed by the ALFA group. In contrast, increased toxicity and an absence of clinical benefit were observed in the EORTC/GIMEMA study, in which single-agent GO administration preceded induction chemotherapy. Finally, the two studies that evaluated GO maintenance therapy were negative. Clinical response to GO is likely to be influenced by CD33 expression level, clonal hierarchy of the leukemic population and drug efflux intensity, all factors related to AML genetics. It has been widely demonstrated that GO benefits patients of favorable and intermediate risk, including those with FLT3-ITD, while not those with an adverse karyotype. All together, these data suggest that the license status of GO might need to be reviewed, at least for some patient subsets. Early outcomes with the SGN-CD33A immunoconjugate in AML are discussed elsewhere in this Review Series.

**Purine analogs**

Randomized studies exploring the addition of purine analogs to ICT are summarized in Table 4. In the Polish Acute Leukemia Group (PALG) study, the addition of cladribine was associated with prolonged OS, although it should be noted that outcomes in the control arm appeared to be suboptimal. Interestingly, addition of cladribine appears to have particularly benefited high-risk patients, notably those aged 50 years or more or those with unfavorable cytogenetics. Clofarabine also demonstrated significant anti-leukemic activity, both as a single agent and in combination with cytarabine in various patient populations. However, it failed to show significant benefit when combined with daunorubicin in the British AML16 trial in newly diagnosed patients. Front-line results from two other trials are imminent, including the combination of clofarabine with 7+3, and clofarabine compared to 7+3 in an ECOG trial. The British AML15 trial in a younger population demonstrated that the fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF) and
idarubicin regimen (FLAG-Ida) yielded more frequent remissions with one course and also reduced the risk of relapse.\textsuperscript{33}

\textit{Sorafenib}

Sorafenib is a multikinase inhibitor with \textit{in vitro} activity in FLT3-ITD AML. In an AML trial from the German Study Alliance Leukemia (SAL), combination of sorafenib with standard induction and IDAC consolidation was evaluated in older patients. Treatment in the sorafenib arm did not result in significant improvement in EFS or OS.\textsuperscript{34} This was also true for subgroup analyses, including the subgroup positive for FLT3-ITD. Results of induction therapy were worse in the sorafenib arm, with higher early mortality and a lower CR rate. The same group has reported preliminary results of a similar trial conducted in younger patients in which sorafenib was added to 7+3 induction and HiDAC consolidations.\textsuperscript{35} No difference in the CR rate was observed, while EFS and relapse-free survival (RFS) were significantly improved in the sorafenib arm. In the subgroup of FLT3-ITD-positive patients, no difference in EFS was observed, however there was a trend for prolonged RFS and OS favoring sorafenib.

\textbf{3. Post-remission therapy}

\textit{HiDAC consolidation}

For younger patients not undergoing HSCT, administration of several HiDAC consolidation courses using cytarabine twice daily at 3 g/m\textsuperscript{2}/dose on day 1, 3 and 5 has been a widely used option since 1994.\textsuperscript{36} Even if the optimal cytarabine dose, schedule of administration and number of cycles need yet to be defined,\textsuperscript{37,38} the use of bolus administration of HiDAC or IDAC during consolidation should be recommended. Interestingly, HiDAC and IDAC regimens are well suited to evaluate the effects of added targeted or non-targeted drugs during consolidation. For instance, a prolonged RFS was observed in the randomized ALFA-0702/CLARA
study in intermediate- and unfavorable-risk patients with clofarabine/IDAC compared to HiDAC consolidation cycles.39

Allogeneic HSCT

One of the most important treatment decisions in AML is to estimate the benefit/risk associated with allogeneic HSCT in first remission for a given patient. Transplantation offers the best means of preventing AML recurrence, but remains associated with higher treatment-related morbidity and mortality (TRM), especially in older patients. In patients with favorable-risk AML, the relapse risk may be low enough and the salvage rate high enough to postpone HSCT to second remission. This strategy has been validated in several donor versus no-donor studies.40,41 In these studies, favorable patients (i.e. those with CBF-AML) from the no-donor group did as well as those from the donor group, while all other patients appeared to benefit from undergoing allograft. One should keep in mind that patients in these studies mostly underwent sibling donor myeloablative conditioning (MAC) transplantation and as such, the benefit associated with HSCT was only demonstrated for patients aged less than 40 years old. Based on another donor versus no-donor analysis, patients with cytogenetically normal (CN) AML and a favorable genotype (defined as mutated CEBPA or NPM1 without FLT3-ITD) were recently categorized in the favorable subgroup.42 As the outcome after allogeneic HSCT from fully matched unrelated donors appears to be similar compared with allogeneic HSCT from matched related donors, all younger patients with intermediate- and unfavorable-risk AML are generally considered candidates for allogeneic HSCT from sibling or fully matched unrelated donors in cases of first CR.7

This HSCT benefit/risk assessment, based on the European LeukemiaNet (ELN) genetic classification only,7 needs however to be reconsidered in the near future. As discussed in another article of this Review Series, the incidence of TRM has been substantially reduced over the last few decades,43 particularly in older patients, by using reduced-intensity conditioning (RIC). Alternative stem cell sources are more widely used and are safer, as illustrated by post-transplant administration of
cyclophosphamide in haplo-identical HSCT. Of particular interest are the recent results of studies evaluating RIC transplantation in middle-aged patients. Using a time-dependent Mantel-Byar comparison in patients over 45 years of age, the MRC AML15 trial showed that compared to chemotherapy, RIC transplantation was associated with longer survival. Two recent studies have even suggested that RIC might be preferred to MAC transplantation in this age range, given the lower TRM as well as better survival in some risk subgroups.

Reliance on genetic profiles as the main treatment-stratifying tool is being increasingly challenged due to multiple recently described genetic mutations and the potential impact of mutated allele frequencies. Not all patients with ELN favorable-risk AML have a favorable outcome; for instance, should we take into account the presence of additional KIT or FLT3 poor-risk mutations in a patient with CBF-AML, or of additional ASXL1, IDH1 or DNMT3A mutations in a patient with NPM1-mutated CN-AML and no FLT3-ITD? Likewise, should HSCT be considered the best post-remission option in ELN intermediate-risk patients with NPM1-mutated FLT3-ITD-positive CN-AML but a low FLT3-ITD allelic ratio? Assessment of minimal residual disease (MRD) using molecular markers or leukemia-associated aberrant immunophenotypes is therefore proposed as a more straightforward, easy-to-use prognostic decision tool, including deciding which patients should be advised to undergo allogeneic HSCT. As in acute lymphoblastic leukemia, MRD has been suggested as ultimately superseding other prognostic factors for HSCT decision making, including genetic factors, as is already the case for CBF-AML. Whether allogeneic HSCT may be the option of choice in poor early MRD responders remains, nevertheless, an open issue.

4. Targeted treatments for specific AML subgroups

Core binding factor AML

A subgroup analysis of the MRC AML15 younger population AML trial along with a subsequent meta-analysis, strongly suggest that the combination of GO with ICT
is associated with a significant OS benefit in CBF-AML, renewing interest in this drug, which is currently unavailable outside the context of clinical studies, for this AML subset.

Frequent KIT mutations or overexpression of the KIT receptor were described some time ago in CBF-AML. Recent studies have evaluated the potential benefit of dasatinib, a potent KIT inhibitor, in these patients. In a French study, patients with persistent MRD or molecular relapse after intensive consolidations were eligible to receive 12 months maintenance with dasatinib if they were not candidate for HSCT.59 No significant impact of dasatinib on time-to-relapse was seen. Two phase 1-2 trials combined dasatinib with upfront ICT led to a currently ongoing phase 3 trial.60,61

**AML with FLT3 gene mutation**

The FLT3-ITD mutation is one of the most frequent bad-prognosis mutations observed in AML, at least in younger or relapsed patients and has led to the evaluation of multikinase or more specific kinase inhibitors in this AML subset. Lestaurntinib associated with chemotherapy failed to improve outcomes in relapsed/refractory (R/R) FLT3-ITD AML patients or during front-line consolidation in the MRC AML15 trial.62,63 Results should soon be available from a large international phase 3 trial in newly diagnosed FLT3-ITD-positive patients in which midostaurin was compared to placebo in association with 7+3. As mentioned above, to date there is no clear evidence of increased clinically significant activity when sorafenib is added to ICT in FLT3-ITD-positive patients. A phase 2 study of sorafenib combined with ICT in older patients, restricted to those diagnosed with FLT3-mutated AML, is expected to shed light on this issue (NCT01253070). On the other hand, sorafenib delivered after HSCT seems to be particularly effective in FLT3-ITD-positive patients.64 Selection of FLT3-resistant mutants has been a general phenomenon observed in most early trials with first or second-generation inhibitors.65 An overview of novel promising FLT3 inhibitors is presented elsewhere in this Review Series.
**AML with NPM1 gene mutation**

Approximately 30% of CN-AML patients have an NPM1 mutation and in contrast to the frequently associated FLT3-ITD, the NPM1 mutation seems to be an early event in most of these cases. Several trials have reported the effects of adding all-trans retinoic acid (ATRA) to chemotherapy in non-APL AML with conflicting results. In the large MRC trial, no significant effect of the addition of ATRA was observed.\(^6\) On the other hand, two studies from the German AML Study Group reported a benefit of the addition of ATRA restricted to NPM1 mutated AML patients.\(^57,68\) An explanation for these contradictory results is yet to be defined. More recently, preclinical studies of arsenic trioxide (ATO) in NPM1 mutated AML from two groups, strongly suggested that ATO may have a beneficial effect in this subset.\(^69,70\) As extensive clinical experience with ATO has been gained in the therapy of APL, clinical studies are planned to confirm or not a beneficial role of ATO in the treatment of NPM1 mutated patients.

**AML with mutated IDH**

Isocitrate dehydrogenase 1 and 2 gene mutations are present in 10 to 15% of AML patients. As detailed in another article of this Review Series, early phase 1/2 results of specific inhibition of IDH2 and IDH1 mutated enzymes are impressive. A phase 3 study will soon be initiated in relapsing IDH2 mutated patients.

**AML with adverse cytogenetic features**

In this hard-to-treat AML population, improvement of early response rate remains an important clinical endpoint, especially when HSCT can be envisioned in a timely manner. However, results of trials with novel drugs are disappointing. In the PALG cladribine study,\(^28\) the subgroup of patients with unfavorable cytogenetics appeared, nevertheless, to have a greater benefit. Similarly, a combination of cladribine, cytarabine, priming with G-CSF, and mitoxantrone (CLAG–M) was reported to be of benefit compared to 7+3 in a large retrospective single center study which mostly
included high-risk AML patients. Among other non-targeted agents, amonafide combined with cytarabine failed to yield a benefit over 7+3 in a secondary AML study. Early results of new drugs, including the CPX-351 liposomal combination, are discussed elsewhere in this Review Series.

5. Treatment of older AML

Outcome in older patients with AML remains dismal, with lower CR rates and very few long-term survivors compared to younger patients. Treatment for older AML patients is thus an active field of antileukemic drug investigation. Even when short-term benefits have been demonstrated, very few older patients survive beyond two years of follow-up, raising the question of the appropriateness of OS as an efficacy endpoint for drug development in this patient population. Age itself does not, however, define a homogeneous patient population. In older patients, prognosis is governed by patient-related and AML-related factors that are only partly age-related. General health status and presence of organ dysfunctions or comorbidities impact ICT tolerance. As observed in younger patients, cytogenetics can also impact efficacy. One predominant bad-risk characteristic of older AML is the increased frequency of prior myelodysplastic syndromes (MDS), although clonal hematopoiesis characterized by the presence of MDS-related gene mutations has also been associated with aging in healthy individuals.

The most important clinical decision remains to estimate the benefit/risk associated with ICT in the individual older patient. As for the decision to recommend HSCT in first CR, there is no unique decision-guiding score. Older patients with favorable-risk AML according to ELN classification are likely to benefit from a standard treatment. In those unlikely to benefit from ICT, low-dose cytarabine (LDAC) has been considered as a possible standard, based on the non-intensive AML14 MRC trial results, despite the fact that patients with adverse cytogenetics did not draw any benefit from LDAC therapy. In two large international trials, the hypomethylating agents decitabine and azacitidine yielded better mid-term results, with longer median and higher 1-year survival than observed in LDAC arms, even if they did not result in
a higher proportion of long-term survivors.\textsuperscript{78,79} Of interest, azacitidine appeared to offer particular benefit to patients with adverse cytogenetics and/or those with myelodysplasia-related changes.\textsuperscript{79}

Current trials in older AML patients often address the effects of the addition of a new agent to LDAC, azacitidine or decitabine. To date, negative results with tipifarnib, ATO, GO, and vosaroxin in combination with LDAC have been reported by the British group.\textsuperscript{80-83} Single-agent sapacitabine or clofarabine also failed to improve outcomes over LDAC.\textsuperscript{84,85} Addition of quizartinib, ganetespib, tosedostat or selinexor to LDAC is currently under investigation. Interesting phase 2 results have been observed when combining the polo-like kinase inhibitor volasertib with LDAC,\textsuperscript{86} or vosaroxin with decitabine in a single-center evaluation.\textsuperscript{87} Too frequently, the evaluation of the efficacy of the combinations is hindered by their poor tolerance in older patients deemed unfit for standard ICT, raising the issue of their evaluation in fitter patients, potentially against ICT.

6. Treatment of relapsed/refractory AML

Treatment of relapsed AML remains poorly defined. Simple clinical and disease parameters such as age, duration of first remission, cytogenetics, and prior HSCT remain the most useful parameters to evaluate treatment effects at relapse.\textsuperscript{88} In most AML subsets (other than APL) the main clinical objective of salvage therapy is to “bridge” patients to HSCT, either with targeted therapies such as $FLT3$ inhibitors or with ICT, at least in patients fit enough to tolerate it. A very large cohort of relapsed AML patients subjected to salvage therapy after being treated frontline in successive MRC AML trials has recently been described.\textsuperscript{89} Analysis of the long-term outcomes clearly established that allogeneic transplantation, when a second response was obtained, strongly benefited intermediate- and high-risk AML subsets based on initial disease characteristics.

Optimal salvage drug combinations, drug doses and administration schedules remain an open issue. In particular, the benefits of the addition of an anthracycline, or any other drug, to cytarabine, and what cytarabine dose should be recommended
are unclear at best. Recently, two large company-sponsored studies evaluated the combination of clofarabine or vosaroxin to IDAC, with OS as the endpoint in R/R AML patients. In the CLASSIC I trial, addition of clofarabine increased the response rate in patients more than 55 years of age, albeit at the expense of increased toxicity and early mortality, but failed to improve OS despite a higher number of patients bridged to HSCT. In the preliminary results of the largest trial ever performed in R/R patients, the VALOR trial, combination of vosaroxin to IDAC similarly increased the response rate across all ages in both relapsed and refractory patients. Nonetheless, despite the absence of a significant increase in early mortality and a large proportion of younger patients bridged to HSCT, this did not translate into a general OS improvement. A significant, although modest, survival improvement was only observed in older patients aged 60 years or more.

Conclusion

In conclusion, despite some advances in the treatment of adult AML patients, many issues remain to be addressed, as reflected by current recommendations. Given the poor long-term outcome for most adult AML patients, although many novel promising drugs or therapeutic approaches are currently under development for this population, their inclusion into prospective clinical trials should be strongly encouraged. In addition, standardization of trial procedures and control arms would greatly assist comparison of trial results and strengthen future treatment recommendations.
Authorship and COI Disclosures

H.D. and C.G. wrote this review article jointly.

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- Advisory Board: Celgene, Pfizer, Sunesis, Agios Pharmaceuticals

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- Advisory Board: Celgene
References


Abstract 6.


Table 1. Randomized studies of anthracycline dose and type for AML induction therapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Patients (N)</th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>Key conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG (refs 2,6)</td>
<td>17-60y</td>
<td>657</td>
<td>D, 90 mg/m² d1-3 A, 100 mg/m² CIV d1-7 cycle 1 *</td>
<td>D, 45 mg/m² d1-3 A, 100 mg/m² CIV d1-7 cycle 1 *</td>
<td>Higher response rate</td>
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<td>Similar toxicity</td>
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<td>Longer OS</td>
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<td>HOVON-SAKK-AMLSG (ref 3)</td>
<td>60y+</td>
<td>813</td>
<td>D, 90 mg/m² d1-3 A, 200 mg/m² CIV d1-7 cycle 1</td>
<td>D, 45 mg/m² d1-3 A, 200 mg/m² CIV d1-7 cycle 1</td>
<td>Higher response rate</td>
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<td>Similar toxicity</td>
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<td>Similar OS †</td>
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<tr>
<td>Korean Group (ref 4)</td>
<td>15-60y</td>
<td>383</td>
<td>D, 90 mg/m² d1-3 A, 200 mg/m² CIV d1-7 cycle 1 **</td>
<td>D, 45 mg/m² d1-3 A, 200 mg/m² CIV d1-7 cycle 1 **</td>
<td>Higher response rate</td>
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<td>Longer EFS and OS</td>
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<td>NCRI AML17 (ref 5)</td>
<td>16-72y</td>
<td>1,206</td>
<td>D, 90 mg/m² d1/3/5 A, 100 mg/m²/12h d1-10 cycle 1 ***</td>
<td>D, 60 mg/m² d1/3/5 A, 100 mg/m²/12h d1-10 cycle 1 ***</td>
<td>Similar response rate</td>
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<td>Higher early death rate with 90 mg/m²</td>
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<td>Similar EFS and OS</td>
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<td>ALFA-9801 (ref 8)</td>
<td>50-70y</td>
<td>468</td>
<td>I, 12 mg/m² d1-3 or d1-4 A, 200 mg/m² CIV d1-7 cycle 1</td>
<td>D, 80 mg/m² d1-3 A, 200 mg/m² CIV d1-7 cycle 1</td>
<td>Higher response rate in one course</td>
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<td>Similar early death rates</td>
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<td>Similar EFS and OS</td>
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<tr>
<td>JALSG AML201 (ref 9)</td>
<td>15-64y</td>
<td>1,057</td>
<td>I, 12 mg/m² d1-3 A, 100 mg/m² CIV d1-7 cycle 1 ****</td>
<td>I, 12 mg/m² d1-3 A, 100 mg/m² CIV d1-7 cycle 1 ****</td>
<td>Higher response rate</td>
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<td>Higher early death rate with control arm</td>
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<td></td>
<td>Similar RFS and OS</td>
</tr>
</tbody>
</table>

* A second 7+3 DA cycle with 45 mg/m²/d daunorubicin was given to patients with residual marrow blasts on d12/14 of cycle 1; ** A second 5+2 DA cycle with 45 mg/m²/d daunorubicin was given to patients with persistent leukemia after cycle 1; *** in this study, all patients but poor-risk received a second DA course with 50 mg/m²/d daunorubicin; **** A second cycle, identical to the first one, was given to patients with persistent leukemia after cycle 1; † A significant EFS and OS benefit was observed in the subgroup of patients aged 60-65 y.
<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Patients (N)</th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG (ref 10)</td>
<td>15-64y</td>
<td>723</td>
<td>A, 2000 mg/m²/12h d1-6</td>
<td>A, 200 mg/m² CIV d1-7</td>
<td>Similar response rate</td>
</tr>
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<td></td>
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<td>D, 45 mg/m² d7-9 cycle 1</td>
<td>D, 45 mg/m² d5-7 cycle 1</td>
<td>Higher early death rate</td>
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<td>Longer RFS in patients aged &lt;50y</td>
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<td>Similar OS</td>
</tr>
<tr>
<td>ALSG (ref 11)</td>
<td>15-60y</td>
<td>301</td>
<td>A, 3000 mg/m²/12h d1/3/5/7</td>
<td>A, 100 mg/m² CIV d1-7</td>
<td>Higher response rate in one course</td>
</tr>
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<td></td>
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<td>D, 50 mg/m² d5-7 E, 75 mg/m² d1-7 cycle 1 **</td>
<td>D, 50 mg/m² d5-7 E, 75 mg/m² d1-7 cycle 1 **</td>
<td>Non significantly higher early death rate</td>
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<td>Longer RFS</td>
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<td>Similar OS</td>
</tr>
<tr>
<td>HOVON-SAKK (ref 12)</td>
<td>18-60y</td>
<td>860</td>
<td>A, 1000 mg/m²/12h d1-5</td>
<td>A, 200 mg/m² CIV d1-7</td>
<td>Similar response rate</td>
</tr>
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<td></td>
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<td></td>
<td>I, 12 mg/m² d5-7 cycle 1</td>
<td>I, 12 mg/m² d5-7 cycle 1</td>
<td>Similar EFS and OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A, 2000 mg/m²/12h d1/2/4/6</td>
<td>A, 2000 mg/m²/12h d1/2/4/6</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Am, 120 mg/m² d3/5/7 cycle 2 ***</td>
<td>Am, 120 mg/m² d3/5/7 cycle 2 ***</td>
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</tr>
<tr>
<td>EORTC-GIMEMA AML12 (ref 13)</td>
<td>15-60y</td>
<td>1,942</td>
<td>A, 3000 mg/m²/12h d1/3/5/7</td>
<td>A, 100 mg/m² CIV d1-10</td>
<td>Higher response rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D, 50 mg/m² d1/3/5 E, 50 mg/m² d1-5 cycle 1 ****</td>
<td>D, 50 mg/m² d1/3/5 E, 50 mg/m² d1-5 cycle 1 ****</td>
<td>Similar early death rate</td>
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<tr>
<td></td>
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<td></td>
<td>Longer RFS and OS in patients aged ≤45y</td>
</tr>
</tbody>
</table>

D: daunorubicin; A: cytarabine; E: etoposide; I: idarubicin; Am: amsacrine; CIV, continuous IV infusion; RFS, relapse-free survival; OS, overall survival.

† During the first 2 years of the study, cytarabine was given at 3000 mg/m² bolus to patients aged <50y, then reduced to 2000 mg/m² bolus due to excessive neurologic toxicity; * In both arms a second cycle, identical to the first one, was given to patients with persistent leukemia after cycle 1, all CR patients from the control arm were then randomized to either standard-dose cytarabine or HiDAC during consolidation, while all CR patients from the experimental arm received HiDAC during consolidation; ** A second, then a third cycle, identical to the first one, was given to patients with persistent leukemia after cycle 1 or 1-2, respectively; *** After cycle 2, CR patients received either allogeneic or autologous HSCT or a third chemotherapy cycle for consolidation; **** In both arms a second cycle, identical to the first one, was given to patients with persistent leukemia after cycle 1, then all CR patients received one IDAC containing consolidation course followed by allogeneic or autologous HSCT.
Table 3. Randomized trials of gemtuzumab ozogamicin (GO) associated with intensive chemotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment phase (age range)</th>
<th>Patients (N)</th>
<th>GO dose and schedule</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG S0106 (ref 19)</td>
<td>Induction (18-60y)</td>
<td>637</td>
<td>GO, 6 mg/m² d4 cycle 1 *</td>
<td>Similar response rate Higher early death rate Similar RFS Similar OS</td>
</tr>
<tr>
<td>NCRI AML15 (ref 20)</td>
<td>Induction (18-60y)</td>
<td>1,113</td>
<td>GO, 3 mg/m² d1 cycle 1 d1 cycle 3 **</td>
<td>Similar response rate Similar RFS and OS Longer OS in favourable AML</td>
</tr>
<tr>
<td>NCRI AML16 (ref 21)</td>
<td>Induction (60y+)</td>
<td>1,115</td>
<td>GO, 3 mg/m² d1 cycle 1</td>
<td>Similar response rate Longer RFS, OS from CR and OS</td>
</tr>
<tr>
<td>ALFA-0701 (ref 22)</td>
<td>Induction Consolidation (50-70y)</td>
<td>278</td>
<td>GO, 3 mg/m² d1/4/7 cycle 1 d1 conso 1 d1 conso 2</td>
<td>Similar response rate Longer EFS, RFS and OS</td>
</tr>
<tr>
<td>GOELAMS 2006 (ref 23)</td>
<td>Induction (18-60y)</td>
<td>254</td>
<td>GO, 6 mg/m² d4 cycle 1 d4 conso 1</td>
<td>Similar response rate Similar EFS and OS Longer EFS in non allo-HSCT patients</td>
</tr>
<tr>
<td>NCRI AML17 (ref 24)</td>
<td>Induction (0-81y)</td>
<td>788</td>
<td>GO, 3 vs 6 mg/m² d1 cycle 1</td>
<td>Similar responses rate Lower early death rate with 3 mg/m² Similar RFS and OS</td>
</tr>
<tr>
<td>EORTC-GIMEMA AML-17 (ref 26)</td>
<td>Prior to induction (61-75y)</td>
<td>472</td>
<td>GO, 6 mg/m² d1/15 prior to cycle 1</td>
<td>Similar response rate Higher early death rate Similar RFS Similar EFS and OS</td>
</tr>
<tr>
<td>HOVON-SAKK-AMLSG (ref 27)</td>
<td>Maintenance (60y+)</td>
<td>232</td>
<td>GO, 6 mg/m² 3 monthly cycles</td>
<td>Similar relapse incidence Similar RFS and OS</td>
</tr>
<tr>
<td>SWOG S0106</td>
<td>Maintenance (18-60y)</td>
<td>174</td>
<td>GO, 5 mg/m²</td>
<td>Similar RFS</td>
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<tr>
<td></td>
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<td>3 monthly cycles</td>
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</tbody>
</table>

EFS, event-free survival; RFS, relapse-free survival; OS, overall survival

* Daunorubicin dose was reduced from 60 mg/m²/d in the control arm to 45 mg/m²/d in the GO arm; ** Additional randomization for GO during cycle 3, irrespective of cycle 1 GO treatment.
### Table 4. Randomized trials of purine analogs associated to intensive chemotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Analogue</th>
<th>Treatment phase (age range)</th>
<th>Patients (N)</th>
<th>Treatment modalities</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALG [ref 28]</td>
<td>Cladribine or</td>
<td>Induction (16-60y)</td>
<td>652</td>
<td>DAC vs DAF vs DA cycle 1</td>
<td>DAC: Higher response rate, similar RFS, longer OS *</td>
</tr>
<tr>
<td></td>
<td>Fludarabine</td>
<td></td>
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<td>DAF: Similar response rate, similar RFS and OS **</td>
</tr>
<tr>
<td>NCRI AML16 [ref 31]</td>
<td>Clofarabine</td>
<td>Induction (60y+)</td>
<td>806</td>
<td>DA vs DClo cycle 1-2</td>
<td>Similar response rate ***</td>
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<td></td>
<td>Similar RFS and OS</td>
</tr>
<tr>
<td>NCRI AML15 [ref 33]</td>
<td>Fludarabine</td>
<td>Induction (0-73y)</td>
<td>3,106</td>
<td>DA vs ADE vs FLAG-Ida cycle 1-2</td>
<td>ADE: similar response rate, RFS and OS</td>
</tr>
<tr>
<td></td>
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<td>FLAG-Ida: Similar response rate ****, higher rate of death in CR, longer RFS,</td>
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<td>similar OS</td>
</tr>
<tr>
<td>ALFA-0702 [ref 39]</td>
<td>Clofarabine</td>
<td>Post-remission (18-60y)</td>
<td>221</td>
<td>CLARA vs HiDAC consolidation cycle 1-3</td>
<td>Longer RFS in non allo-HSCT patients</td>
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<td>Similar OS</td>
</tr>
<tr>
<td>CLASSIC I [ref 11]</td>
<td>Clofarabine</td>
<td>First salvage (55y+)</td>
<td>320</td>
<td>CLARA vs IDAC up to 3 cycles</td>
<td>Higher response rate</td>
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<td>Higher early death rate</td>
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<td>Longer EFS</td>
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<td>Similar OS</td>
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</tbody>
</table>

DA: daunorubicin + cytarabine; DAC: DA + cladribine; DAF: DA + fludarabine; ADE: DA + etoposide; IDAC: intermediate-dose cytarabine; CLARA: clofarabine + IDAC; DClo: daunorubicin + clofarabine; FLAG-Ida: fludarabine + IDAC + G-CSF + idarubicin; HiDAC: high-dose cytarabine; HSCT: hematopoietic stem cell transplantation. * longer OS in patients aged 50y+, those with initial leucocyte count >50x10^9/L, and those with unfavorable cytogenetics; ** longer OS in patients with unfavorable cytogenetics; *** Less CR in one course after DClo; **** More CR in one course after FLAG-Ida.
An update of current treatments for adult acute myeloid leukemia

Hervé Dombret and Claude Gardin

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