Clinical management of primary non-acute promyelocytic leukemia acute myeloid leukemia: practice Guidelines by the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

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ABSTRACT

As many options are now available to treat patients with *de novo* acute myeloid leukemia, the Italian Society of Hematology and two affiliated societies (SIES and GITMO) commissioned a project to an Expert Panel aimed at developing clinical practice guidelines for acute myeloid leukemia treatment. After a systematic comprehensive literature review, the Expert Panel formulated recommendations for the management of primary acute myeloid leukemia (with the exception of acute promyelocytic leukemia) and graded them according to the supporting evidence. When evidence was lacking, consensus-based statements have been added. First-line therapy for all newly diagnosed patients eligible for intensive treatment should include one cycle of induction with standard dose cytarabine and an anthracycline. After achieving complete remission, patients aged less than 60 years should receive consolidation therapy including high-dose cytarabine. Myeloablative allogeneic stem cell transplantation from an HLA-compatible sibling should be performed in first complete remission: 1) in children with intermediate-high risk cytogenetics or who achieved first complete remission after the second course of therapy; 2) in adults less than 40 years with an intermediate-risk; in those aged less than 55 years with either high-risk cytogenetics or who achieved first complete remission after the second course of therapy. Stem cell transplantation from an unrelated donor is recommended to be performed in first complete remission in adults 30 years old or younger, and in children with very high-risk disease lacking a sibling donor. Alternative donor stem cell transplantation is an option in high-risk patients without a matched donor who urgently need transplantation. Patients aged less than 60 years, who either are not candidate for allogeneic stem cell transplantation or lack a donor, are candidates for autologous stem cell transplantation. We describe the results of a systematic literature review and an explicit approach to consensus techniques, which resulted in recommendations for the management of primary non-APL acute myeloid leukemia.

Key words: acute myeloid leukemia, clinical practice guidelines, stem cell transplantation.

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Introduction

The management of acute myeloid leukemia (AML), whose overall incidence is about 3-4/100,000 per year,[1] with more than half of the cases occurring in patients aged 60 years or older, still represents a challenge to hematologists.[2] Treatment options range from supportive care to intensive programs of chemotherapy, including autologous and allogeneic stem cell transplantation (SCT). Despite significant advances in the management of treatment-related complications, the high

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incidence of relapse and ineligibility of many elderly patients for intensive chemotherapy programs have so far meant low probability of both disease-free survival (DFS) and overall survival (OS).[1] In this article, recommendations for the therapy of *de novo* AML, with the exception of acute promyelocytic leukemia (APL) which requires very specific therapeutic approaches, are presented. The guidelines are intended to support the clinical practice of hematologists, oncologists and internists who care for leukemia patients.

Design and Methods

Organization and design

The methodology used for developing SIE guidelines has been extensively reported elsewhere.[3] The working group was composed of eight senior hematologists and two literature reviewers. Pubmed and the Cochrane Library were searched for relevant publications since 1995. Major hematology, oncology and general medicine journals (Blood, Journal of Clinical Oncology, British Journal of Haematology, Bone Marrow Transplantation, Haematologica, Lancet, Leukemia, New England Journal of Medicine) were scanned for publications since 1995. Proceedings of international hematology meetings held since 2005 were also scanned. The list of papers was updated in January 2008. Full papers were assigned an evidence level, according to the Scottish Intercollegiate Guideline Network.[4] Based on the reviewed literature, the members of the Expert Panel formulated some evidence-based recommendations; expertise-based recommendations were added when relevant areas could not be addressed by the available evidence, but indirect evidence could support a statement. A first round of consensus for the proposed recommendations was obtained through paper questionnaires, according to the Delphi Panel technique. The full body of recommendations was definitively approved during a meeting held in Bologna on March 10th, 2008. The guidelines were reported according to the COGS checklist by the Conference on Guideline Standardization. The present guidelines are expected to be updated in 2012.

Definitions

The present guidelines apply to patients with *de novo* AML, according to WHO classification, which updated and modified the FAB diagnostic criteria.[5,6] Thereafter, the guidelines do not apply to patients with AML secondary to myelodysplastic syndrome or chronic myeloproliferative disorders, previous exposure to radiation therapy or alkylating agents or topoisomerase II inhibitors. Standard definitions for response were adopted[7] (Table 1).

Table 1. Response criteria in acute myeloid leukemia.

Response criterion	Neutrophils (μL)	Platelets (μL)	Bone marrow blasts (%)	Other
Early treatment assessment	NA	NA	<5	
Morphological leukemia-free state	NA	NA	<5	Flow-cytometry, no EMD
Morphological CR	>1,000	>100,000	<5	Transfusion independent, no EMD
Cytogenetic CR	>1,000	>100,000	<5	Cytogenetics normal, no EMD
Molecular CR	>1,000	>100,000	<5	Molecular negative, no EMD
Partial remission	>1,000	>100,000	decrease to 5-25	Blasts<5% if Auer rod positive

EMD: extramedullary disease; CR: complete remission (adapted from: Cheson et al.[7])

Guidelines

Pre-treatment evaluations

Bone marrow (BM) evaluation of an AML patient provides important prognostic information and identification of specific blast markers for disease monitoring.[7] There is no consensus yet about the panel to be employed for flow cytometry characterization of myeloid blasts.[8,9] Cytogenetics is, together with age and white blood cell count, one of the most important prognostic factors to stratify patients into groups at standard, intermediate and high risk of relapse (Table 2).[10-14] Conventional cytogenetic analysis is not always informative, especially in cases of cryptic translocations leading to *AML1/ETO*, *CBFB/MYH11* and *MLL* fusion transcript. In cases of normal or failed cytogenetics, fluorescence *in situ* hybridization (FISH) for *MLL* fusion transcript and PCR analysis for *AML1/ETO* and *CBFB/MYH11* are recommended. FISH for monosomy 7 detection is also recommended in pediatric patients, due to the prognostic value of this aberration.[15] It has recently been shown that the presence of FLT3 mutations, especially in the form of internal tandem duplication (ITD), correlates with a high risk of relapse.[16-20] Conversely, mutation of nucleophosmin (NPM1) in the absence of FLT3 ITD[21] identifies a favorable risk subgroup of patients with normal standard cytogenetics.[20-24] Finally, mutations of *CEBPA* and abnormal expression of *BAALC* or *MN1* genes confer favorable and adverse prognostic relevance respectively, and should be investigated.[25] Within the group of patients with core binding factor (CBF) leukemia, a c-kit mutation identifies a subgroup at high risk of relapse.[26,27] The availability of these new prognostic markers allows a more refined stratification of patients according to risk and may translate in a more rational treatment of AML patients.

Trephine BM biopsy, although required by WHO classification, is not routinely performed; it may be useful in cases of unsuccessful marrow aspiration, especially in patients with M7 AML, and to identify NPM mutated AML.[28] The clinical assessment should include echocardiography and evaluation of co-morbidities or active infections that could preclude or postpone the start of intensive therapy.

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Recommendations

An effort should be made to enrol all patients with primary AML into clinical trials.

Besides the diagnostic assays, all patients with primary (non-APL) AML should comply with the following requirements before starting treatment:

- *flow cytometry characterization of immunophenotype of bone marrow blasts;*
- *standard cytogenetics on bone marrow cells;*
- *molecular analysis for established prognostic subgroups (see Table 2 on Cytogenetic-Molecular Risk). Detection of AML1/ETO and CBFB/MYH11 anomalies is a minimum requirement;*
- *storing of bone marrow cells;*

In specific patient subgroups, additional assessments should also be performed:

- *patients who show core binding factor anomalies, (i.e. t(8;21) or inv(16)) should also be investigated for c-kit mutational analysis;*
- *metaphase FISH (preferentially on bone marrow blasts) for MLL gene translocations and mutational analysis for FLT3, NPM1, CEBPA are strongly recommended in cases with normal or failed cytogenetics;*
- *FISH for established aberrations is reserved for cases in which both cytogenetics and molecular analysis were not informative. FISH for CALM/AF10 should be done in cases with 11q rearrangements MLL-negative;*
- *in pediatric patients FISH for monosomy 7 is also useful.*

HLA typing (high-resolution molecular typing of classes I and II) of the patient and, when available, of his/her siblings should be performed at diagnosis for patients aged less than 55 years, free of severe comorbidities and not affected by Down's syndrome.

Induction therapy

The combination of cytarabine and an anthracycline is the standard induction chemotherapy for AML. The conventional two-drug regimen of daunorubicin plus cytarabine has been reported to result in a CR rate of approximately 65%.[29-34] A comparison between anthracyclines given in association with cytarabine was investigated by different groups. Idarubicin appeared to be more effective than daunorubicin, though the doses of idarubicin and daunorubicin may not have been equivalent.[29-33] A meta-analysis of randomized trials comparing idarubicin (usually at the dosage of 10-12 mg/m^2/day for three days) and daunorubicin (45-60 mg/m^2) showed that the use of idarubicin in association with cytarabine resulted in a higher CR rate, but provided only a slight survival benefit, that disappeared after longer follow-up.[34] No significant difference between daunorubicin and mitoxantrone has been reported.[35]

A multicenter randomized trial (EORTC/GIMEMA AML10) of 2,157 patients reported a significantly shorter DFS after CR in patients receiving daunorubicin instead of mitoxantrone or idarubicin for induction and consolidation therapy; however, this study was only reported in abstract form.[36]

Some trials explored the potential advantage of adding a third drug, i.e. thioguanine, to the classical two-drug induction therapy, though little evidence is available to conclude that a three-drug regimen is a better therapy.[37,38]

Table 2. Cytogenetic- molecular risk in acute myeloid leukemia.

Risk	Pattern
High	Complex karyotype
	-7/7q-;-5/5q-
	t(11q21-23)/MLL; MLL ampl; CALM/AF10
	inv(3)/t(3;3)
	t(6;9)
	t(9;22)
	t(8;16); inv(8)
	t(3;5)
	normal karyotype: FLT3$^+$
Intermediate	+8 (isolated)
	t(9;11)
	Normal karyotype
Low	inv(16)/t(16;16); CBFB/MYH11
	*t(8;21); AML1/ETO
	Normal karyotype: NPM$^+$,FLT3$^-$
	Normal karyotype: CEBPA$^+$

**Core Binding Factors Leukemia, in the absence of KIT mutations.*

One study suggested that the addition of etoposide during induction therapy may improve response duration.[39] Induction therapy including fludarabine and cytarabine proved to be safe and feasible in elderly patients, but it did not improve outcome in comparison to the classical two-drug induction treatment.[40-42]

The role of high-dose cytarabine in induction therapy is controversial. Some randomized trials showed prolongation of DFS, especially in younger patients,[43,44] while other trials did not confirm any clinical advantage[45,46] with a higher toxicity and treatment-related mortality than conventionally dosed cytarabine-based induction chemotherapy.

As far as the number of induction courses is concerned, it is difficult to support the recommendation of two induction courses through the standard evidence system, because no recent trial has been conducted to formally demonstrate an advantage in terms of relapse-free and/or overall survival. However, it has been shown that the lack of achievement of an *early response*, defined as the clearance of blasts to a percentage lower than 10-15% in bone marrow at day +14-16 (a condition known as *persistent leukemia*) has an important prognostic value.[47] Some authors recommend that patients with persistent leukemia at early assessment should be given a second course of induction therapy. In cases of a two-course induction strategy, a cycle including mitoxantrone and intermediate or high dose cytarabine (HAM) should be considered.[47]

Due to on the one hand their increased risk of developing treatment-related complications, including cardiac toxicity, and on the other hand to their favorable response to cytotoxic treatment, children with Down's syndrome are eligible for specific protocols of induction therapy with reduced toxicity.[48] In patients with Fanconi anemia, induction therapy is usually complicated by severe extra-medullary toxicity and prolonged period of aplasia, attributable to the impairment of the hematopoietic reservoir.[49]

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An important challenge is represented by the treatment of elderly patients: front-line palliative care, without giving remission-induction chemotherapy, is associated with significantly reduced survival in patients older than 65 years, with no favorable impact on the number of days of hospitalization.[50] Some authors recommend stratifying older patients, assigning to investigational treatments those with comorbidities or a poor prognosis due to unfavorable cytogenetics, and assigning the others to standard chemotherapy.[51]

A high white cell count (greater than 100×10^9/L) at diagnosis is generally regarded as a poor prognostic factor for early death. There are no randomized studies showing an advantage of leukapheresis. However, this procedure is generally safe and may be considered in patients with AML presenting with a high white cell count.[52]

Empirical broad spectrum antimicrobial therapy is mandatory for febrile patients who are profoundly neutropenic.[53] Prophylactic oral antibiotics may be appropriate in patients with expected prolonged, profound granulocytopenia (lower than 100/mm^3 for two weeks). Fluoroquinolones have been shown to decrease the incidence of gram-negative infection and time to first fever in randomized trials.[54] Serial surveillance cultures may be helpful in such patients to detect the presence or acquisition of resistant organisms. As far as platelet transfusions are concerned, available evidence suggests that all patients with platelet counts lower or equal than 10×10^9/L must be given platelet transfusions. In those with a platelet count between 10 and 20×10^9/L, platelet transfusions should be administered in cases of fever and/or infection, while above 20×10^9/L the only indication for platelet transfusion is represented by clinically relevant hemorrhage.[55]

Placebo-controlled randomized studies evaluated post-induction chemotherapy administration of prophylactic myeloid growth factors, including granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) in adult patients with *de novo* AML[56-61] and found no significant differences in primary outcomes, despite a significant reduction in the number of days with neutropenia and/or fever, hospitalization and/or antibiotic/antifungal therapy. G-CSF priming showed a significant increase in CR rate only in the GIMEMA study,[56] while an improvement in DFS and OS was reported in another multicenter randomized trial[62] in standard risk patients aged 18-60 years.

Recommendations

Newly diagnosed patients with primary (non-APL) AML should receive, as soon as possible, one cycle of "standard induction therapy" including cytarabine (100-200 mg/m^2/day), administered by continuous seven day-long intravenous infusion and one of the following agents, administered for three days: daunorubicin (45-60 mg/m^2/day), idarubicin (10 mg/m^2/day), mitoxantrone (10 mg/m^2/day) [grade A]. Induction therapy including high-doses of cytarabine cannot be recommended for any specific subgroup of patients [grade B].

"Standard induction therapy" is not recommended for children with Down's syndrome or Fanconi anemia developing AML, due to the high risk of life-threatening complications, and for adults who show at least one of the following characteristics: a) advanced age (older than 80 years), b) severe comorbidity, c) poor and not potentially reversible performance status. These latter patients should rather receive the best supportive therapy, cytoreductive therapy (attenuated doses and/or oral administration) and/or experimental therapies with significantly lower non-hematologic toxicities [grade D]. Due to the very poor long-term prognosis, patients with high risk cytogenetics (Table 2) and aged over 65 years who therefore cannot receive allogeneic SCT, are recommended not to receive "standard induction therapy": they should rather receive experimental therapies with limited non-hematologic toxicities, cytoreductive agents and the best supportive therapy [grade C].

"Standard induction therapy" can be temporarily delayed in patients with documented active infection or a potentially reversible decline in performance status. Anti-infective and/or cytoreductive agents should be administered in the meanwhile [grade D]. Leukapheresis can be considered in patients with hyperleukocytosis (>100×10^9/L) [grade C]. Leukapheresis should be performed before starting any induction therapy in children with a leukocyte count above 200×10^9/L, especially when associated with life-threatening, either disseminated intravascular coagulation or tissue lysis syndrome [grade D].

An early bone marrow morphological and immunophenotypic evaluation on day 14-16 after the start of "standard induction therapy" can be performed within a clinical trial [grade D]. Patients with persistent leukemia at early evaluation should receive a further cycle of induction therapy as soon as possible when clinically eligible [grade D]. Assessment of response (Table 1) to induction therapy is recommended to be performed at the time of hematopoietic recovery and no later than day 30 after the start of the cycle of induction therapy [grade D]. In the context of clinical trials, immunophenotypic, cytogenetic (karyotype and/or FISH) and molecular evaluation is recommended to be performed along with morphological evaluation for the assessment of response [grade D].

After the first induction course, all children who achieve a complete or partial response and the adults who achieve a partial response should receive a second induction course [grade B]. Response should be re-evaluated also after the second induction course [grade D].

The use of myeloid growth factors during induction therapy to induce sensitization of leukemic cells to chemotherapy (priming effect) can be considered although it cannot be routinely recommended [grade A]. G-CSF administration after induction therapy is recommended, especially in elderly patients and in patients with post-chemotherapy febrile neutropenia, in order to reduce the duration of neutropenia and the related complications [grade B]. The scheduling of G-CSF should adhere to local protocols.

Consolidation chemotherapy

A single induction course is virtually always followed by a 100% relapse rate;[63] therefore, post-remission therapy is routinely used in patients with AML. Usually, consolidation chemotherapy associates cytarabine at different dosages with other drugs; however, there is no clear advantage in the use of one regimen compared to others and of combination therapy compared to high-dose cytarabine alone.[64,65]

The effect of cytarabine dose intensity has been inves-

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tigated: large randomized clinical trials have shown better results with high-dose cytarabine in comparison with standard or intermediate doses. The advantage associated with more intensive doses of cytarabine (3 g/m^2×6 doses) was found to be particularly significant for patients who had not previously received high-dose cytarabine and for those with low cytogenetic risk: in such patients, consolidation with high-dose cytarabine was associated with an outcome similar to that obtained treating patients with an autograft.[66-68] Conversely, higher-dose therapy had no benefit in the post-remission management of elderly patients (aged 60 years or older) with *de novo* AML, since the clinical benefit was jeopardized by toxicity.[66] AML in Down's syndrome patients is extremely sensitive to chemotherapy consolidation therapies, especially those including high-dose Ara-C.[69]

The optimal number of consolidation courses has been specifically investigated: for patients who are not candidates for transplantation, the duration of post-remission consolidation therapy should not exceed 3-4 cycles.[66] Patients eligible for either autologous or allogeneic transplant, should receive a shorter consolidation, e.g. 1-2 cycles with high-dose chemotherapy. This is also useful for peripheral blood stem cell mobilization in patients who are candidates for autologous transplantation and is often used as a bridge to allogeneic transplantation.[70]

All patients with a given marker identified at diagnosis should be monitored for persistence of Minimal Residual Disease (MRD) after consolidation and before proceeding to the subsequent planned treatment. The approach to patients with documented persistence of MRD has not yet been standardized, so that the level of evidence is still low.

The role of post-consolidation maintenance therapy has not been clearly defined: in pediatric patients it has been employed by the German group[71] without clear evidence of an advantage in terms of leukemia-free survival. Furthermore, in children, maintenance therapy may induce chemotherapy resistance and reduce response to salvage therapy in patients who experience leukemia relapse.[72]

A favorable effect on DFS has been observed with several schedules of maintenance chemotherapy for adult and elderly patients not submitted to SCT, even if there is not enough evidence to support such a recommendation.[46,73,74] More recently, in a multicenter randomized trial, an improvement in DFS and OS was demonstrated with maintenance in elderly patients in first complete remission after intensive induction chemotherapy.[75]

Recommendations

Patients in first complete remission should receive a consolidation treatment, as soon as the hematologic recovery from induction therapy has occurred [grade B].

Children are candidates for post-remissional, consolidation therapy either alone or associated (in cases of intermediate/high risk cytogenetics) with SCT. Patients with Down's syndrome have a particularly favorable response to consolidation therapy including high-dose Ara-C [grade D].

Adult patients aged under 60 years should receive post-remission consolidation chemotherapy based on high-dose cytosine arabinoside (3 g/m^2×6 doses); the number of cycles should not exceed 3-4 [grade A].

Potential candidates for allogeneic SCT should receive a shorter intensive consolidation including intermediate/high dose cytosine arabinoside in order to spare undue toxicity [grade D]. Potential candidates for autologous SCT should receive at least one intensive consolidation cycle including intermediate/high dose cytosine arabinoside before collecting stem cells and performing autograft [grade D].

Elderly patients (over 60 years) should not receive high-dose cytosine arabinoside-based consolidation therapy and no more than 2 consolidation cycles [grade C].

G-CSF administration is recommended after consolidation chemotherapy in order to reduce the duration of neutropenia and the related complications [grade C].

All patients with cytogenetic and/or molecular markers identified at diagnosis should be monitored for persistence of MRD after consolidation therapy has been completed and before proceeding to the subsequent planned treatment [grade D].

For patients who are not candidates to SCT, maintenance chemotherapy cannot be recommended [grade D].

Allogeneic stem cell transplantation

Allogeneic transplantation from an HLA matched sibling donor has been used for more than two decades and continues to be considered an optimal approach for prevention of relapse after remission, due to the graft-versus-leukemia effect. However, given the still significant acute transplant-related mortality (TRM) and long-term sequelae, its use remains an object of debate and ongoing investigation. Clinical trials comparing allogeneic SCT with other post-remissional therapies have produced inconsistent results.

After careful assessment of risks and benefits, intermediate and high risk patients (considering WBC counts, cytogenetics, and time to achieve remission as risk factors) are considered suitable candidates for allogeneic SCT from an HLA identical sibling.[76,77] However, data derived from a literature review show a complex and variable scenario. Two metanalyses of randomized trials[78,79] exploring treatment options for adult and pediatric AML patients in first CR, and employing both natural randomization based on donor availability and intention-to-treat analysis, showed a significant improvement in DFS and OS (hazard ratio 1.4) with allogeneic SCT from an HLA-identical sibling donor. The improvement was, however, limited to adult patients with high risk cytogenetics and to pediatric patients in the high- and intermediate-risk groups.[78-80] A subsequent large naturally randomized trial demonstrated a significantly lower incidence of relapse and better DFS in patients belonging to the intermediate- and poor-risk cytogenetic group receiving allogeneic SCT; the benefit was even greater in patients under 40 years of age.[81]

Other risk factors can identify categories of patients who benefit from allogeneic transplantation, such as those with late achievement of CR.[70] The effect of allogeneic SCT in other risk classes, defined by new genetic risk factors, has been retrospectively investigated: so

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far, there is no strong evidence that FLT3 status (the most common genetic mutation identified) should be considered an indicator for transplantation.[82] Prospective randomized clinical trials with subgroup analysis for *FLT3* mutation, as for other genetic risk factors, are warranted to address this question. Notwithstanding, there are convincing data suggesting that the subgroup of patients with intermediate cytogenetics and mutant *NPM1* without *FLT3-ITD* mutations have more favorable prognosis and, therefore, allogeneic SCT is not a rational procedure for such patients.[25]

In the absence of an HLA-identical family donor, it seems reasonable to offer allogeneic SCT from a matched unrelated donor (MUD) to patients with poor-risk disease, either for biological features or for late achievement of CR.[76] With the use of MUD transplantation, a long-term OS comparable to that obtained with a sibling donor, and far exceeding that observed with autotransplant, has been observed by some authors in this high-risk cohort.[83] However, the evidence supporting an advantage with MUD-SCT in high-risk patients without a sibling donor is weak.[84] T-cell depleted allogeneic SCT from an HLA-haplotype mismatched relative emerges as a viable, alternative option for AML patients without matched donors and/or those who urgently need transplantation, especially when the donor shows alloreactivity of natural killer cells towards the recipient.[85]

Cord blood from an unrelated donor represents a further alternative source of stem cells for pediatric and adult AML patients without matched donors and/or those who urgently need transplantation.[86,87] Promising results in terms of reduction of TRM have been reported in adults given two different cord blood units.[88] Moreover, it has been reported that even 2 HLA disparities between donor and recipient can be tolerated for cord blood transplant.[89] Alternative donor SCT should be performed in centers with an active program in the field, since the procedure requires special expertise.

The choice of the stem cell source to be used cannot be based on the results of prospective comparative studies, which are lacking. Retrospective analyses did not show a survival advantage for either peripheral blood or bone marrow derived progenitor cells[90] except in patients receiving a high dose of bone marrow stem cells.[91]

The introduction of reduced intensity conditioning (RIC) regimens has enabled the use of allogeneic transplantation in the elderly. Evidence for an advantage with RIC SCT in patients over 50 years with intermediate-high risk disease in first CR is weak: it relies on retrospective analyses, without genetic randomization and within cohorts with a short follow-up.[92-94] Data show that in patients over 50 years, there was no statistical difference in DFS and OS after RIC transplant, compared with myeloablative SCT, irrespective of disease status. In multivariate analysis, the advantage in terms of significantly lower acute GVHD and TRM was offset by a higher relapse rate, 3-year DFS and OS being similar. In patients over 50 years receiving a low dose total body irradiation-based RIC regimen, a comparison between related and unrelated SCT showed no statistical difference in 2-year OS.[95]

Recommendations

Myeloablative allogeneic SCT from a fully matched sibling donor is recommended to be performed in first complete remission for all children with intermediate-high risk cytogenetics and for adults with high-risk cytogenetics (Table 2), provided that they are aged under 55 years and do not carry severe comorbidities [grade A]. Myeloablative allogeneic SCT from a fully matched sibling donor is recommended to be performed in first complete remission also for adult patients with intermediate-risk cytogenetics with the exception of NPM1 mutant and FLT3-ITD negative cases, provided that they are aged under 40 years and do not carry severe comorbidities [grade C]. Myeloablative allogeneic SCT from a fully matched sibling donor is recommended to be performed for patients who achieved a first complete remission only after having received a second course of induction therapy, irrespectively of their cytogenetic risk, provided that they are aged under 55 years and do not carry severe comorbidities [grade D].

No source of allogeneic stem cells (peripheral blood or bone marrow) can be recommended to be preferred for myeloablative allogeneic SCT [grade D].

If no fully matched sibling donor is available, it is recommended to consider allogeneic SCT from an unrelated donor for all adult patients in first complete remission aged under 30 years with high-risk cytogenetics, or who achieved first complete remission only after a second course of induction therapy [grade D]. Myeloablative allogeneic SCT from an unrelated donor is not recommended in patients older than 50 years who achieved complete remission after induction therapy [grade D]. Children with M7 AML, a complex karyotype, monosomy of chromosome 7, or high levels of MRD measured by flow cytometry after consolidation therapy are eligible for SCT from an unrelated volunteer [grade D].

Alternative donor (i.e. mismatched-related, cord blood) SCT should be performed only by centers with an active program in the field, in high cytogenetic risk AML adult patients without a matched (related or unrelated) donor and/or who urgently need transplantation [grade D].

Alternative stem cell donors should also be considered for all the children who are candidates for transplantation from an unrelated donor, but who lack such a matched donor or urgently need the allograft [grade D].

Allogeneic SCT with a RIC regimen should be considered in high-risk patients aged over 55 years or with severe comorbidities [grade D].

Autologous stem cell transplantation

Although data about the superiority of autologous SCT in first CR over *conventional* consolidation chemotherapy are controversial, both in the adult and pediatric population, the decrease in toxicity has made autologous SCT a feasible option for younger patients (and for 20% of elderly ones) who lack an HLA matched donor. A 45% 5-year OS rate in high-risk (with 31% DFS) and 64% in good-risk patients have been observed in a large cohort of patients with a median follow-up of 9.5 years after autologous SCT.[96] In other trials, a significant reduction in the incidence of relapse has been observed in good- and intermediate-risk patients.[97] Conversely, in 2 meta-analyses of 6 controlled trials conducted up to 1996 involving adult patients, autologous SCT was shown to improve event-free survival by about 25%,

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without any effect on OS, compared with standard dose consolidation.[98,99] Subsequently published randomized trials confirmed these results.[67,100] Nonetheless, retrospective analyses comparing autologous SCT to MUD transplant in patients in first CR lacking an HLA identical family donor showed an advantage with the use of autologous SCT.[101] The decrease in toxicity has made autologous SCT a feasible option also in 20% of elderly patients: comorbidity, extreme age, or poor mobilization are the main reasons for not performing autologous SCT.[102] A meta-analysis of a pediatric population[79] failed to demonstrate a survival benefit for autologous SCT in comparison to conventional post-remissional chemotherapy.

In detail, 2 randomized trials showed a significant reduction in relapse in children given autologous SCT, which did not translate into an advantage in terms of survival due to an increased mortality (POG 8891)[103] or to a higher chance of being rescued by a second line treatment for patients given chemotherapy as consolidation treatment (MRC AML10).[104] A more recent randomized study comparing conventional post-remissional chemotherapy and autologous SCT showed a comparable relapse incidence.[105]

Stem cell harvest is usually performed after the last consolidation chemotherapy cycle. Different non-randomized trials provided compelling evidence in favor of a reduced relapse rate when *ex vivo* purging with a cyclophosphamide derivative, such as mafosfamide, is employed.[106-108] Patients with persistent first CR for more than six months probably do not need autograft as they have a high chance of being already cured.

Recommendations

Consolidation autologous SCT is recommended for patients eligible for high-dose chemotherapy who are not candidate for allogeneic SCT from a fully HLA matched donor [grade B]. Children with Down's syndrome should not be considered for autologous SCT [grade B]. Patients are recommended to receive autologous SCT within six months of achievement of first CR [grade D]. Patients with persistent first CR for more than six months should not receive autologous SCT [grade D]. Stem cell harvesting should be performed when the best "in vivo" purging has been completed, i.e. after the last consolidation chemotherapy cycle [grade D]. Peripheral stem cell should be mobilized with the administration of myeloid growth factors (usually G-CSF) after the consolidation chemotherapy [grade D]. The adequate number of peripheral stem cells to be reinfused is 2.5×10^6 per kilogram of patient weight [grade D]. Response to autologous SCT should be assessed after recovery of at least 500 neutrophils/μL [grade D]. There is no evidence to support maintenance chemotherapy after autologous SCT in patients with a first CR [grade D].

Discussion

The Expert Panel provided recommendations by answering the most relevant clinical questions regarding AML patients: which is the diagnostic and prognostic value of pre-treatment evaluations? Which patients are candidates for intensive chemotherapy? Which is the best induction regimen in eligible patients? Which are the post-remissional treatment options, including autologous or allogeneic transplantation?

The most interesting advance in AML treatment strategy is the opportunity provided by the availability of clinical and biological prognostic factors, to stratify patients according to their probability of relapse and thus to optimize and tailor post-remissional treatment. Significant prognostic information can be obtained at diagnosis, searching for cytogenetic or molecular aberrations, and during the treatment course, monitoring *persistent leukemia* early after induction treatment and MRD after consolidation therapy. Although risk stratification still relies on conventional cytogenetics, in the future knowledge about the prognostic impact of genetic aberrations will provide the basis for an individualized and tailored treatment, and hopefully for novel targeted therapies.

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Authorship and Disclosures

EM was a member of the Expert Panel and wrote the paper; MM contributed to literature search, literature review and to writing the paper; GB co-ordinated the consensus meetings; ST conceived the study, co-ordinated the guideline production process and was a member of the Expert Panel; MV, AB, GM, FL, FF, CM were members of the Expert Panel and revised the paper.

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References

1. Deschler B, Lubbert M. Acute myeloid leukaemia: epidemiology and etiology. Cancer 2006;107: 2099-107.
2. Ferrara F. Unanswered questions in acute myeloid leukaemia. Lancet Oncol;2004;5:443-50.
3. Barosi G, Carella A, Lazzarino M, Marchetti M, Martelli M, Rambaldi A, et al. Management of nodal indolent (non marginal-zone) non-Hodgkin's lymphomas: practice guidelines from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. Haematologica 2005;90:1236-57.
4. Harbour R, Miller J. A new system for grading recommendations in evidence based guide-lines. Br Med J 2001;323:334-6.
5. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting - Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835-49.
6. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. Ann Intern Med 1985;103: 620-5.
7. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment

Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.
8. Bain BJ, Barnett D, Linch D, Matutes E, Reilly JT. General Haematology Task Force of the British Committee for Standards in Haematology (BCSH), British Society of Haematology. Revised guidelines on immunophenotyping in acute leukaemias and chronic lymphoproliferative disorders. Clin Lab Haematol 2002;24:1-13
9. Del Vecchio L, Brando B, Lanza F, Ortolani C, Pizzolo G, Semenzato G, Barro G, Italian Society for Cytometry. Recommended reporting format for flow cytometry diagnosis of acute leukemia. Haematologica 2004;89:594-8.
10. Byrd JC, Mrozek K, Dodge RK, Carrol AJ, Edwards CG, Arthur DC, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood 2002;100: 4325-36.
11. Chessells JM, Harrison CJ, Kempski H, Webb DK, Wheatley K, Hann IM, et al. Clinical features, cytogenetics and outcome in acute lymphoblastic and myeloid leukaemia of infancy: report from the MRC Childhood Leukaemia working party. Leukemia 2002;16:776-84.
12. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood 1998;92:2322-33.
13. Grimwade D, Walker H, Harrison G, Oliver F, Chatters S, Harrison CJ, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. Blood 2001;98:1312-20.
14. Junghanss C, Waak M, Knopp A, Kleine HD, Kundt G, Leithauser M, et al. Multivariate analyses of prognostic factors in acute myeloid leukemia: relevance of cytogenetic abnormalities and CD34 expression. Neoplasma 2005;52:402-10.
15. Hasle H, Alonzo TA, Auvrignon A, Behar C, Chang M, Creutzig U, et al. Monosomy 7 and deletion 7q in children and adolescents with acute myeloid leukemia: an international retrospective study. Blood 2007;109: 4641-7.
16. Kiyoi H, Naoe T, Nakano Y, Yokota S, Minami S, Miyawaki S, et al. Prognostic implication of FLT3 and N-RAS gene mutations in acute myeloid leukemia. Blood 1999;93: 3074-80.
17. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood 2001; 98:1752-59.
18. Frohling S, Schlenk RF, Breitruck J, Benner A, Kreitmeier S, Tobis K, et al. AML Study Group Ulm. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood 2002;100:4372-80.
19. Boissel N, Cayuela JM, Preudhomme C, Thomas X, Grardel N, Fund X, et al. Prognostic significance of FLT3 internal tandem repeat in patients with de novo acute myeloid leukemia treated with reinforced courses of chemotherapy. Leukemia 2002;16: 1699-704.
20. Boissel N, Leroy H, Brethon B, Philippe N, de Botton S, Auvrignon A, et al. Incidence and prognostic impact of c-Kit, FLT3, and Ras gene mutations in core binding factor acute myeloid leukemia (CBF-AML). Leukemia 2006;20:965-70.
21. Döhner H. Implication of the Molecular Characterization of Acute Myeloid Leukemia. Hematology 2007:412-419. (Education program book ASH 2007)
22. Schnittger S, Schoch C, Kern W, Mecucci C, Tschulik C, Martelli MF, et al. Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype. Blood 2005;106:3733-9.
23. Cazzaniga G, Dell'Oro MG, Mecucci C, Giarin E, Masetti R, Rossi V, et al. Nucleophosmin mutations in childhood acute myelogenous leukemia with normal karyotype. Blood 2005; 106:1419-22.
24. Falini B, Mecucci C, Tiacci E, Alcalay M, Rosati R, Pasqualucci L, et al. GIMEMA Acute Leukemia Working Party. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med 2005;352:254-66.
25. Schlenk RF, Döhner K, Krauter J, Fröhling S, Corbacioglu A, Bullinger L, et al. German-Austrian Acute Myeloid Leukemia Study Group. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med 2008;358:1909-18.
26. Cairoli R, Beghini A, Grillo G, Nadali G, Elice F, Ripamonti CB, et al. Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. Blood 2006;107:3463-68.
27. Shimada A, Taki T, Tabuchi K, Tawa A, Horibe K, Tsuchida M, et al. KIT mutations, and not FLT3 internal tandem duplication, are strongly associated with a poor prognosis in pediatric acute myeloid leukemia with t(8;21): a study of the Japanese Childhood AML Cooperative Study Group. Blood 2006;107:1806-9.
28. Falini B, Martelli MP, Bolli N, Bonasso R, Ghia E, Pallotta MT, et al. Immunohistochemistry predicts nucleophosmin (NPM) mutations in acute myeloid leukemia. Blood 2006;108:1999-2005.
29. Wiernik PH, Banks PL, Case DC Jr, Arlin ZA, Periman PO, Todd MB, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. Blood 1992;79: 313-9.
30. Vogler WR, Velez-Garcia E, Weiner RS, Flaum MA, Bartolucci AA, Omura GA, 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;10:1103-11.
31. Berman E, Heller G, Santorsa J, McKenzie S, Gee T, Kempin S, et al. Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia. Blood 1991;77: 1666-74.
32. Mandelli F, Petti MC, Ardia A, Di PIetro N, Di Raimondo F, Ganzina F, et al. A randomised clinical trial comparing idarubicin and cytarabine to daunorubicin and cytarabine in the treatment of acute non-lymphoid leukaemia. A multicentric study from the Italian Co-operative Group GIMEMA. Eur J Cancer 1991;27:750-5.
33. Reiffers J, Huguet F, Stoppa AM, Molina L, Marit G, Attal M, et al. A prospective randomized trial of idarubicin vs daunorubicin in combination chemotherapy for acute myelogenous leukemia of the age group 55 to 75. Leukemia 1996;10: 389-5.
34. Berman E, Wiernik P, Vogler R, Velez-Garcia E, Bartolucci A, Whaley FS. Long-term follow-up of three randomized trials comparing idarubicin and daunorubicin as induction therapies for patients with untreated acute myeloid leukemia. Cancer 1997;80:2181-5.
35. Arlin Z, Case DC Jr, Moore J, Wiernik P, Feldman E, Saletan S, 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;4:177-83.
36. Mandelli F, Vignetti M, Suciu S, Stasi R, Petti MC, Meloni G, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: final results of a randomized trial of the EORTC and GIMEMA

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Leukemia Groups (AML-10). Annual Meeting of the American Society of Hematology; 2003.
37. Preisler H. Comparison of three remission induction regimens and two postinduction strategies for the treatment of acute nonlymphocytic leukemia: a cancer and leukemia group B study. Blood 1987;69:1441-9.
38. Hann IM, Stevens RF. 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;89:2311-8.
39. Bishop JF, Lowenthal RM, Joshua D, Matthews JP, Todd D, Cobcroft R, et al. Etoposide in acute nonlymphocytic leukaemia. Blood 1990;75:27-32.
40. Estey EH, Thall PF. Comparison of idarubicin + Ara-C, fludarabine + ara-C, and topotecan + ara-C-based regimens in treatment of newly diagnosed acute myeloid leukemia, refractory anemia with excess blasts in transformation, or refractory anemia with excess blasts. Blood 2001; 98:3575-83.
41. Ossenkoppele GJ, Graveland WJ, Sonneveld P, Daenen SM, Biesma DH, Verdonck LF, et al. The value of fludarabine in addition to ARA-C and G-CSF in the treatment of patients with high-risk myelodysplastic syndromes and AML in elderly patients. Blood 2004;103:2908-13.
42. Ferrara F, D'Arco AM, De Simone M, Mele G, Califano C, Pocali B, et al. Fludarabine and cytarabine as continuous sequential infusion for elderly patients with acute myeloid leukemia. Haematologica 2005;90: 776-84.
43. Bishop JF, Matthews JP, Young GA, Szer J, Gillett A, Joshua D, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood 1996;87: 1710-7.
44. Geller RB, Burke PJ, Karp JE, Humphrey RL, Braine HG, Tucker RW, et al. A two-step timed sequential treatment for acute myelocytic leukemia. Blood 1989;74:1499-506.
45. Weick JK, Kopecky KJ, Appelbaum FR, Head DR, Kingsbury LL, Balcerzak SP, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. Blood 1996;88:2841-51.
46. Büchner T, Hiddemann W, Wörmann B, Löffler H, Gassmann W, Haferlach T, 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;93:4116-24.
47. Kern W, Haferlach T, Schoch C, Loffler H, Gassmann W, Heinecke A, et al. Early blast clearance by remission induction therapy is a major independent prognostic factor for both achievement of complete remission and long-term outcome in acute myeloid leukemia: data from the German AML. Blood 2003;101: 64-70.
48. Rao A, Hills RK, Stiller C, Gibson BE, de Graaf SS, Hann IM, et al. Treatment for myeloid leukaemia of Down syndrome: population-based experience in the UK and results from the Medical Research Council AML 10 and AML 12 trials. Br J Haematol 2006;132:576-83.
49. Butturini A, Gale RP, Verlander PC, Adler-Brecher B, Gillio AP, Auerbach AD. Hematologic abnormalities in Fanconi anemia: an International Fanconi Anemia Registry study. Blood 1994;84:1650-5.
50. Lowenberg B, Zittoun R, Kerkhofs H, Jehn U, Abels J, Debusscher L, et al. On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. J Clin Oncol 1989;7:1268-74.
51. Estey EH. How I treat older patients with AML. Blood 2000;96: 1670-3.
52. Thiebaut A, Thomas X, Belhabri A, Anglaret B, Archimbaud E. Impact of pre-induction therapy leukapheresis on treatment outcome in adult acute myelogenous leukemia presenting with hyperleukocytosis. Ann Hematol 2000;79:501-6.
53. Hughes WT, Armstrong D, Bodey GP, Brown AE, Edwards JE, et al. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. Clin Infect Dis 1997;25: 551-73.
54. Leibovici L, Paul M. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer 2006;107:1743-51.
55. Rebulla P, Finazzi G, Marangoni F, Avvisati G, Gugliotta L, Tognoni G, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. N Engl J Med 1997;337:1870-5.
56. Amadori S, Suciu S, Jehn U, Stasi R, Thomas X, Marie JP, et al. Use of glycosylated recombinant human G-CSF (lenograstim) during and/or after induction chemotherapy in patients 61 years of age and older with acute myeloid leukemia: final results of AML-13, a randomized phase-3 study. Blood 2005;106:27-34.
57. Heil G, Hoelzer D, Sanz MA, Lechner K, Liu Yin JA, Papa G, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group. Blood 1997;90:4710-8.
58. Dombret H, Chastang C, Fenaux P, Reiffers J, Bordessoule D, Bouabdallah R, et al. A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. AML Cooperative Study Group. N Engl J Med 1995;332:1678-83.
59. Godwin JE, Kopecky KJ, Head DR, Willman CL, Leith CP, Hynes HE, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). Blood 1998;91:3607-15.
60. Stone RM, Berg DT, George SL, Dodge RK, Paciucci PA, Schulman P, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. N Engl J Med 1995;332:1671-77.
61. Rowe JM, Andersen JW, Mazza JJ, Bennett JM, Paietta E, Hayes FA, et al. Randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood 1995;86:457-62.
62. Lowenberg B, van Putten W, Theobald M, Gmur J, Verdonk L, Sonneveld P, et al. Effect of priming with granulocyte colony-stimulating factor on the outcome of chemotherapy for acute myeloid leukemia. N Engl J Med 2003;349: 743-52.
63. Buchner T, Urbanitz D, Hiddemann W, Ruhl H, Ludwig WD, Fisher J, et al. Intensified induction and consolidation with or without maintenance chemotherapy for acute myeloid leukemia (AML): two multicenter studies of the German AML Cooperative Group. J Clin Oncol 1985;3:1583-9.
64. Moore JO, George SL, Dodge RK, Amrein PC, Powell BL, Kolitz JE, et al. Sequential multiagent chemotherapy is not superior to high-dose cytarabine alone as postremission intensification therapy for acute myeloid leukemia in adults under 60 years of age: Cancer and Leukemia Group B Study 9222. Blood 2005;105:3420-7.
65. Stone RM, Berg DT, George SL, Dodge RK, Paciucci PA, Schulman PP, et al. Postremission therapy in older patients with de novo acute myeloid leukemia: a randomized trial comparing mitoxantrone and intermediate-dose cytarabine with

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standard-dose cytarabine. Blood 2001;98:548-53.
66. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. N Engl J Med 1994;331:896-903.
67. Breems DA, Boogaerts MA, Dekker AW, van Putten WL, Sonneveld P, Huijgens PC, 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. Br J Haematol 2005;128:59-65.
68. Fopp M, Fey MF, Bacchi M, Cavalli F, Gmuer J, Jacky E, et al. Post-remission therapy of adult acute myeloid leukaemia: one cycle of high-dose versus standard-dose cytarabine. Leukaemia Project Group of the Swiss Group for Clinical Cancer Research (SAKK). Ann Oncol 1997; 8:251-7.
69. Webb DK. Optimizing therapy for myeloid disorders of Down syndrome. Br J Haematol 2005;131:3-7.
70. Jourdan E, Boiron JM, Dastugue N, Vey N, Marit G, Rigal-Huguet F, et al. Early allogeneic stem-cell transplantation for young adults with acute myeloblastic leukemia in first complete remission: an intent-to-treat long-term analysis of the BGMT 21 experience. J Clin Oncol 2005;23: 7676-84.
71. Creutzig U, Zimmerman M, Ritter J, Reinhardt D, Hermann J, Henze G, et al. Treatment strategies and long-term results in paediatric patients treated in four consecutive AML-BFM trials. Leukemia 2005;19:2030-42.
72. Perel Y, Auvrignon A, Leblanc T, Vannier JP, Michel G, Nelken B, et al. Impact of addition of maintenance therapy to intensive induction and consolidation chemotherapy for childhood acute myeloblastic leukemia: results of a prospective randomized trial, LAME 89/91. Leucamie Aique Myeloide Enfant. J Clin Oncol 2002;20:2774-82.
73. Robles C, Kim KM, Oken MM, Bennett JM, Letendre L, Wiernik PH, et al. Low-dose cytarabine maintenance therapy vs observation after remission induction in advanced acute myeloid leukemia: an Eastern Cooperative Oncology Group Trial (E5483). Leukemia 2000;14:1349-53.
74. Büchner T, Hiddemann W, Berdel WE, Wormann B, Schoch C, Fonatsch C, et al. 6-Thioguanine, cytarabine, and daunorubicin (TAD) and high-dose cytarabine and mitoxantrone (HAM) for induction, TAD for consolidation, and either prolonged maintenance by reduced monthly TAD or TAD-HAM-TAD and one course of intensive consolidation by sequential HAM in adult patients at all ages with de novo acute myeloid leukemia (AML): a randomized trial of the German AML Cooperative Group. J Clin Oncol 2003;21:4496-504.
75. Gardin C, Turlure P, Fagot T, Thomas X, Terre C, Contentin N, 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;109:5129-35.
76. Ljungman P, Urbano-Ispizua A, Cavazzana-Calvo M, Demirer T, Dini G, Einsele H, et al. Allogeneic Transplantation: definitions and current practice in Europe (EBMT Special Report) Bone Marrow Transplant 2006;37:439-49.
77. Cornelissen JJ, Lowenberg B. Role of allogeneic stem cell transplantation in current treatment of acute myeloid leukemia. Hematology (Am Soc Hematol Educ Program) 2005: 151-5.
78. Yanada M, Matsuo K, Emi N, Naoe T. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a metaanalysis. Cancer 2005;103:1652-8.
79. Bleakley M, Lau L, Shaw PJ, Kaufman A. Bone marrow transplantation for paediatric AML in first remission: a systematic review and meta-analysis. Bone Marrow Transplant 2002;29:843-52.
80. Suciu S, Mandelli F, De Witte T, Zittoun R, Gallo E, Labar B, 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;102:1232-40.
81. Cornelissen JJ, Van Putten WL. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? Blood 2007;109:3658-66.
82. Gale RE, Hills R, Kottaridis PD, Srirangan S, Wheatley K, Burnett AK, Linch DC. No evidence that FLT3 status should be considered as an indicator for transplantation in acute myeloid leukemia (AML): an analysis of 1135 patients, excluding acute promyelocytic leukemia, from the UK MRC AML10 and 12 trials. Blood 2005;106:3658-65.
83. Cook G, Clark RE, Crawley C, Mackinnon S, Russel N, Thomson K, et al. The Outcome of Sibling and Unrelated Donor Allogeneic Stem Cell Transplantation in Adult Patients with Acute Myeloid Leukemia in First Remission Who Were Initially Refractory to First Induction Chemotherapy. Biol Blood Marrow Transplant 2006;12:293-300.
84. Gale RP. Delphi-panel analysis of appropriateness of high-dose therapy and bone marrow transplants in adults with acute myelogenous leukemia in 1st remission. Leuk Res 1999;23:709-18.
85. Aversa F, Terenzi A, Tabilio A, Falzetti F, Carotti A, Ballanti S, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. J Clin Oncol 2005;23:3447-54.
86. Rocha V, Cornish J, Sievers EL, Filipovich A, Locatelli F, Peters C, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood 2001;97: 2962-71.
87. Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med 2004;351: 2276-85.
88. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, McGlave PB, Miller JS, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood 2005;105:1343-7.
89. Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang MJ, Champlin RE, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med 2004;351: 2265-75.
90. Ringdén O, Labopin M, Bacigalupo A, Arcese W, Schaefer UW, Willemze R, et al. Transplantation of peripheral blood stem cells as compared with bone marrow from HLA-identical siblings in adult patients with acute myeloid leukemia and acute lymphoblastic leukemia. J Clin Oncol 2002;20: 4655-64.
91. Gorin NC, Labopin M. Marrow versus peripheral blood for geno-identical allogeneic stem cell transplantation in acute myelocytic leukemia: influence of dose and stem cell source shows better outcome with rich marrow. Blood 2003;102:3043-51.
92. Aoudjhane M, Labopin M, Gorin NC, Shimoni A , Ruutu T, Kolb HJ, et al. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). Leukemia 2005;19:2304-12.
93. Schmid C, Schleuning M, Hentrich M, Markl GE, Gerbitz A, Tischer J, et al. High antileukemic efficacy of an intermediate intensity conditioning regimen for allogeneic stem cell transplantation in patients with high-risk acute myeloid leukemia in

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first complete remission. Bone Marrow Transplant 2008;41:721-7.
94. Herr AL, Labopin M, Blaise D. HLA-identical sibling allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning compared to autologous peripheral blood stem cell transplantation for elderly patients with de novo acute myeloid leukemia. Leukemia 2007;21:129-35.
95. Hegenbart U, Niederwieser D, Sandmaier BM, Maris MB, Shizuru JA, Greinix H, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. J Clin Oncol 2006;24:444-53.
96. Smith EP, Nademanee A. Bone marrow transplantation: the City of Hope experience. Clin Transpl 1995:291-310.
97. Burnett AK, Goldstone AH, Stevens RM, Hann IM, Rees JK, Gray RG, Wheatley K. 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 Research Council Adult and Children's Leukaemia Working Parties. Lancet 1998;351:700-8.
98. Levi I, Grotto I, Yerushalmi R, Ben Bassat I, Shpilberg O. Meta-analysis of autologous bone marrow transplantation versus chemotherapy in adult patients with acute myeloid leukemia in first remission. Leuk Res 2004;28:605-12.
99. Nathan PC, Sung L. Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a meta-analysis. J Natl Cancer Inst 2004;96:38-45.
100. Tsimberidou AM, Stavroyianni N, Viniou N, Papaioannou M, Tiniakou M, Marinakis T, 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;97:1721-31.
101. Lazarus HM, Perez WS, Klein JP, Kollman C, Bate-Boyle B, Bredeson CN, et al. Autotransplantation versus HLA-matched unrelated donor transplantation for acute myeloid leukaemia: a retrospective analysis from the Center for International Blood and Marrow Transplant Research. Br J Haematol 2006;132:755-69.
102. Ferrara F, Palmieri S, Celentano M, De Simone M, Pollio F, D'Amico MR, et al. Feasibility of autologous peripheral blood stem cell transplantation in elderly patients with acute myeloid leukemia. Leuk Lymphoma 2006 57:1593-8.
103. Ravindranath Y, Yeager AM, Chang MN, Steuber CP, Krisher J, Grahm-Pole J, et al. Autologous bone marrow transplantation versus intensive consolidation chemotherapy for acute myeloid leukemia in childhood. N Engl J Med 1996;334:1428-34.
104. Stevens RF, Hann IM, Wheatley K, Gray RG. Marked improvements in outcome with chemotherapy alone in paediatric acute myeloid leukemia: results of the United Kingdom Medical Research Council's 10th AML trial. Br J Haematol 1998;101:130-40.
105. Woods WG, Neudorf S, Gold S, Sanders J, Buckley JD, Barnard DR, et al. A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission: a report from Children's Cancer Group. Blood 2001;97:56-62.
106. Gorin NC, Aegerter P, Auvert B, Meloni G, Goldstone AH, Burnett A, et al. Autologous bone marrow transplantation for acute myelocytic leukemia in first remission: a European survey of the role of marrow purging. Blood 1990;75:1606-14.
107. Miller CB, Rowlings PA, Zhang MJ, Jones RJ, Piantadosi S, Keating A, et al. The effect of graft purging with 4-hydroperoxycyclophosphamide in autologous bone marrow transplantation for acute myelogenous leukemia. Exp Hematol 2001;29:1336-46.
108. Locatelli F, Labopin M, Ortega J, Meloni G, Dini G, Messina C, et al. Factors influencing outcome and incidence of long-term complications in children who underwent autologous stem cell transplantation for acute myeloid leukemia in first complete remission. Blood 2003;101:1611-9.

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