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Guidelines on the treatment of acute myeloid leukemia: Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular
Project guidelines: Associação Médica Brasileira – 2015

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Introduction

The guidelines project is a joint initiative of the *Associação Médica Brasileira and the Conselho Federal de Medicina*. It aims to bring together information in medicine to standardize conduct in order to help decision-making during treatment. The data contained in this article were prepared by and are recommended by the *Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular* (ABHH). Even so, all possible conducts should be evaluated by the physician responsible for treatment depending on the patient's setting and clinical status.

This article presents the guidelines for the treatment of acute myeloid leukemia (AML). The expert group of the ABHH mainly focused on issues related to chemotherapy and the

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selection of patient subgroups for which there are specific recommendations for treatment. The indications, but not the actual treatment protocols for bone marrow transplantation, were analyzed.

Description of the method used to gather evidence

These Guidelines were drafted by elaborating 12 clinically relevant questions related to the treatment of AML. The questions were structured using the Patient/Problem, Intervention, Comparison and Outcome (PICO) system, allowing the generation of evidence search strategies in the key scientific databases (MEDLINE PubMed, Lilacs, SciELO, Embase, Cochrane Library, Premedline via OVID). The data recovered was critically analyzed using discriminatory instruments (scores) according to the type of evidence – JADAD for randomized clinical trials and the Newcastle Ottawa scale for non-randomized studies. After identifying studies that potentially substantiate recommendations, the level of evidence and degree of recommendation were calculated using the Oxford Classification.[1]

Summary of the degree of recommendation and level of evidence

A: Major experimental and observational studies
B: Minor experimental and observational studies
C: Case reports (non-controlled studies)
D: Opinion without critical evaluation based on consensus, physiological studies or animal models

Aims

The aim of these guidelines is to contribute to decision making in the treatment of AML.

Which anthracycline agent is the most effective in inducing remission of acute myeloid leukemia?

P – Patients undergoing induction treatment for AML
I – Anthracycline agent (daunorubicin, doxorubicin, idarubicin)
C –
O – Complete remission rate, overall survival, and disease-free survival

Two different induction treatments were compared in under 18-year-old patients (mean age: 7.9 years) with *de novo* AML: cytarabine, idarubicin and etoposide (AIE) and cytarabine, daunorubicin and etoposide (EDA). The AIE regimen was cytarabine (100 mg/m^2/day) as a continuous infusion on Days 1 and 2 and 30-min infusions on Days 3–8, idarubicin (12 mg/m^2/day) as 30-min infusions on Days 3–5 and etoposide (150 mg/m^2/day) as 120-min infusions on Days 6–8. The EDA regimen was cytarabine (100 mg/m^2/day) as continuous infusions on Days 1 and 2, and 30-min infusions on Days 3–8), daunorubicin (30 mg/m^2) as 30-min infusions every 12 h on Days 3–5) and etoposide (150 mg/m^2/day) as 120-min infusions on Days 6–8. After the exclusion of patients with myelosarcoma, secondary AML, myelodysplastic syndrome (MDS) and Down syndrome, and with 22% of patients having favorable karyotypes, a significantly higher percentage of patients had blast counts $\leq$5% by the 15th day after induction with the AIE regimen compared to the ADE regimen (83% vs. 69%, respectively; p-value = 0.01) (A).[2]

There was no significant differences between the groups in respect to complete remission (CR) (87% for AIE and for ADE), deaths (5% for AIE and 3% for ADE; p-value = 0.41), cardiac or hematologic toxicity or for the presence of grade 3 and 4 mucositis after induction therapy (A).[2]

On analyzing under 65-year-old adult patients with *de novo* AML stratified into two induction treatment groups: idarubicin (12 mg/m^2/day) for three days or daunorubicin (50 mg/m^2/day) for five days both associated with cytarabine (100 mg/m^2/day) by 24-h continuous infusions for seven days, the CR was similar after the first cycle (64.1% vs. 61.1%, respectively; p-value = 0.39). The same regimen was repeated at 3–4-week intervals when patients did not achieve CR after the first cycle with the overall CR rate increasing to 77.9% (78.2% for idarubicin vs. 77.5% for daunorubicin; p-value = 0.79). Although few patients were characterized as M6 by the French-American-British classification (FAB) system (3.12%), this group responds better to the idarubicin regimen after the first cycle [odds ratio (OR): 78% vs. 38%; p-value = 0.037]. However, there is no significant difference between the two anthracyclines in respect to the other FAB subtypes of AML, cytogenetic risk groups, age, the initial white blood cell count, the percentage of positive myeloperoxidase blasts or performance status (A).[3]

Induction treatment with daunorubicin (50 mg/m^2/day), mitoxantrone (12 mg/m^2/day) or idarubicin (10 mg/m^2/day) on Days 1, 3 and 5 associated with cytarabine (100 mg/m^2/day) as a ten-day continuous infusion and etoposide (100 mg/m^2/day) as a 1-h infusion for five days results in a CR of 63.6% in 15- to 60-year-old patients with primary or secondary AML. There is no evidence of serious cardiac, pulmonary, neurologic or metabolic comorbidities or uncontrolled infections and normal hepatic and renal function with this regimen. In cases of partial response, a second cycle is performed using the same regimen as the first cycle and the CR increases to 68.5% with no significant differences between the treatment arms (mitoxantrone vs. daunorubicin: p-value = 0.63; and daunorubicin vs. idarubicin: p-value = 0.49) (A).[4]

Patients with *de novo* AML or secondary AML due to MDS and normal heart function stratified into three age groups (15–50 years, 51–60 years and over 60 years old) were evaluated in respect to induction regimens. The use of idarubicin (IDA – 12–13 mg/m^2/day for three days) or daunorubicin (DNR – 45 mg/m^2/day for three days), both in combination with cytarabine (100 mg/m^2/day by seven-day continuous infusion) were compared. A second cycle using the same drug was administered if there were more than 5% leukemic blasts in the bone marrow at Day 14. There was a better, albeit not necessarily statistically significant, CR for the idarubicin group

(70–74% vs. 57–59%; p-value = 0.032–0.09). When evaluated separately, there was no significant difference between the groups after the first and after the second cycle. When the evaluation was performed for the three age groups, lower CR rates were observed as the age increased (15–50 years: 86–91% vs. 70–80%; 51–60 years: 67–71% vs. 45–65%; >60 years: 50–68% vs. 44–53% for the IDA and DNR groups, respectively). There was no significant difference in hematologic and non-hematologic toxicity for both groups regardless of age (A).[5–8]

On comparing daunorubicin (DNR – 80 mg/m^2/day for three days), idarubicin (IDA4 – 12 mg/m^2/day for four days), and idarubicin (IDA3 – 12 mg/m^2/day for three days), all associated with cytarabine (200 mg/m^2/day as a seven-day continuous infusion) in 50- to 70-year-old patients, the overall CR was 66%. CR rates of 61%, 67% and 70% were recorded for the DNR, IDA4 and IDA3 arms, respectively (p-value = 0.25). However, when patients received a second induction cycle, all with mitoxantrone (12 mg/m^2/day for two days) associated with cytarabine (1 g/m^2 over 1 h every 12 h for four days), the CR increased to 77%. The difference between the three comparison arms was significant (p-value = 0.04) with the CR being 70%, 78% and 83% for the DNR, IDA4 and IDA3 arms, respectively. The CR was significantly higher in the IDA3 arm when compared to the high-dose DNR arm (p-value = 0.007), with a tendency of better rates in the subgroup with unfavorable cytogenetics (74% vs. 48%; p-value = 0.07). Consequently, the CR was higher in patients receiving idarubicin than in those receiving daunorubicin (80% vs. 70%; p-value = 0.03). There were no significant differences in the mortality rates, length of hospitalization, cytopenias, grade 3 or 4 infection rates, bleeding episodes or the duration of antibiotic therapy between the three groups during induction (A).[9]

Induction therapy for *de novo* AML in 55- to 75-year-old patients using cytarabine (100 mg/m^2/day) as a seven-day continuous infusion associated with idarubicin (8 mg/m^2/day) for five days or daunorubicin (50 mg/m^2/day) for three days was compared. There were no significant differences in the CR (IDA: 67.9% vs. DNR: 61.1%; p-value = 0.29) or hematologic or non-hematological toxicity (A).[10]

In over 65-year-old patients with *de novo* AML or AML secondary to MDS (FAB: refractory anemia with excess blasts in transformation – RAEB-T), daunorubicin (45 mg/m^2/day) for four days was compared with idarubicin (9 mg/m^2/day) for four days both associated with cytarabine (200 mg/m^2/day) by a seven-day continuous infusion. After the initial induction chemotherapy cycle, a second cycle of cytarabine (500 mg/m^2) in a 1-h infusion every 12 h for three days associated with mitoxantrone (12 mg/m^2/day) for two days was administered when CR was not achieved. The overall CR rate was 57% (53.8% after the first induction cycle); the CR rate for the DNR arm was 54% and for the IDA arm it was 59% (p-value = 0.28). The mortality rate in both groups was 10% (A).[11]

Three induction therapies were compared in over 55-year-old treatment-naive AML patients without serious heart conditions, and normal liver and kidney function: daunorubicin (45 mg/m^2/day) for three days or idarubicin (12 mg/m^2/day) for three days or mitoxantrone (12 mg/m^2/day) for three days, associated with cytarabine (100 mg/m^2/day) by seven-day continuous infusion. The overall CR rate was 39.7–42%, with no significant difference between the anthracyclines used. However, when only under 70-year-old patients of that group were evaluated, the CR of the idarubicin arm was better than the daunorubicin arm (55% vs. 46%, respectively; p-value = 0.04) (A).[12]

Recommendations: On comparing the efficacy of induction therapy using the anthracyclines, idarubicin and daunorubicin in AML patients of different ages, although the reduction in the blast count was faster with the first cycle of idarubicin, there were no significant differences in the CR or toxicity of the two drugs.

What dose (100 mg/m^2/day and 200 mg/m^2/day) of cytarabine (Ara-C or Arabinoside-C) is the most effective in the induction therapy of acute myeloid leukemia patients?

P – Patients undergoing induction treatment for AML
I – Cytarabine (Ara-C or Arabinoside-C) – 100 mg/m^2/day
C – Cytarabine (Ara-C or Arabinoside-C) – 200 mg/m^2/day
O – Complete remission rate, overall survival, and disease-free survival

On comparing induction therapy for AML patients using cytarabine (100 mg/m^2/day) or cytarabine (200 mg/m^2/day) as a seven-day continuous infusion associated with daunorubicin (45 mg/m^2/day) in under 60-year-old patients or (30 mg/m^2/day) in over 60-year-old patients, the CR was 61% with no significant difference between doses (p-value = 0.29). There was also no significant difference in the CR rate when the over and under 60-year-old patients were evaluated separately (p-value = 0.68 vs. p-value = 0.08, respectively). However, there was a 7% lower risk of death during induction therapy for the under 60-year-old patients in the group that received 100 mg/m^2/day [needed to harm (NNH): 15; p-value = 0.04] and a 6% decrease in over 60-year-olds (NNH: 17; p-value = 0.51). The main cause of death was infections in both the 100 mg/m^2/day and the 200 mg/m^2/day groups (A).[13]

Two induction regimens were evaluated in 18- to 60-year-old patients with *de novo* AML. The first group received cytarabine (200 mg/m^2/day) during the first cycle and cytarabine (1 g/m^2) every 12 h as a 3-h continuous infusion in a second cycle, and the second group received cytarabine (1 g/m^2) every 12 h in the first cycle and cytarabine (2 g/m^2) every 12 h in the second cycle. There was no significant difference in CR (34% vs. 35%, respectively) and overall survival (OS) between the two groups (40% vs. 42%, respectively). The higher dose of cytarabine resulted in a higher incidence of grade 3 and 4 toxicity, longer hospital stay and longer delays in neutrophil and platelet engraftment (A).[14]

Two different induction regimens were compared in AML patients aged 16–60 years old. The first, TAD cycle was cytarabine (100 mg/m^2/day) as continuous infusions on Days 1 and 2 and then cytarabine (200 mg/m^2/day) as 30-min infusions every 12 h on Days 3–8 associated with daunorubicin (60 mg/m^2/day) as 30-min infusions on Days 3–5 and

thioguanine (100 mg/m^2/day) orally on Days 3 and 9. This was followed by another cycle using the same doses. The second regimen was one TAD cycle, followed by a second HAM cycle with cytarabine (3 g/m^2) in 3-h infusions every 12 h on Days 1–3 associated with mitoxantrone (10 mg/m^2/day) in 30-min infusions on Days 3–5. There was no significant difference between the two groups in respect to the CR (67% vs. 71%, respectively; p-value = 0.072). The times to neutrophil and platelet engraftment were lower for the group that received the TAD-TAD regimen than those that received the TAD-HAM regimen (16 days vs. 20 days, respectively; p-value = 0.0001) (A).[15]

A continuous seven-day infusion of cytarabine (100 mg/m^2/day) associated with daunorubicin (50 mg/m^2/day) Days 1–3 and etoposide (75 mg/m^2/day) on Days 1–7 was compared with cytarabine (3 g/m^2) every 12 h on Days 1, 3, 5 and 7, associated with daunorubicin (50 mg/m^2/day) on Days 1–3 and etoposide (75 mg/m^2/day) on Days 1–7. CR was attained in 74% [95% confidence interval (CI): 66–81%] of the group submitted to standard dose cytarabine and 71% (95% CI: 63–78%) of the group submitted to high-dose cytarabine (p-value = 0.7). Significantly more patients in the high-dose cytarabine group discontinued induction therapy due to toxicity (1% vs. 9%, respectively; p-value = 0.003) (A).[16]

The use of cytarabine (10 mg/m^2) subcutaneously every 12 h for 21 days was compared with cytarabine (200 mg/m^2/day) as a seven-day continuous infusion associated with rubidazone (100 mg/m^2/day – derived from daunorubicin) for four days as induction therapy in over 65-year-old patients with *de novo* AML. The outcomes were CR, partial remission, treatment failure, and death in 32%, 22%, 36% and 10%, respectively of patients receiving subcutaneous cytarabine, and 52%, 2%, 15% and 31%, respectively of those receiving intensive therapy. That is, the number of CR patients and deaths were higher in the group that received high-dose cytarabine, while partial remission and treatment failure were more frequent in those submitted to low-dose cytarabine (p-value <0.001). Grade 3 and 4 toxicity, infectious complications and prolonged cytopenias were significantly higher in the intensive therapy group (p-value <0.01) (A).[17]

Recommendations: Due to the lower risk of death using 100 mg/m^2/day of cytarabine compared to 200 mg/m^2/day of cytarabine in the induction therapy of AML patients and no significant difference in the CR between the two groups, the lower dose is more appropriate. This is true for all age groups.

What dose of daunorubicin (45, 60 or 90 mg/m^2/day) is the most effective for induction therapy of acute myeloid leukemia in young patients (<60 years)?

P – Under 60-year-old patients undergoing induction treatment for AML

I – Daunorubicin (45, 60 or 90 mg/m^2/day)

C – Daunorubicin (45, 60 or 90 mg/m^2/day)

O – Complete remission rate, overall survival, and disease-free survival

Over six years, 17- to 60-year-old patients with AML were treated with cytarabine (100 mg/m^2/day) by seven-day continuous infusion associated with daunorubicin at doses of 45 mg/m^2/day or 90 mg/m^2/day for three days. Bone marrow biopsies were performed between Day 12 and 14 after induction therapy, and if the patient continued with leukemic blasts in the bone marrow, a second cycle was administered with the same doses of cytarabine and daunorubicin (45 mg/m^2/day). The overall CR rate was 63.9% (95% CI: 59.9–67.8), 57.3% in the group that received a dose of 45 mg/m^2 and 70.6% in the group that received a high dose of daunorubicin (p-value <0.001). Of the patients in this study, 72% of the 45 mg/m^2/day group and 83.3% of the high-dose group achieved CR after the first induction cycle (p-value = 0.01); thus only 11.4% achieved CR after the second cycle of chemotherapy. There was no significant difference in the rate of hematological and non-hematological toxicity (grades 3–5) or the death rates during induction between the two groups (A).[18]

Two doses of daunorubicin, 45 mg/m^2/day and 90 mg/m^2/day for three days, associated with cytarabine (200 mg/m^2/day) by seven-day continuous infusion were compared in a population of 15- to 60-year-old AML patients. Patients with CML in the blast phase and those with promyelocytic leukemia were excluded and all participants had adequate renal and hepatic function and normal heart function. The CR was superior in the group that received the high dose of daunorubicin (72% vs. 82.5%; p-value = 0.01) with a significant difference after the first induction cycle (56.1% vs. 71.1% for 45 mg/m^2 and high-dose, respectively; p-value = 0.04), and therefore a 15% reduction in the need to perform a second cycle of chemotherapy. There was no significant difference regarding the hematological and non-hematological adverse events between the two groups (A).[19]

One study compared daunorubicin (45 mg/m^2/day) for three days, and a second cycle when necessary at the same dose, with daunorubicin (75 mg/m^2/day) for three days, and a second cycle of 60 mg/m^2/day when there were more than 5% of blasts in the bone marrow. All cycles were associated with cytarabine (100 mg/m^2/day) by continuous infusion and etoposide (100 mg/m^2/day) in 30-min infusions, both for seven days. The participants were 13- to 67-year-old patients (mean 33 years) with *de novo* AML. Patients with secondary AML or promyelocytic leukemia according to the FAB classification were excluded, as were patients with severely impaired heart function. The overall CR was 65%, 58.9% in the group that received two cycles of 45 mg/m^2/day of daunorubicin and 77% in the group that received 75 mg/m^2/day and 60 mg/m^2/day of daunorubicin (p-value = 0.04). When the CR was evaluated after the first cycle of chemotherapy, the result was significantly better in the group that took the higher dose of daunorubicin (85.1% vs. 60.8%; p-value = 0.02). There was no significant difference between the two groups in respect to hematologic and non-hematologic toxicity (A).[20]

Recommendations: In adult patients with AML, high doses of daunorubicin (60–90 mg/m^2/day) associated with cytarabine (100 or 200 mg/m^2/day) increase the CR rate in induction therapy, both after the first and second cycles of chemotherapy without increasing the hematologic or non-hematologic toxicity when compared to a dose of 45 mg/m^2/day of daunorubicin.

What dose of daunorubicin (45, 60 or 90 mg/m^2) is the most effective for induction therapy of acute myeloid leukemia in elderly patients (>60 years)?

P – Over 60-year-old patients undergoing induction treatment for AML
I – Daunorubicin (45, 60 or 90 mg/m^2)
C – Daunorubicin (45, 60 or 90 mg/m^2)
O – Complete remission rate, overall survival, and disease-free survival

Elderly AML patients (61–75 years old) not including patients with the M3 subtype were evaluated using two induction regimens. All patients had normal liver and kidney function, no recent history of myocardial infarction or other severe cardiovascular disease and had no documented active infection. Cytarabine (100 mg/m^2/day) was administered as a seven-day continuous infusion for all patients but one group received daunorubicin (45 mg/m^2/day) for three days and the other, liposomal daunorubicin (80 mg/m^2/day) for three days with repeated second cycles using the same doses as the first cycle if the patient did not achieve CR. Of the patients receiving the standard dose of daunorubicin, 11.5% achieved CR after the second cycle of chemotherapy compared to 9.6% of patients receiving the high dose liposomal daunorubicin regimen. There was no significant difference in respect to CR between the groups (p-value = 0.94) (A).[21] Considering treatment failure including cases of drug resistance and deaths during the induction period, there was no significant difference between the groups (p-value = 0.33) with the leading cause of death being infections (A).[21]

Two induction regimens were evaluated in 60- to 83-year-old patients (mean: 67 years old) with *de novo* or secondary AML and a performance status ≤2 according to the World Health Organization (WHO) classification. Daunorubicin (45 mg/m^2/day) in 3-h infusions for three days was compared with daunorubicin (90 mg/m^2/day) in 3-h infusions for three days, both associated with cytarabine (200 mg/m^2/day) in a seven-day continuous infusion followed by a second cycle where both groups received cytarabine (1 g/m^2) every 12 h for six days. The overall CR was 54% in the group that received the conventional dose and 64% for the high-dose group (p-value = 0.002) (A).[22]

When each cycle was evaluated, the CR rate after the first cycle using high doses of daunorubicin was better than in the group that received the conventional dose (52% vs. 35% respectively; p-value <0.001), with no significant difference after the second cycle. There was also no significant difference between the two groups in respect to hematologic and non-hematologic toxicity, and mortality after induction therapy (A).[22]

Recommendations: There is controversy about the use of conventional doses and high doses of daunorubicin in induction therapy in relation to the CR of elderly AML patients. However, increasing the dose does not increase the hematological and non-hematological toxicity, or the number of treatment-related deaths.

What is the number of induction cycles (1 or 2) that is the most effective in the induction of acute myeloid leukemia patients?

P – Patients undergoing induction treatment for AML
I – One cycle of chemotherapy
C – Two cycles of chemotherapy
O – Complete remission rate, overall survival, and disease-free survival

Under 65-year-old adult patients with *de novo* AML stratified into two induction therapy groups – idarubicin (12 mg/m^2/day) for three days or high-dose daunorubicin (50 mg/m^2/day) for five days, both regimens associated with cytarabine (100 mg/m^2/day) as a seven-day continuous infusion, had similar CR after the first cycle (64.1% vs. 61.1%; p-value = 0.39). If the patient did not achieve CR after the first cycle, the same regimen was repeated at a 3- to 4-week interval which increased the overall CR rate to 77.9% (78.2% for idarubicin and 77.5% for daunorubicin; p-value = 0.79) (A).[6]

Regimens using daunorubicin (80 mg/m^2/day) for three days (DNR), idarubicin (12 mg/m^2/day) for four days (IDA4), and idarubicin (12 mg/m^2/day) for three days (IDA3), all associated with cytarabine (200 mg/m^2/day) in a seven-day continuous infusion were compared in 50- to 70-year-old patients. There was an overall CR rate of 66% with no significant difference between the groups (61% DNR, 67% IDA4, and 70% IDA3; p-value = 0.25). However, when patients received a second cycle of mitoxantrone (12 mg/m^2/day) for two days associated with cytarabine (1 g/m^2/day) in 1-h infusions every 12 h for four days, the CR rate increased to 77% with a significant difference (p-value = 0.04) between the three groups (70%, 78% and 83% for the DNR, IDA4 and IDA3 arms, respectively) (A).[7]

Three induction regimens were compared in 15- to 60-year-old patients with primary or secondary AML and with no evidence of severe heart, pulmonary, neurological or metabolic disease or uncontrolled infection, and with normal hepatic and renal function. The CR rate was 63.6% after an induction cycle of daunorubicin (50 mg/m^2/day) or mitoxantrone (12 mg/m^2/day) or idarubicin (10 mg/m^2/day) on Days 1, 3 and 5 associated with cytarabine (100 mg/m^2/day) in a ten-day continuous infusion and etoposide (100 mg/m^2/day) in 1-h infusions for five days. In cases of partial response, a second cycle was administered with the same drug as the

first cycle, and the CR rate increased to 68.5%, with no significant difference between the treatment arms (mitoxantrone vs. daunorubicin: p-value = 0.63; idarubicin vs. daunorubicin: p-value = 0.49) (A).[23]

A large number of over 18-year-old, treatment-naive patients with *de novo* or secondary AML was assessed after being grouped in several therapeutic induction schemes: cytarabine (100–200 mg/m^2/day) as a continuous infusion associated with daunorubicin (45–60 mg/m^2/day), idarubicin (12 mg/m^2/day) or mitoxantrone (12 mg/m^2/day). The overall CR rate was 64%; 74% of the total entered into remission after the first induction cycle and 26% of the remaining after the second cycle; this represents a 16.5% increase in the CR after the second cycle of induction chemotherapy (p-value = 0.001) (A).[23]

Recommendations: It is common to perform a second induction cycle of chemotherapy in patients with AML who have 5% or more blasts in the bone marrow 10–14 days after the first cycle; the complete response rate increases significantly after the second chemotherapy cycle.

What dose of cytarabine (400 mg/m^2 or 1 g/m^2 or 1.5 g/m^2 or 3 g/m^2) is the most effective in the consolidation treatment of young acute myeloid leukemia patients?

P – Patients undergoing induction treatment for AML
I – Use of cytarabine (400 mg/m^2/day, 1 g/m^2, 1.5 g/m^2 or 3 g/m^2)
C –
O – Complete remission rate, overall survival, and disease-free survival

Young patients (16–60 years with a mean of 47 years old) with *de novo* or secondary AML were evaluated for OS and disease-free survival (DFS) using different doses of cytarabine during consolidation treatment.

All patients took the same drugs during the induction phase and those who achieved CR were stratified according to prognostic factors by cytogenetics. High-risk or intermediate-risk patients with matched donors were referred for allogeneic bone marrow transplantation. However, low-risk patients and those who did not have HLA-compatible donors were submitted to consolidation.

Consolidation chemotherapy was performed in 52% of the patients who were in CR after two cycles of induction. Cytarabine (1 g/m^2) every 12 h for six days (total 12 g/m^2) or cytarabine (3 g/m^2) every 12 h for six days (total 36 g/m^2) was administered associated with mitoxantrone 10 g/m^2 for three days in both cases. There was no significant difference in the non-hematological grade 3 and 4 toxicity between the two groups. However, the group that received 36 g/m^2 of cytarabine presented neutropenia (24 days – 95% CI: 22–26 days) longer than the group taking 12 g/m^2 (18 days – 95% CI: 17–19 days; p-value = 0.004), but there was no difference in the infectious complications rate between groups (A).[24] Patients who used the highest dose of cytarabine required more red blood cell transfusions (8 vs. 6; p-value = 0.03), but there was no difference in the need for platelet concentrate transfusions (A). [24] In the analysis of intention to treat, the estimated 5-year OS was 30% (95% CI: 25–35%) for the group that received intermediate-dose cytarabine and 33% (95% CI: 28–38%) for the group that received high-dose cytarabine (p-value = 0.77). The 5-year DFS was estimated at 37% (95% CI: 31–44%) for the intermediate-dose group and 38% (95% CI: 31–45%) for the high-dose group (p-value = 0.86) (A).[24]

Two different consolidation chemotherapy regimens were compared in 15- to 60-year-old patients with *de novo* AML (except promyelocytic leukemia) with favorable cytogenetics, who received one or two induction cycles and achieved CR. Arm 1 of the trial was mitoxantrone (12 mg/m^2/day) on Days 1–3, cytarabine (500 mg/m^2/day) on Days 1–3 and on Days 8–10 and etoposide (200 mg/m^2/day) on Days 8–10. Arm 2 comprised cytarabine (3 g/m^2/day) on Days 1, 3 and 5 for four cycles followed by maintenance with daunorubicin (45 mg/m^2/day) on Day 1 and cytarabine (100 mg/m^2/day) on Days 1–5.

Relapse occurred in 52% of patients submitted to consolidation therapy; 51.6% in Arm 1 and 48.3% in Arm 2 (mean time: 9.9 months vs. 10.7 months, respectively) (A).[25] DFS was 13.7 months (95% CI: 11.3–22.5 months) in Arm 1 and 23.3 months (95% CI 15.7–47 months) in Arm 2, with the 5-year disease-free survival (DFS) being 6% higher in Arm 2 (p-value = 0.24). The OS was 55.6 months in Arm 1 and 62.9 months in Arm 2, with a 5-year OS 2% higher in Arm 2 (p-value = 0.82). Thus, there was no significant difference between the two arms in respect to the cumulative incidence of relapse and mortality related to consolidation therapy (A).[25]

Arm 1 was associated with greater non-hematological grade 3 or 4 toxicity compared to Arm 2 (maximum percentages: diarrhea 24% vs. 3%, nausea/vomiting, 26% vs. 3%, and serious infection 39% vs. 19%, respectively). Severe heart and lung side effects were observed mainly in Arm 1. Concerning hematological toxicity, patients in Arm 2 received more transfusions than Arm 1 due to repeating cycles of chemotherapy (A).[25]

Two consolidation therapies were evaluated in 15- to 65-year-old patients with AML, including those with promyelocytic leukemia. Group A received cytarabine (100 mg/m^2/day) in a seven-day continuous infusion and Group B received cytarabine (3 g/m^2) in 1-h infusions every 12 h for six days, both associated with daunorubicin (45 mg/m^2/day) for three days. The cytogenetic risk was not classified and all patients achieved CR after two induction chemotherapy cycles. The toxicity, DFS and OS were evaluated.

Grade 3 and 4 toxicity was 36.6% higher in Group B (NNH: 3; p-value <0.0001), mainly as infections, gastrointestinal disorders (nausea, vomiting or diarrhea) and neurological disorders (ataxia, stroke or disorientation). The DFS was 10.8 months for Group A and 12.2 months for Group B (p-value = 0.18), while the OS was 24.6 months in Group A and 32.6 months in Group B (p-value = 0.07), with no significant difference when the groups were followed up for 2, 3 and 5 years (A).[26]

Of 693 over 16-year-old patients with *de novo* AML in first CR after induction with cytarabine and daunorubicin at standard doses, 596 were randomized to one of three regimens of four consolidation cycles. The first group received cytarabine (100 mg/m^2/day) by continuous intravenous infusion for five days, the second received cytarabine (400 mg/m^2/day) by continuous infusion for five days, and the third group received cytarabine (3 g/m^2) in a 3-h infusion every 12 h on Days 1, 3 and 5. Over a 52-month follow-up, the probability of survival in CR for under 60-year-old patients was 24% for the 100 mg/m^2/day cytarabine group, 29% for the 400 mg/m^2/day cytarabine group and 44% for the 6 g/m^2/day cytarabine group (p-value = 0.002) (A).[27]

Recommendations: There is no significant difference between different doses of cytarabine in the consolidation therapy of AML in respect to DFS and OS. However, the study that compared standard-dose cytarabine (100 mg/m^2/day) with high dose (6 g/m^2/day) did not inform the cytogenetic risk. There are no studies comparing doses of 1 g/m^2/day, 1.5 g/m^2/day, 2 g/m^2/day and 3 g/m^2/day. The total dose of 6 g/m^2/day for three days seems to be associated with greater hematologic toxicity, and compared with the standard regimen of 100 mg/m^2/day, it is also associated with higher non-hematologic toxicity.

What dose of cytarabine (400 mg/m^2/day, 2 g/m^2/day, 3 g/m^2/day, 4 g/m^2/day or 6 g/m^2/day) is the most effective in consolidating young acute myeloid leukemia patients with favorable prognosis [<60 years, leukocyte count at diagnosis <30,000 or <50,000/mm^3 with cytogenetics: t(8;21)/AML1-ETO/RUNX1-RUNX1T1, inv(16)/t(16;16)/CBFbeta/MYH11, core binding factor leukemia, FLT3-negative or FLT3-ITD-negative/NPM1-mutated]?

P – AML patients with favorable prognosis [<60 years, with white blood cell count at diagnosis <30,000 or <50,000/mm^3 with cytogenetics t(8;21)/AML1-ETO/RUNX1-RUNX1T1, inv(16)/t(16;16)/CBFbeta/MYH11, core binding factor leukemia, FLT3-negative or FLT3-ITD-negative/NPM1-mutated]
I – Use of cytarabine (400 mg/m^2, 2 g/m^2/day, 3 g/m^2/day 4 g/m^2/day, or 6 g/m^2/day)
C –
O – Complete remission rate, overall survival, and disease-free survival

Patients (16–60 years; mean of 47 years) with *de novo* or secondary AML were evaluated for OS and DFS using different doses of cytarabine during consolidation treatment. All patients had the same regimen during induction and those who achieved CR were stratified by prognosis according to cytogenetics. High-risk and intermediate-risk patients who had HLA-compatible donors were referred for allogeneic bone marrow transplantation. Low-risk patients and those who had no compatible donor underwent consolidation chemotherapy.

Consolidation chemotherapy was administered to 52% of the patients who were in CR after two induction cycles. The regimens used were cytarabine 1 g/m^2 every 12 h for six days (total 12 g/m^2) or cytarabine 3 g/m^2 every 12 h for six days (total 36 g/m^2), both associated with mitoxantrone 10 g/m^2/day for three days.

There was no significant difference in the non-hematological grade 3 and 4 toxicity between the two groups. However, the group that received 36 g/m^2 presented neutropenia longer than the group of patients who received 12 g/m^2 [24 days (95% CI: 22–26) vs. 18 days (95% CI: 17–19); p-value = 0.004]. However, there was no difference in the infectious complications rate between the two groups. Patients who used the highest dose of cytarabine required more red blood cell transfusions (8 vs. 6; p-value = 0.03) but there was no difference in the need for platelet concentrate transfusions (A).[24]

Chemotherapy consolidation was evaluated in 15- to 60-year-old patients with *de novo* AML (except promyelocytic leukemia) with favorable cytogenetics, who received one or two chemotherapy induction cycles and achieved CR. Two different groups were compared. Arm 1 received mitoxantrone 12 (mg/m^2/day) on Days 1–3 associated with cytarabine (500 mg/m^2/day) on Days 1–3 and etoposide (200 mg/m^2/day) on Days 8–10 associated with cytarabine (500 mg/m^2/day) also on Days 8–10. Arm 2 received cytarabine (3 g/m^2/day) on Days 1, 3 and 5 for four cycles followed by maintenance with daunorubicin (45 mg/m^2/day) on Day 1 and cytarabine (100 mg/m^2/day) on Days 1–5.

Fifty-two percent of patients who were submitted to consolidation therapy relapsed, 51.6% in Arm 1 and 48.3% in Arm 2 (9.9 months vs. 10.7 months, respectively). The mean DFS was 13.7 months (95% CI: 11.3–22.5 months) in Arm 1 and 23.3 months (95% CI: 15.7–47 months) in Arm 2, with a 5-year DFS 6% higher in Arm 2 (p-value = 0.24). The OS was 55.6 months in Arm 1 and 62.9 months in Arm 2, with the 5-year OS being 2% higher in Arm 2 (p-value = 0.82). Thus, there was no significant difference between the two arms in respect to the cumulative incidence of relapse and mortality related to consolidation (A).[25]

Arm 1 had more non-hematological grade 3 or 4 toxicity than Arm 2: diarrhea 24% vs. a maximum of 3% in each cycle, respectively, nausea/vomiting 26% vs. a maximum of 3% in each cycle, respectively, and severe infection 39% vs. no more than 19% in each cycle, respectively. Severe cardiac and pulmonary effects were observed mainly in Arm 1. In regards to hematological toxicity, patients in Arm 2 received more transfusions than those in Arm 1 due to the repeating cycles of chemotherapy (A).[25]

Young 15- to 64-year-old patients with *de novo* AML (except promyelocytic leukemia according to the FAB classification), that after one or two chemotherapy induction cycles achieved CR were divided into two consolidation treatment groups. The first received high-dose cytarabine repeated for three cycles and the second a standard dose of cytarabine for four cycles. The mean follow-up was 48 months (range: 5–78 months).

The high-dose group received 2 g/m^2 in 3-h infusions every 12 h (total 4 g/m^2) for five days with each cycle starting one week after the recovery of neutrophil, leukocyte, and platelet counts to more than 1.5×10^9/L, 3.0×10^9/L and 100.0×10^9/L, respectively. The standard-dose group included several regimens: mitoxantrone (7 mg/m^2/day) as 30-min infusions for three days or daunorubicin (50 mg/m^2/day) as 30-min infusions for three days, or aclarubicin (20 mg/m^2/day) as 30-min infusions for five days or etoposide (100 mg/m^2/day) as 1-h infusions for five days, together with vincristine (0.8 mg/m^2) bolus on Day 8 and vindesine (2 mg/m^2) bolus on Day 10. All the above regimens were associated with cytarabine (200 mg/m^2/day) as a 24-h continuous infusion for five days. Each consolidation cycle was started as soon as possible after the recovery of the neutrophil, leukocyte and platelet counts.

The 5-year DFS for the high-dose and standard-dose groups were 43% and 39%, respectively (p-value = 0.724). However, when patients with favorable cytogenetics were evaluated alone, the DFS was 18% higher in the high-dose group (p-value = 0.05). There was no significant difference in the 5-year OS between the consolidation regimens for the total group of patients or for patients with favorable cytogenetics (p-value = 0.954 and p-value = 0.174, respectively) (A).[28]

When cytarabine 100 mg/m^2/day as a seven-day continuous infusion was compared with cytarabine 3 g/m^2 every 12 h as a continuous infusion for six days, both associated with daunorubicin 45 mg/m^2/day for three days, there was greater grade 3 and 4 toxicity (infection, gastrointestinal effects, and neurological effects) in the high-dose group (p-value = 0.0001). However, there was no significant difference between the two groups in respect to the mean OS and DFS of 15- to 65-year-old patients with *de novo* AML during a follow-up of 85 months (A).[26]

Recommendations: The overall survival and disease-free survival of 15- to 65-year-old AML patients with a favorable prognosis does not improve using a higher dose of cytarabine in the consolidation regimen. However, hematological and non-hematological grade 3 and 4 toxicity increases as the dose increases.

What dose of cytarabine (400 mg/m^2/day, 2 g/m^2/day, 3 g/m^2/day, 4 g/m^2/day or 6 g/m^2/day) is the most effective in the consolidation of young acute myeloid leukemia patients with poor or intermediate prognosis [leukocyte count at diagnosis ≥30,000/mm^3, complex karyotypes (≥3 chromosomal abnormalities), secondary acute myeloid leukemia, changes in chromosome 3 or 7]?

P – AML patients with poor or intermediate prognosis [≤60 years, with white blood cell count at diagnosis ≥30,000/mm^3, complex karyotypes (≥3 chromosomal abnormalities), secondary AML, changes in chromosome 3 or 7) undergoing consolidation therapy.

I – Use of cytarabine (400 mg/m^2/day, 2 g/m^2/day, 3 g/m^2/day, 4 g/m^2/day, or 6 g/m^2/day)

C –

O – Complete remission rate, overall survival, and disease-free survival

Young patients, aged 15–64 years old, with *de novo* AML (except promyelocytic leukemia by the FAB classification), who achieved CR after one or two chemotherapy induction cycles were divided into two groups for consolidation therapy. The high-dose group received high doses of cytarabine repeated for three cycles and the standard-dose group received standard doses of cytarabine for four cycles. Patients were evaluated over a mean follow-up period of 48 months (range: 5–78 months).

The high-dose group received 2 g/m^2 in 3-h infusions every 12 h for five days with each cycle starting one week after neutrophil, leukocyte and platelet counts recovery to more than 1.5×10^9/L, 3.0×10^9/L and 100.0×10^9/L respectively. The standard-dose group received several regimens: mitoxantrone (7 mg/m^2/day) in a 30-min infusion for three days or daunorubicin (50 mg/m^2/day) in a 30-min infusion for three days, or aclarubicin (20 mg/m^2/day) in a 30-min infusion for five days or etoposide (100 mg/m^2/day) in a 1-h infusion for five days together with vincristine (0.8 mg/m^2) bolus on Day 8 and vindesine (2 mg/m^2) bolus on Day 10. All of the above regimens were associated with cytarabine (200 mg/m^2/day) as a 24-h continuous infusion for five days. Each consolidation cycle was started as soon as possible after the recovery of the neutrophil, leukocyte and platelet counts.

The 5-year DFS for the high-dose and standard-dose groups were 43% and 39%, respectively (p-value = 0.724). However, when patients with intermediate prognosis were evaluated alone, the 5-year DFS was 38% for the high-dose group and 39% for the standard-dose group (p-value = 0.403) and the 5-year OS were 53% and 54%, respectively (p-value = 0.482). For patients with unfavorable cytogenetics, the 5-year DFS was 19% higher in the high-dose group (33% vs. 14%; p-value = 0.364) and the 5-year OS were 39% (high-dose) and 21% (standard-dose) (p-value = 0.379) (A).[28]

Two other consolidation regimens (IcE and ICE) were evaluated in 15- to 60-year-old patients with *de novo* AML (except promyelocytic leukemia) who achieved CR after one or two induction cycles. The IcE regimen comprises idarubicin (12 mg/m^2/day) on Days 1 and 2 associated with cytarabine (100 mg/m^2/day) in a continuous infusion on Days 1–5 and etoposide (75 mg/m^2/day) in a 1-h infusion on Days 1–7. ICE comprises idarubicin (9 or 12 mg/m^2) bolus on Days 1–3 associated with cytarabine (3 g/m^2) as a 3-h infusions every 12 h on Days 1, 3, 5 and 7 and etoposide (75 mg/m^2/day) on Days 1–5.

Of the 202 patients in remission after induction, 103 received ICE and 99 received IcE. The 3-year relapse-free survival was 49% and 46% for the groups treated with ICE and IcE, respectively, and the 3-year OS was 61% in the group receiving ICE and 62% in the group receiving IcE (95% CI: 51–71% vs. 52–71%, respectively); there was no significant difference between the groups. There was no difference in response between the two consolidation schemes in any of the risk subgroups determined by cytogenetics (A).[29]

Recommendation: In the consolidation of 15- to 64-year-old patients with AML and intermediate or unfavorable prognosis, there is no significant difference in overall survival or disease-free survival using the different doses of cytarabine evaluated.

Which chemotherapy regimen (cytarabine with or without anthracycline and dose of cytarabine) is the most effective in the consolidation of elderly acute myeloid leukemia patients (>60 years)?

P – Elderly patients (>60 years) with AML undergoing consolidation treatment
I – Cytarabine with anthracycline
C – Cytarabine without anthracycline
O – Complete remission rate, overall survival, and disease-free survival

Over 60-year-old patients (61–87 years) with primary or secondary AML (excluding those with severe comorbidities) were followed up for a median of 68 months. Patients received two induction cycles of cytarabine (100 mg/m^2/day) in a seven-day continuous infusion, associated with daunorubicin (45 mg/m^2/day) on Days 3–5, and a consolidation cycle of cytarabine (1 g/m^2) every 12 h on Days 1–5 and ansacrine (100 mg/m^2/day) on Days 1–5. The OS and DFS were 9.7% and 14%, respectively (B).[30]

After induction therapy with cytarabine (100 mg/m^2/day) as a seven-day continuous infusion and daunorubicin (45 mg/m^2/day) or idarubicin (12 mg/m^2/day) for three days, AML patients in CR received consolidation treatment with cytarabine (100 mg/m^2) every 12 h for five days, thioguanine (100 mg/m^2) orally every 12 h for five days and daunorubicin (50 mg/m^2) or idarubicin (15 mg/m^2) on the first day of chemotherapy. The cycles were repeated at 3- to 4-week intervals for three cycles. Over 60-year-old Patients had a mean OS of 235 days in the group that received idarubicin in their consolidation regimen and 209 days in the group that received daunorubicin, with no significant difference between the two groups (p-value = 0.58) (A).[11]

Elderly patients (55–75 years old) with *de novo* AML, excluding those diagnosed with myeloproliferative syndromes, were evaluated after induction therapy with cytarabine associated with daunorubicin or idarubicin, and consolidation therapy with cytarabine (50 mg/m^2/day) subcutaneously for five days together with daunorubicin (30 mg/m^2/day) or idarubicin (8 mg/m^2/day) for three days. There was no significant difference between the two groups in respect to non-hematological toxicity, including sepsis and infectious complications, except for fever that was higher in the group of patients who received idarubicin (p-value = 0.001). The three-year DFS was significantly higher (p-value = 0.016) in the group that received idarubicin rather than daunorubicin (mean of 647 days vs. 283 days) in the subgroup of 65- to 75-year olds (A).[8]

Cytarabine (1 g/m^2) as a 1-h continuous infusion every 12 h for four days associated with daunorubicin (80 mg/m^2/day) or idarubicin (12 mg/m^2/day) on Day 1 of the first cycle and Days 1 and 2 of the second cycle were administered in 50- to 70-year-old patients with *de novo* AML (except AML M3 according to the FAB classification). The estimated event-free survival at two years was 23.5% (95% CI: 19.5–28%) and at four years it was 18% (95% CI: 14–22%). The median OS was 17 months, with estimates for two years of 38% (95% CI: 34–44%) and four years of 26.5% (95% CI: 22–32%) (A).[7]

Of 416 patients aged 65 years or older (median: 72 years) with *de novo* or AML secondary to MDS (FAB: refractory anemia with excess blasts in transformation – RAEB-T), 236 achieved CR after induction with cytarabine (200 mg/m^2/day) for seven days and daunorubicin (45 mg/m^2/day) or idarubicin (9 mg/m^2/day) for four days. If a CR was not achieved by the first induction cycle, a second cycle of cytarabine (500 mg/m^2) was infused over 1 h every 12 h for three days associated with mitoxantrone (12 mg/m^2) every 12 h for two days. Granulocyte-colony stimulating factor was used from Day 9 of treatment until recovery of the bone marrow. Among patients in CR, 164 were randomized between two consolidation groups. The first regimen consisted of one cycle similar to the induction regimen and the second comprised six monthly cycles of daunorubicin (45 mg/m^2) or idarubicin (9 mg/m^2) on Day 1 and cytarabine (60 mg/m^2) subcutaneously every 12 h on Days 1–5. Multivariate analysis showed that the chance of staying alive and in CR were 1.59 and 1.51 times higher for the group receiving six cycles with low-dose cytarabine (p-value = 0.04 and p-value = 0.05, respectively) (A).[4]

Of 693 over 16-year-old patients with *de novo* AML in first CR after induction with standard doses of cytarabine and daunorubicin, 596 were randomized to one of three regimens of four consolidation cycles. The first group received Cytarabine (100 mg/m^2/day) by continuous intravenous infusion for five days, the second received Cytarabine (400 mg/m^2/day) by continuous infusion for five days, and the third group received 3 g/m^2) in a 3-h infusion every 12 h on Days 1, 3 and 5. After a follow-up of 52 months, the probability of CR for over 60-year-old patients was 16% or less for the three cytarabine groups (p-value = 0.19) (A).[27]

Recommendations: There is no consensus on the best consolidation strategy for elderly patients.

Is allogeneic transplant more effective than chemotherapy in the consolidation of young acute myeloid leukemia patients with favorable prognoses and with unfavorable or intermediate prognoses?

P – Young patients with AML favorable, intermediary or unfavorable prognosis undergoing consolidation treatment
I – Chemotherapy
C – Allogeneic transplantation
O – Complete remission rate, overall survival, and disease-free survival

The majority of patients with AML, who achieve CR, relapse after conventional chemotherapy. So far, allogeneic bone marrow transplantation (BMT) is considered the only curative treatment. This procedure influences the OS, but depends on the existence of an HLA-compatible donor and is associated with considerable morbidity and mortality. In this scenario, the definition of to whom receives and when allogeneic transplant is indicated becomes an important issue in the management of AML patients; cytogenetic and molecular factors guide this decision.

A randomized study published by the European Group showed that 16- to 67-year-old patients with advanced MDS or MDS transforming into AML, or AML secondary to MDS with intermediate or unfavorable cytogenetics after 83 months of follow-up, who underwent one or two induction cycles followed by a consolidation cycle with idarubicin 10 mg/m^2/day on Days 4–6 and cytarabine 500 mg/m^2 as a 2-h infusion every 12 h on Days 1–6 were divided into two groups after CR. Patients in first remission who had HLA-compatible donors underwent allogeneic BMT and those without compatible donors were submitted to a second consolidation cycle followed by autologous BMT. The results were better for patients who performed allogeneic BMT with a hazard ratio (HR) in multivariate analysis of 0.58 (99% CI: 0.22–1.5; p-value = 0.14) for OS and 0.46 (95% CI: 0.22–1.5; p-value = 0.08) for DFS (A).[31]

In a meta-analysis, Koreth et al. evaluated the DFS and OS of under 60-year-old AML patients with favorable, intermediate and unfavorable cytogenetics submitted to allogeneic BMT in the first CR after starting chemotherapy compared to patients who continued in chemotherapy. After a follow-up of 19–222 months, no benefit was seen in relation to DFS for the AML group with favorable cytogenetics (HR: 1.06; 95% CI: 0.80–1.42), however the results were better after allogeneic BMT compared to chemotherapy alone for patients with intermediate (HR: 0.76; 95% CI: 0.68–0.85) and unfavorable cytogenetics (HR: 0.69; 95% CI: 0.57–0.84) (A). [32] The OS was better after BMT compared to chemotherapy alone for the intermediate cytogenetics (HR: 0.83; 95% CI: 0.74–0.93) and unfavorable cytogenetics groups (HR: 0.73; 95% CI: 0.59–0.90), but not for the favorable cytogenetics group (HR: 1.07; 95% CI: 0.83–1.38) (A).[32]

The German group monitored 18- to 60-year-old patients with *de novo* or secondary AML and trisomy 8 (+8) alone or with an additional aberration, except t(8;21), inv(16), t(16;16), t(15;17), 11q23 abnormalities or complex karyotypes, who received two cycles of induction chemotherapy, followed by (a) high-dose cytarabine (60%), (b) autologous BMT (14%), or (c) allogeneic BMT (16%) (A).[33] The patients who were submitted to allogeneic BMT were younger than the other two groups [32 (range: 18–55) vs. 51 (range: 19–59) years; p-value = 0.001] but there was no significant difference in the OS between the different consolidation treatment strategies. The 3-year OS rate was 37% (95% CI: 23–52%) for high-dose cytarabine, 34% (95% CI: 3–65%) for autologous BMT and 45% (95% CI: 22–68%) for allogeneic BMT (p-value = 0.63) (A).[33] However, treatment-related mortality was higher for patients submitted to allogeneic BMT compared to those who were not (27% vs. 4%; p-value = 0.01), despite the 3-year relapse rate being lower (27% vs. 69%; p-value = 0.002). This lower probability of relapse was seen in a greater 3-year DFS; 49% (95% CI: 25–72%) for those who underwent allogeneic BMT, 23% (95% CI: 0–51%) for those who received high-dose cytarabine and 28% (95% CI: 14–41%) for those submitted to autologous BMT (p-value <0.05) (A).[33]

Seven hundred and thirty-four 16- to 60-year-old patients were followed up in the European Organization for Research and Treatment of Cancer-Gruppo Italiano Malattie Ematologiche dell'Adulto (EORTC-GIMEMA) AML-10 study. After one or two induction treatment cycles, the patients received a consolidation chemotherapy cycle, and while under 46-year olds with HLA-identical donors were submitted to allogeneic BMT, the remaining patients underwent autologous BMT. The 4-year DFS was 52.2% for patients who underwent allogeneic BMT compared to 42.2% for those submitted to autologous BMT (HR: 0.80; 95% CI: 0.64–0.99; p-value = 0.44). The incidence of relapse was 30.4% for the allogeneic BMT group compared to 52.5% after autologous BMT. The OS was 58.3% vs. 50.8% for allogeneic and autologous BMT, respectively. The DFS in patients with or without HLA-identical donors was similar in patients with low- and intermediate-risk cytogenetics. However, the DFS was 43.4% and 18.4% for allogeneic and autologous BMT, respectively in patients with high-risk cytogenetics. This difference was even more pronounced in young (15–35 years old) patients (p-value = 0.036) (A).[34] Therefore, the strategy to perform allogeneic BMT early in first CR has led to better results of survival, especially in younger patients and those with unfavorable risk cytogenetics (p-value = 0.18) (A).[34]

Brunet et al. evaluated 16- to 60-year-old patients with AML (except M3 by FAB classification) with no history of MDS or previous use of cytotoxic drugs or radiation. Patients were submitted to induction therapy with one or two cycles of ICE chemotherapy [idarubicin (10 mg/m^2/day) as 30-min infusions on Days 1, 3 and 5, cytarabine (100 mg/m^2/day) as continuous infusions on Days 1–10 and etoposide (100 mg/m^2/day) as 1-h infusions on Days 1–5]. This was followed by a consolidation cycle with intermediate-dose cytarabine (500 mg/m^2) as 2-h infusions every 12 h on Days 1–6 associated with mitoxantrone (12 mg/m^2/day) over 15 min on Days 4–6 and then patients were stratified into different intensification treatments depending on age and cytogenetic risk. Patients with low-risk cytogenetics received two cycles of cytarabine (3 mg/m^2) as 2-h infusions every 12 h on Days 1, 3 and 5. Allogeneic BMT was performed in under 50-year-old patients with intermediate- or high-risk cytogenetics and HLA-identical donors, and autologous BMT was performed in over 50-year olds or those without HLA-identical donors. The groups were evaluated for treatment-related mortality, OS and DFS.

Treatment-related mortality was 23 ± 9% for allogeneic BMT; 3 ± 3% for under 50-year olds who underwent autologous BMT; 23 ± 6% for over 50-year olds submitted to autologous BMT and 14 ± 7% for those who received the high-dose cytarabine regimen. There was no significant difference between the different treatment regimens in respect to the 4-year OS (41 ± 9%, 52 ± 8%, 38 ± 8%, and 61 ± 6%, respectively). A significant difference was observed for the DFS only in over 50-year-old patients who underwent autologous BMT compared to those under 50 who also were submitted to autologous BMT (48% ± 8 vs. 17 ± 9%, respectively; p-value = 0.03) (A).[35] In this study, the DFS in under 50-year-old patients was similar in the groups submitted to autologous and allogeneic BMT.

Recommendation: Allogeneic transplant is more effective in young patients with HLA-identical donors and unfavorable or intermediate-risk cytogenetics. Candidates for allogeneic BMT are defined as individuals in first complete remission after the initiation of treatment with unfavorable or intermediate-risk cytogenetics; these patients have evident improvement in overall survival rates and disease-free survival. There is no proven benefit for patients with favorable cytogenetics.

Is autologous transplant more effective than chemotherapy in the consolidation of young acute myeloid leukemia patients with favorable prognosis and in patients with unfavorable or intermediate cytogenetic?

P – Young patients with AML favorable, intermediary or unfavorable prognosis undergoing consolidation treatment
I – Chemotherapy
C – Autologous transplantation
O – Complete remission rate, overall survival, and disease-free survival

The best strategy after intensification of remission for AML patients with favorable risk or intermediate risk and without a compatible bone marrow donor is still widely debated, given that there is no robust evidence for therapeutic modalities apart from allogeneic transplantation, which is considered the only curative alternative.

Nathan et al. published a meta-analysis comparing a group of patients in first remission submitted to autologous hematopoietic stem cell transplantation (HSCT) to a group who received intensive chemotherapy. Six studies totaling 1044 patients randomized for autologous HSCT or intensive chemotherapy were included the meta-analysis. The authors concluded that patients who received autologous HSCT had better DFS, but the OS was similar in both groups (A).[36]

Another randomized study evaluated 16- to 67-year old patients with advanced MDS, MDS transforming into AML or AML secondary to MDS, who after achieving CR, received consolidation therapy of high-dose cytarabine. Patients who did not have a HLA-compatible donor were submitted to autologous HSCT or a second cycle of high-dose cytarabine. The 4-year OS of patients submitted to autologous HSCT or a second consolidation cycle of high-dose cytarabine was 37% and 27%, respectively. The HRs in multivariate analysis were 1.22 (95% CI: 0.65–2.27) for OS and 1.02 (95% CI: 0.56–1.85) for DFS (A).[31]

Another publication analyzed 18- to 60-year-old patients with *de novo* or secondary AML and trisomy 8 (+8) alone or with an additional aberration (except t(8;21), inv(16), t(16;16), t(15;17) abnormality 11q23, or complex karyotype), who received two induction cycles, followed by a high-dose cytarabine (60%), autologous HSCT (14%) or allogeneic HSCT (16%). There was no significant difference in the OS between the three regimens. The 3-year OS was 37% (95% CI: 23–52%) for high-dose cytarabine, 34% (95% CI: 3–65%) for autologous BMT and 45% (95% CI: 22–68%) for allogeneic BMT (p-value = 0.63) (A).[32] However, the treatment-related mortality was higher for patients submitted to allogeneic BMT than those of the other regimens (27% vs. 4%; p-value = 0.01), despite the 3-year relapse rate being lower (27% vs. 69%; p-value = 0.002). This lower probability of relapse is seen in the higher 3-year DFS: 49% (95% CI: 25–72%) for those who underwent allogeneic BMT, 23% (95% CI: 0–51%) for those who received high-dose cytarabine and 28% (95% CI: 14–41%) for those submitted to autologous BMT (p-value <0.05) (A).[33]

Moreth et al., in a systematic review, analyzed 24 clinical trials involving under 60-year-old patients with *de novo* or secondary AML with follow-ups of 1–222 months. Patients with a HLA-compatible donor after the first CR underwent allogeneic BMT, while those without a HLA-compatible donor received autologous BMT or chemotherapy or both. The three groups were compared and the HR for relapse and death due to allogeneic BMT was 0.80 (95% CI: 0.74–0.86). The allogeneic BMT procedure provided significant benefits in respect to the DFS in high-risk (HR 0.69; 95% CI: 0.57–0.84) and intermediate-risk cytogenetics patients (HR 0.76; 95% CI: 0.68–0.85), but there was no significant benefit for low-risk patients (HR: 1.06; 95% CI: 0.80–1.42) (A).[32]

In a prospective study of 16- to 60-year-old AML patients (except M3 by the FAB classification) with no history of MDS or previous use of cytotoxic drugs or radiation, patients were stratified by risk related to cytogenetics and age after induction therapy. Favorable cytogenetics was defined as t(8;21) and inv(16), and the cut off point for indicating for allogeneic HSCT was 50 years old. After stratification depending on age and cytogenetic risk, patients were evaluated for treatment-related mortality, OS and DFS. Low-risk patients received two cycles of cytarabine (3 g/m^2) as 2-h infusions every 12 h on Days 1, 3 and 5. Under 50-year-old patients with intermediate- or high-risk cytogenetics and HLA-identical donors were submitted to allogeneic BMT, and over 50-year olds and individuals without HLA-identical donors underwent autologous BMT. The treatment-related mortality was $23 \pm 9\%$ for allogeneic BMT, $3 \pm 3\%$ for autologous BMT in under 50-year olds and $23 \pm 6\%$ for over 50-year olds and $14 \pm 7\%$ for those who received high-dose cytarabine. There was no significant difference in the 4-year OS between the different regimens ($41 \pm 9\%$, $52 \pm 8\%$, 38 ± 8 and $61 \pm 6\%$, respectively). A significant difference was observed for the DFS only for under 50-year-old patients who underwent autologous BMT compared to over 50-year olds also submitted to autologous BMT ($48\% \pm 8$ vs. $17 \pm 9\%$, respectively; p-value = 0.03) (A).[35] This study found that age, cytogenetics and white blood cell count at diagnosis are the adverse factors most associated with relapse. Of the low-risk cytogenetics patients who did not receive transplants, those with t(8;21) had higher DFS than those with inv(16). In terms of leukemia-free survival, the results of autologous and allogeneic transplants were similar when the mortality associated with allogeneic BMT is considered (A).[35]

In an analysis of 16- to 60-year-old patients in the EORTC-GIMEMA AML-10 study, patients received one consolidation chemotherapy cycle after one or two induction treatment cycles. Under 46-year olds with HLA-identical donors were submitted to allogeneic BMT and the remaining patients

underwent autologous BMT. The 4-year DFS was 52.2% for patients who underwent allogeneic BMT compared to 42.2% for those submitted to autologous BMT (HR: 0.80; 95% CI: 0.64–0.99; p-value = 0.44)(A).[34] The relapse rate was lower in allogeneic BMT than in autologous BMT (30.4% vs. 52.5%, respectively). The OS was 58.3% vs. 50.8% in allogeneic and autologous BMT, respectively (p-value = 0.18) (A).[34] The DFS in patients with or without HLA-identical donors was similar for those with low- and intermediate-risk cytogenetics. However, the DFS was 43.4% and 18.4% for allogeneic and autologous BMT, respectively in patients with high-risk cytogenetics. This difference was even more pronounced in young (15–35 years old) patients (p-value = 0.036) (A).[34] In this study, early allogeneic BMT led to better outcomes in patients with intermediate- and high-risk cytogenetics (A).[34]

Recommendations: Autologous bone marrow transplantation or intensive chemotherapy with cytarabine are indicated for patients without HLA-compatible donors or with favorable cytogenetics. However, there is controversy about the best consolidation treatment option for patients at intermediate risk, who are not candidates for allogeneic transplantation.

What are the complete remission, overall survival and disease-free survival rates for acute myeloid leukemia patients with favorable cytogenetics submitted to chemotherapy?

P – Adult patients with AML and karyotype considered favorable
I – Chemotherapy
C –
O – Complete remission rate, overall survival, disease-free survival

Two hundred and seventy-eight 50- to 70-year-old AML patients were analyzed, 33% (93 patients) of whom had mutations of the NPM1 gene (nucleofosmine 1), and 79 had type A, B or D mutations. All were previously treated with induction chemotherapy using daunorubicin (60 mg/m^2/day) on Days 1–3 and cytarabine (200 mg/m^2/day) as a continuous infusion on Days 1–7. Of the patients with NPM1 mutations, 74.2% achieved CR and of these, 65.6% were tested for minimal residual disease (MRD); results were positive in 46 and negative in 15 patients. The mutation conferred a 3.66-fold risk of relapse (95% CI: 1.10–12.15; p-value = 0.035), but no significant impact on the OS of patients (A).[37]

NPM1-positive and NPM1-negative patients in the group of FLT3-ITD-negative individuals were compared; there was a 7% lower OS rate (95% CI: 0.2–0.4; p-value <0.001) and an 8% lower DFS rate for NPM1-positive individuals (95% CI: 0.1–0.3; p-value <0.001) (A).[38]

Seventy patients diagnosed with AML with a mean age of 66 years (23–87 years) treated with fludarabine (30 mg/m^2/day) on Days 1–4, cytarabine (2 g/m^2/day) every 12 h on Days 1–4 and idarubicin (12 mg/m^2/day) on Days 2–4 were evaluated for the presence of the NPM1 mutation; 20 patients (29%) had the mutation. Thirty-six patients (51%) were treated with all trans-retinoic acid (ATRA) in combination with chemotherapy. The CR rate was 63% with no difference between patients with or without the NPM1 mutation (70 vs. 60%; p-value = 0.43) and there was no significant difference between patients who received ATRA and those who did not (71% vs. 69%; p-value = 0.62). The addition of ATRA in the induction therapy did not increase the OS, DFS or event-free survival (A).[39]

The MRD was analyzed in 278 AML patients, 163 with t(8;21) and 115 with inv(16) mutations after induction therapy [AD (cytarabine and daunorubicin), ADE (cytarabine, daunorubicin and etoposide) or FLAG-Ida (fludarabine, cytarabine, idarubicin, and filgrastim)] and after consolidation [MACE (Amsacrine, cytarabine, and etoposide) or MidAC (Mitozantrone and cytarabine) or two doses of Ara-C]. Patients were also randomized to receive gemtuzumab ozogamicin in the induction and/or consolidation therapy. The average follow-up was 36 months (range: 2–79 months). The overall CR for patients with the t(8;21) and inv(16) mutations were 97% and 92%, respectively, and the cumulative incidences of relapse were 18% and 23%, respectively. The evaluation of MRD by quantitative reverse transcription polymerase chain reaction (RT-PCR) was negative in peripheral blood and bone marrow samples of 8% of patients with t(8;21) after induction therapy, in 40% after the consolidation cycles and 70% after the follow-up. For the inv(16) mutation, the results were negative in peripheral blood and bone marrow samples for 6% of the patients after induction, 44% after three cycles of consolidation and 69% after the follow-up (A).[40]

Mutational analysis of 18 genes was carried out in 398 under 60-year-old AML patients who were randomly assigned to receive high-dose or standard-dose induction therapy with daunorubicin. At least one somatic change was identified in 97.3% of the patients. Among the changes, positivity for the CEBPα, t(8;21) and inv(16) mutations were associated with better OS (p-value = 0.05, p-value <0.001 and p-value <0.001, respectively). The favorable effect of the NPM1 mutation was restricted to patients with the NPM1 and IDH1 or IDH2 mutations. The 3-year OS for these patients with favorable cytogenetics was 19%. Patients with the NPM1 mutation submitted to induction therapy with high-dose daunorubicin had an OS of 44% compared with 25% of those who received standard doses (A).[41]

The molecular profile of 135 AML patients with normal karyotype was evaluated after consolidation treatment with chemotherapy alone (n = 41) following one autologous transplantation (n = 40), two autologous transplants (n = 17) or after allogeneic transplants (n = 37). Forty-six (34%) FLT3-ITD-negative patients were positive for NPM1 mutations while the remaining patients had other molecular changes. The mean follow-up was 86 months (range: 16–118 months). In the univariate analysis, the 4-year leukemia-free survival and OS were significantly higher in NPM1-positive/FLT3-ITD-negative patients compared to the group with other molecular changes (61% vs. 43% and 72% vs. 48%; p-value = 0.02 and p-value = 0.01, respectively). For the NPM1-positive/FLT3-ITD-negative group,

there was no benefit with other proposed consolidation regimens (4-year leukemia-free survival of 71% for allogeneic HSCT, 56% for autologous HSCT and 60% for chemotherapy, with OS of 73%, 71% and 60%, respectively; p-value > 0.05) (A).[42]

The response to ATRA associated to daunorubicin, cytarabine and thioguanine (DAT) was investigated in the induction therapy of 1075 non-promyelocytic AML patients. The NPM1 and CEPBA mutations were identified in 207 and 35 patients, respectively. The 8-year OS for the group with the NPM1 mutation was 47% when treated with ATRA and 39% without ATRA, while it was 35% and 47%, respectively for those with the CEBPA mutation. The 8-year relapse-free survival for the group with the NPM1 mutation was 42% in the group treated with ATRA and 37% in the group without ATRA, and with the CEBPA mutation, it was 28% and 29%, respectively (A).[43]

Recommendations: The 3-year overall survival (OS) was 19% for adult non-promyelocytic AML patients with favorable cytogenetic changes [t(8;21) or inv(16)] using the different therapeutic modalities. The CR was 97% for the t(8,21) mutation and 92% for inv(16).
In NPM1-positive/FLT3-ITD-negative patients, the CR ranges from 63% to 74.2%; the 8-year OS ranges from 39% to 47%. The 4-year leukemia-free survival for patients with the NPM1 mutation is 61% and at 8 years, it is 37–42%.
For the CEBPα mutation, the 8-year OS ranges from 35% to 47% and leukemia-free survival ranges from 28% to 29%.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A.

PICO 1
Which anthracycline agent is the most effective in inducing remission of acute myeloid leukemia?

P – Patients undergoing induction treatment for AML
I – Anthracycline agent (daunorubicin, doxorubicin, idarubicin)
C –
O – Complete remission rate, overall survival, and disease-free survival

((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4530
1st Selection: 11 articles

PICO 2
What dose (100 mg/m^2/day and 200 mg/m^2/day) of cytarabine (Ara-C or Arabinoside-C) is the most effective in the induction therapy of acute myeloid leukemia patients?

P – Patients undergoing induction treatment for AML
I – Cytarabine or Ara-C or Arabinoside-C – 100 mg/m^2/day
C – Cytarabine or Ara-C or Arabinoside-C – 200 mg/m^2/day
O – Complete remission rate, overall survival, and disease-free survival

((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Cytarabine) AND (Therapy/broad [filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4530
1st Selection: 5 articles

PICO 3
What dose of daunorubicin (45, 60 or 90 mg/m^2/day) is the most effective for induction therapy of acute myeloid leukemia in young patients (<60 years)?

P – Under 60-year-old patients undergoing induction treatment for AML
I – Daunorubicin (45, 60 or 90 mg/m^2/day)
C – Daunorubicin (45, 60 or 90 mg/m^2/day)
O – Complete remission rate, overall survival, and disease-free survival

((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4533
1st Selection: 3 articles

PICO 4
What dose of daunorubicin (45, 60 or 90 mg/m^2) is the most effective for induction therapy of acute myeloid leukemia in elderly patients (>60 years)?

P – Over 60-year-old patients undergoing induction treatment for AML
I – Daunorubicin (45, 60 or 90 mg/m^2)
C – Daunorubicin (45, 60 or 90 mg/m^2)
O – Complete remission rate, overall survival, and disease-free survival

((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4533
1st Selection: 2 articles

PICO 5

Q What is the number of induction cycles (1 or 2) that is the most effective in the induction of acute myeloid leukemia patients?

P – Patients undergoing induction treatment for AML
I – One cycle of chemotherapy
C – Two cycles of chemotherapy
O – Complete remission rate, overall survival, and disease-free survival

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((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4533
1st Selection: 4 articles

PICO 6

What dose of cytarabine (400 mg/m^2 or 1 g/m^2 or 1.5 g/m^2 or 3 g/m^2) is the most effective in the consolidation treatment of young acute myeloid leukemia patients?

P – Patients undergoing induction treatment for AML
I – Use of cytarabine (400 mg/m^2/day, 1 g/m^2, 1.5 g/m^2 or 3 g/m^2)
C –
O – Complete remission rate, overall survival, and disease-free survival

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((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4530
1st Selection: 3 articles

PICO 7

What dose of cytarabine (400 mg/m^2/day, 2 g/m^2/day, 3 g/m^2/day, 4 g/m^2/day or 6 g/m^2/day) is the most effective in consolidating young acute myeloid leukemia patients with favorable prognosis [<60 years, leukocyte count at diagnosis <30,000 or <50,000/mm^3 with cytogenetics: t(8;21)/AML1-ETO/RUNX1-RUNX1T1, inv(16)/t(16;16)/CBFbeta/MYH11, Core binding factor leukemia, FLT3-negative or FLT3-ITD-negative/NPM1-mutated]?

P – AML patients with favorable prognosis [<60 years, with white blood cell count at diagnosis <30,000 or <50,000/mm^3 with cytogenetics t(8;21)/AML1-ETO/RUNX1-RUNX1T1, inv(16)/t(16;16)/CBFbeta/MYH11, Core binding factor leukemia, FLT3-negative or FLT3-ITD-negative/NPM1-mutated]
I – Use of cytarabine (400 mg/m^2, 2 g/m^2/day, 3 g/m^2/day 4 g/m^2/day, or 6 g/m^2/day)
C –
O – Complete remission rate, overall survival, and disease-free survival

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((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4530
1st Selection: 4 articles

PICO 8

What dose of cytarabine (400 mg/m^2/day, 2 g/m^2/day, 3 g/m^2/day, 4 g/m^2/day or 6 g/m^2/day) is the most effective in the consolidation of young acute myeloid leukemia patients with poor or intermediate prognosis [leukocyte count at diagnosis ≥30,000/mm^3, complex karyotypes (≥3 chromosomal abnormalities), secondary acute myeloid leukemia, changes in chromosome 3 or 7]?

P – AML patients with poor or intermediate prognosis [≥60 years, with white blood cell count at diagnosis ≥30,000 or <50,000/mm^3 complex karyotypes (≥3 chromosomal abnormalities), secondary AML, changes in chromosome 3 or 7) undergoing consolidation therapy.
I – Use of cytarabine (400 mg/m^2/day, 2 g/m^2/day, 3 g/m^2/day, 4 g/m^2/day, or 6 g/m^2/day)
C –
O – Complete remission rate, overall survival, and disease-free survival

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((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4530
1st Selection: 2 articles

PICO 9

Which chemotherapy regimen (cytarabine with or without anthracycline and dose of cytarabine) is the most effective in the consolidation of elderly acute myeloid leukemia patients (>60 years)?

P – Elderly patients (>60 years) with AML undergoing consolidation treatment
I – Cytarabine with anthracycline
C – Cytarabine without anthracycline
O – Complete remission rate, overall survival, and disease-free survival

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((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4530
1st Selection: 5 articles

PICO 10

Is allogeneic transplant more effective than chemotherapy in the consolidation of young acute myeloid leukemia patients

with favorable prognoses and with unfavorable or intermediate prognoses?
P – Young patients with AML favorable, intermediary or unfavorable prognosis undergoing consolidation treatment
I – Chemotherapy
C – Allogeneic transplantation
O – Complete remission rate, overall survival, and disease-free survival

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((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4530
1st Selection: 5 articles

PICO 11
Is autologous transplant more effective than chemotherapy in the consolidation of young acute myeloid leukemia patients with favorable prognosis and in patients with unfavorable or intermediate cytogenetic?
P – Young patients with AML favorable, intermediary or unfavorable prognosis undergoing consolidation treatment
I – Chemotherapy
C – Autologous transplantation
O – Complete remission rate, overall survival, and disease-free survival

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((Leukemia, Myeloid, Acute) NOT (Leukemia, Promyelocytic, Acute OR Promyelocytic) AND (Daunorubicin OR Doxorubicin OR Idarubicin OR Amsacrine OR Cytarabine) AND (Therapy/broad[filter] OR Comparative study OR Comparative studies OR Epidemiologic methods)) = 4530
1st Selection: 6 articles

PICO 12
What are the complete remission, overall survival and disease-free survival rates for acute myeloid leukemia patients with favorable cytogenetics submitted to chemotherapy?
P – Adult patients with AML and karyotype considered favorable
I – Chemotherapy
C –
O – Complete remission rate, overall survival, disease-free survival

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(Acute Myeloid Leukemia OR Leukemia, Acute Myelogenous OR Leukemia, Myeloblastic, Acute OR Leukemia, Myelocytic, Acute OR Leukemia, Myelogenous, Acute OR Leukemia, Nonlymphoblastic, Acute OR Leukemia, Nonlymphocytic, Acute OR AML) AND (genetic mutation OR chromosome aberrations OR chromosome abnormalities OR mutation* OR Core Binding Factor alpha Proteins OR Runx Proteins OR Polyomavirus Enhancer A Binding Protein 2 OR Polyomavirus Enhancer Binding Protein 2, Alpha Subunit OR Runt Domain Factor OR Acute Myeloid Leukemia Proteins OR PEBP2A Transcription Factors OR Transcription Factors, PEBP2A OR CEBPA OR t(8:21) OR t(16) OR inv(16) OR inv(16) fusion protein, human OR NPM1 OR FLT3) AND random* = 73
1st Selection: 7 articles

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