



## Original article

# Current treatment preferences in acute myeloid leukemia: a survey in Brazil



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## ABSTRACT

**Introduction:** : Most adults with acute myeloid leukemia (AML) will eventually relapse from their disease. The combination of 7-day cytarabine and an anthracycline on days 1–3 (the so called “7 + 3” regimen) can be considered standard of care of younger patients with AML. However, the treatment of the elderly ineligible for intensive chemotherapy remains a challenge. Low-dose of subcutaneous cytarabine or hypomethylating agents (HMA) have been studied this group. There are no studies investigating physician practice variation in treating AML in Brazil.

**Methods:** : We developed a survey with ten questions in order to explore the approach to AML in Brazil.

**Results:** : The sample size comprised 100 hematologists. Most reported regular (63%) or occasional (29%) treatment of AML patients. Karyotype analysis and polymerase chain reaction were available in 88% and 71% of institutions, respectively. Next generation sequencing analysis was used in 7% of institutions. Younger patients receive the “7 + 3” protocol with continuous infusion of cytarabine and anthracycline in 98% of cases. The preferred anthracycline is daunorubicin (64%), followed by idarubicin (34%). The most prescribed daunorubicin dose was 60 mg/m<sup>2</sup> (56%). Consolidation after CR with high cytarabine doses (HIDAC) was indicated by 84% of hematologists and 70% use 3 g/m<sup>2</sup> twice a day for 3 days. Elderly and unfit patients received HMA (47%) as the preferred treatment.

**Conclusion:** : We showed that the most prevalent AML treatments were according to current guidelines. There is room to improve on the availability of diagnostic tools and the capacity to perform bone marrow transplantation.

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## Introduction

Despite substantial progress in the treatment of newly diagnosed acute myeloid leukemia (AML), most adults will eventually relapse from their disease.<sup>1</sup> The combination of 7-day cytarabine and an anthracycline on days 1–3 (the so called “7+3” regimen) can be considered standard of care of younger patients with non-promyelocytic AML. After obtaining complete remission (CR), the administration of several consolidation courses using higher doses of cytarabine has been the most common option for younger patients, with few exceptions.<sup>2</sup>

The treatment of the elderly ineligible for intensive chemotherapy remains a challenge. Low-dose of subcutaneous cytarabine or hypomethylating agents (HMA) have been studied this group, but the treatment outcome is inferior compared with that of younger patients.<sup>3,4</sup>

In a recent publication, the *Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular* (ABHH) recommended the “7+3” regimens with cytarabine 100 mg/m<sup>2</sup> plus daunorubicin (60–90 mg/m<sup>2</sup>) and considered that idarubicin did not improve the rate of CR. For consolidation after CR, the same guideline considered that there are no studies comparing the doses of 1–3 g/m<sup>2</sup>/day, but cytarabine 6 g/m<sup>2</sup>/day for three days seems to be associated with increased toxicity. Finally, no definitive strategy was proposed for induction or consolidation treatment of the elderly.<sup>5</sup>

There are no studies investigating physician practice variation in treating AML in Brazil.

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## Methods

We developed a survey to explore the approach to AML in Brazil. Ten questions were developed for this survey. Four questions queried the type of institution and available diagnostic tools. Five presented clinical scenarios and elicited treatment decisions. One final question tried to identify new drugs to be incorporated in AML treatment. The Portuguese language was used for writing the questions and all questions are listed in the Appendix. The respondents, all with expertise in the treatment of AML, were contacted by using the email list from the ABHH that comprised a population of 2621 hematologists. The questionnaire was available online from March 15, 2018 to May 11, 2018. The first 100 responses were selected for analysis. The questions were answered online using a software designed for professional surveys (Survey Monkey™). A strategy preferred for more than 50% of responders was considered typical. Descriptive statistics were reported for practice characteristics.

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## Results

### Physicians and institutional characteristics

The sample size comprised 100 hematologists from Brazil. Physicians considered themselves as AML specialists in 4% of cases. Four (4%) treat AML patients only in the context of

bone marrow transplantation. Most reported regular (63%) or occasional (29%) treatment of AML patients.

Hospitals were classified as private, public, university hospital or mixed (public and private) in 29%, 14%, 22% and 35% of cases, respectively. Karyotype analysis and polymerase chain reaction (for some mutations) are available in 88% and 71% of institutions, respectively. Next generation sequencing analysis is used in 7% of institutions. Autologous, allogeneic, matched unrelated and haploidentical stem-cell transplants are performed in 34%, 45%, 4% and 29% of hospitals, respectively. In addition, 45% of hospitals do not execute transplants for treating AML.

### Medical decision making

Younger patients selected to intensive chemotherapy receive the “7+3” protocol with continuous infusion of cytarabine and anthracycline in 98% of cases. The preferred anthracycline is daunorubicin (64%), followed by idarubicin (34%). The daunorubicin (DNR) dose varies from 45 mg/m<sup>2</sup> (4%) to 90 mg/m<sup>2</sup> (19%), but the most prescribed dose is 60 mg/m<sup>2</sup> (56%). Bone marrow evaluation fourteen days after the beginning of chemotherapy (D14) is recommended by 55% of physicians and 43% evaluate the bone marrow after ≥21 days. Consolidation after CR, if transplant is not planned, with high cytarabine doses (HIDAC) is indicated by 84% of hematologists and 70% use 3 g/m<sup>2</sup> twice a day for 3 days (6 doses). Analysis of respondents showed a wider variation in management approaches to elderly and unfit patients. HMA is the preferred treatment (47%), mainly azacytidine (31%). Low cytarabine doses and hydroxyurea are the choice to 32% and 9%, respectively, followed by palliative care (5%) and inclusion in a clinical trial (3%).

### New drugs for treating AML

The new drugs expected for more than 50% of physicians were midostaurin (63%) and gentuzumab ozogamicin (52%). These were followed by sorafenib (46%), venetoclax (36%), CPX-351 (17%), enasidenib (11%), quizartinib (9%) and bortezomib (6%).

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## Discussion

We showed that the typical treatment sequence (>50% of cases) for younger patients with AML was chemotherapy with “7+3”, using 60 mg/m<sup>2</sup> of daunorubicin, with of bone marrow evaluation on day 14. After CR, high dose cytarabine with 3 g/m<sup>2</sup> twice a day for 3 days (six doses) was used for consolidation. The treatment of elderly and unfit patients was heterogeneous but HMA were more frequent.

The “7+3” protocol remained the standard treatment of AML for more than 40 years. In the late 1980s, idarubicin was introduced and randomized trials reported higher CR rates for idarubicin. Meta-analyses comparing regimens containing idarubicin, high dose daunorubicin and conventional dose daunorubicin (45 mg/m<sup>2</sup>) showed that the conventional dose produced inferior CR rates. Moreover, daunorubicin is considered equivalent to idarubicin if the relative dose ratio (daunorubicin/idarubicin) is ≥5.<sup>6,7</sup> We found in this study

that the most prescribed anthracycline was daunorubicin (60 mg/m<sup>2</sup>), that is according to current practices.

Treatment choice for younger patients may include bone marrow transplantation and usually depends on leukemia risk stratification. Since cytogenetically normal AML (CN-AML) occurs in approximately 50% of newly diagnosed cases, molecular genetic analysis is highly recommended. However, this technology is not available in ~30% of our institutions. Moreover 45% of institutions are not able to perform bone marrow transplants. Although the median age at diagnosis is around 70 years, the treatment of elderly and unfit patients with AML remains controversial.<sup>8</sup> As expected for this group, we noticed a considerable variation in medical decision among physicians. No strategy was preferred for more than 50% of physicians. Inclusion in a clinical trial can be considered a good option but was not a frequent strategy (only 3%), reflecting the low prevalence of ongoing clinical trials in Brazilian institutions.

Given the relatively small numbers of subjects in our study, clear-cut inference regarding AML treatment choices may be biased.

In the year 2017 the US Food and Drug Administration approved four new drugs for treating AML patients: midostaurin, enasidenib, gemtuzumab ozogamicin (GO) and CPX-351. Since this survey was launched in the first semester of 2018, it was expected that physicians were eager for the incorporation of these four drugs. However, the drugs sorafenib and venetoclax were highly awaited in comparison with enasidenib and CPX-351.

## Conclusion

The most prevalent AML treatments were according to current guidelines. There is room to improve on the availability of diagnostic tools and the capacity to perform bone marrow transplantation. The incorporation of emerging drugs is highly expected by most of physicians.

## Conflicts of interest

The authors declare no conflicts of interest.

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