Clinical outcomes of AML patients treated with Azacitidine in Portugal: A retrospective multicenter study

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ABSTRACT

Retrospective data was collected from 77 elderly acute myeloid leukemia (AML) patients treated with Azacitidine (AZA) and 50 elderly AML patients treated with intensive chemotherapy (IC) from 4 Portuguese Hospitals.

Median OS was 10.6 months in those receiving AZA as 1st line. Response (overall response rate 44%) had a significant impact on overall survival (p= < 0.0001). Median OS of the comparator IC cohort was significantly inferior to that observed in the cohort treated with AZA in first line (p=0.0104).

These results support the efficacy of AZA in AML in the elderly in any line of treatment.

1. Introduction

Acute Myeloid Leukemia (AML) is a clinically, morphologically and genetically heterogeneous disease characterized by clonal expansion of myeloid blasts in peripheral bone marrow (BM), blood or other tissues [1]. The incidence of AML increases with age, particularly after 65 years old, and the median age at diagnosis is around 70 years [2]. Age in itself is one of the most powerful prognostic factors for survival in AML [3–5]. Elderly patients not only present more comorbidities and worse performance status [6] but also have more adverse molecular features compared to younger patients [7–9]. Due to the presence of comorbidities and poor performance status, intensive chemotherapy (IC) or allogeneic stem cell transplant is often unsuitable for a large proportion of elderly patients with AML, resulting in early mortality and prolonged hospitalization [5,10]. However, when feasible, treatment is associated with better survival when compared to best supportive care only but the median overall survival achieved with IC in the elderly is only 5–13 months [11,12]. Therefore, there is an increasing need for new treatment options for elderly patients with AML.

The AZA-001 phase III trial has demonstrated effectiveness of azacitidine (AZA) in a dose of 75 mg/m2 daily for 7 consecutive days in patients with high-risk myelodysplastic syndromes [13]. A subset analysis of the AZA-001 trial restricted to patients with 20–30% BM blasts [14], demonstrated superior efficacy of AZA when compared with conventional care regimens, leading to AZA international approval for the treatment of low BM blast count (20–30%) WHO-defined AML.

These results raise the question of the potential use of AZA in AML irrespectively of the BM blast count. This is supported by the identification of somatic mutations of genes involved in epigenetic regulation in approximately 30% of AML patients [15]. Consequently several groups have assessed and reported the efficacy of AZA in patients with AML [16–19]. More recently a randomized phase III trial comparing first-line AZA to conventional therapies, including intensive chemotherapy, in elderly patients with AML revealed that AZA achieved clinically meaningful survival benefit compared to conventional treatments [20].

We present herein a multi-centre retrospective analysis of 77 AML patients who were treated with AZA in first line or due to relapsed / refractory disease. The main aim was the characterization of the efficacy and safety of AZA treatment in elderly AML patients. We also conducted an exploratory comparison of overall survival between patients receiving 1st line treatment with AZA and elderly AML patients treated with IC alone.
## 2. Methods

Patients with AML, who received at least 1 cycle of AZA, were selected for inclusion. The comparator group comprised 50 matched patients from a historical cohort of AML patients from a single Institute. These patients were treated with IC and never received AZA.

Patient data was collected retrospectively from patient files from 4 Portuguese Institutions following written informed consent. The study was approved by the Ethical Committee of Instituto Português de Oncologia de Lisboa, Francisco Gentil, EPE and all data treated according to the Declaration of Helsinki.

Responses were defined according to IWG criteria [21].

Overall survival (OS) was defined as time from start of treatment with AZA (either 1st or 2nd line) or ICT (1st line) to death from any cause or last follow-up. Patients were censored at the time of BMT but not of other subsequent treatments.

Progression-free survival (PFS) was defined as time from start of treatment until disease relapse/progression or death from any cause. Patients were censored at the time of BMT.

OS and PFS were estimated using the Kaplan-Meier method. Survival curves of the different treatment groups were compared using the log-rank test (univariate analysis). All tests were two-tailed and P-values less than 0.05 were considered to be statistically significant. All analyses were performed using R¹[22].

## 3. Results

Seventy-seven patients treated with AZA and 50 elderly AML patients treated with ICT were included.

Table 1 shows the demographic and diagnostic data for the AZA and ICT treated cohorts. It is noteworthy that almost half the population treated with AZA had secondary AML and that one fifth had high risk cytogenetics. Of the patients treated with AZA in 2nd line, 4 had <5% blasts at the time of AZA start and were deemed unfit for consolidation chemotherapy. A further five had 5–20% blasts with dysplastic features after induction.

Other than higher age in the ICT control group, there was no significant difference between patients treated with AZA or ICT in first line.

Treatment details are shown in Table 2. All patients received the standard AZA regimen (75 mg/m² 1–7) except for 35 patients treated at IPOFGL, who received 100 mg/m² 1–5 [23]. AZA was used as first line therapy in 51 (66%) of patients. All those who were treated in second line had received IC as first line treatment and had refractory or relapsed disease. All patients were treated with AZA until progression or death with no limit to the number of cycles.

Between start of AZA and last follow up, 43% of patients required hospital admissions. Median duration of hospital stay was 10 days (range 1–60). Half of these were due to disease progression and unrelated to AZA treatment. Only 39% of admissions were attributed to infectious complications during treatment.

### 3.1. Treatment outcomes

Responses were assessed by bone marrow examination after a median of 4 cycles of AZA and after induction chemotherapy in the ICT group. Table 3 summarizes the responses obtained. In the AZA treated cohort, marrow responses were achieved in 44% of the total cohort, 30% of which were complete responses. Disease stability was obtained in 29% and progression was seen in 27% at time of response assessment. Median duration of response in the whole AZA cohort was 6.6 months (0.4–37) and 7.4 months (0.4–37) in those treated with AZA 1st line. The latter was significantly longer than that observed in the cohort treated with ICT alone (3.7 months; p 0.01).

Four (3.3%) patients treated with AZA were not evaluable for survival. Median follow-up time in patients was 12.4 months in patients receiving AZA as first line treatment and 6.9 months in patients treated in second or subsequent lines.

During this period 49 deaths were reported. The main cause of death was disease progression in 41 cases (84%).

Median observed overall survival for patients receiving AZA in first line was 10.6 months and 8.5 months for those treated in second or subsequent lines (p=0.301). The 12-month overall survival was 45.9% (95% CI: 33.1–63.8%) in patients receiving AZA as first line and 41.9% (95% CI: 24.5–71.7%) for those treated in second or subsequent lines (Fig. 1).

Marrow response to AZA had a significant impact in overall survival. The median survival observed in patients achieving CR or PR was 15.3 months, in patients with SD was 13.7 months and in patients with PD was 4.1 months (p < 0.0001). Pairwise comparisons show a significant difference in overall survival between PD and CR +PR and between PD and SD (p=0.0005 and < 0.0001, respectively) but not between CR+PR and SD (p=0.4977). The 12-month overall survival was 58.3% (95% CI: 42.7–79.6%) in patients with CR or PR; 61.9% (95% CI: 42.9–89.3%) in patients with SD and 6.5% (95% CI: 1.0–42.0%) in patients with PD (Fig. 2).

Transfusion independence also had a significant impact in overall survival. The median survival observed in patients with transfusion independence was significantly higher than that in patients without transfusion independence (15.4 vs 7.2 months, respectively; p=0.0011). The 12-month overall survival was 64.8% (95% CI: 47.7–88.0%) in patients with transfusion independence and 31.8% (95% CI: 19.9–51.0%) in patients without transfusion independence (Fig. 3).

### 3.2. Comparative survival analysis

Median age at diagnosis of the comparator group was 74.5 years-

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¹ All others.
² chromosome 7; >3 abnormalities.

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old (range: 66–86) and 44% (22 patients) were female (Table 1). The median time from diagnosis to start of IC in this comparator group was 0.13 months (range: 0–9.2 months) (Table 2). All patients treated with OCT alone received only supportive care prior to induction chemotherapy.

The median follow-up was 4.3 months (range: 0.1–43.4). There were 48 deaths and only 2 patients were still alive at the time of last

### Table 2
Treatment details.

|                           | AZA N (%) N=77 | AZA 1stline N (%) N=51 | ICT N (%) N=50 | p-value AZA 1st line vs ICT |
|---------------------------|----------------|------------------------|---------------|-----------------------------|
| Time from diagnosis to start of AZA, months | 1.4 [0–89.3] | 0.6 [0–48.3] | 1.3 [0–9.2] | 0.195                        |
| First line treatment      |                |                        |               |                             |
| AZA, n (%)                |                |                        |               |                             |
| ICT (3+7)                 | 24 (31%)       | 51 (100%)              |               |                             |
| Dauno 90 + ARAC 100       | 10 (20%)       |                        |               |                             |
| Dauno 60 + ARAC 100       |                |                        |               |                             |
| Ida 12 + ARAC 100         |                |                        |               |                             |
| Total no of cycles        |                |                        |               |                             |
| Median [min-max]          | 6 [1–28]       | 1.7 [1–3]              |               |                             |

AZA=azacitidine; ICT=intensive chemotherapy; Dauno 90+ARAC 100=Daunorubicin 90 mg/m² D1-3, Cytarabine 100 mg/m² D1-7; Dauno 60+ARAC 100=Daunorubicin 60 mg/m² D1-3, Cytarabine 100 mg/m² D1-7; Ida 12+ARAC 100=Idarubicin 12 mg/m² D1-3, Cytarabine 100 mg/m² D1-7.

### Table 3
Response to therapy.

|                           | AZA (%) N=51 | ICT (%) N=50 | p-value AZA vs ICT |
|---------------------------|--------------|--------------|--------------------|
| Overall response (PR + CR)|              |              |                    |
| Partial response          | 34 (44%)     | 26 (51%)     | 38 (76%)           |
| Complete response         | 24 (31%)     | 19 (37%)     | 27 (54%)           | 0.02               |
| Stable disease            | 22 (29%)     | 13 (25%)     | 12 (24%)           |
| Progression/refractory    | 21 (27%)     | 12 (24%)     | 12 (24%)           |

Transfusion independence

|                           | AZA (%) N=51 | ICT (%) N=50 | p-value |
|---------------------------|--------------|--------------|---------|
| No                        | 44 (57%)     | 27 (53%)     | N/A     |
| Yes                       | 30 (39%)     | 24 (47%)     | N/A     |
| Unknown                   | 3 (4%)       |              | N/A     |

Fig. 1. Survival estimates for patients treated with AZA according to line of treatment.

Fig. 2. Survival according to marrow response.

Fig. 3. Survival according to transfusion independence.
follow-up. Median overall survival observed in this comparator cohort was 5.4 months (95% CI: 2.0–10.2 months) and the 12-month OS was 31.8% (95% CI: 21.1–47.8%). This was significantly inferior to that observed in the cohort treated with AZA in first line (p < 0.0104) (Fig. 4).

4. Discussion

There is an important need for new treatment options for AML in elderly patients. Their frailty imposes limitations upon the aggressiveness of the treatment which can be administered [6,24]. In addition, the poor prognostic disease features often seen in this population mean that refractoriness and relapse are more frequent [10]. Treatments for this population require an optimal balance of tolerability and efficacy. The main aim in most cases is to prolong survival and reduce the impact of cytopenias without undue toxicity.

AZA has demonstrated efficacy in high risk MDS, reducing transfusion requirements and prolonging survival. In this setting it had proven to be well tolerated including by those more elderly [25]. Based on this experience, several groups have tested the efficacy and safety of AZA in elderly patients with AML with promising results [16,17,19,26].

Our results are in line with previous reports that AZA is efficacious in the treatment of AML regardless of the blast count. The response rates and the overall survival observed in our study are in consonance to those reported by other groups [16,17,19,26]. It is noteworthy that the rates of CR obtained with AZA are equivalent to those obtained in some published series of elderly patients treated with IC [11].

Improved survival in our cohort was significantly associated with any quality of response, including maintenance of stable disease. This suggests that AZA is capable of delaying progression, and thus prolong survival, even if no hematological or marrow improvement are obtained. This supports its use in this population until frank progression is detected or until the patient receives another more definitive treatment, such as allogeneic bone marrow transplant.

Another significant finding of our analysis is the efficacy of AZA in those who are refractory or relapsed following IC. The fact that survival from start of AZA is similar in first and second line patients indicates that relapsed/refractory patients benefit equally.

The comparison of the cohort treated with AZA first line with the comparator group treated only with IC highlights the advantages brought by the former treatment modality. It is important to note that this finding has not been confirmed in a randomized trial [20]. However, 41% of the trial patients were treated with AZA following failure with ICT whereas our comparator group never received AZA. As AZA has demonstrated efficacy as second line therapy, this could explain the difference in our findings. The significantly lower survival of the IC cohort indicates that this population benefits from less intensive treatment options which target other pathophysiological processes.

The retrospective nature and the limited numbers of patients in our study urge caution in the interpretation of our results. The collaborative nature of the study helps reduce bias which may be introduced by single centre data.

However our study adds new evidence to the use of AZA in elderly patients with AML and indicates that it is at least not inferior to conventional IC. The response rates and survival data here presented support its use in first line in those who are not candidates for IC and in second line in those who are refractory or relapsed following IC. This and future collaborative studies will add to trial data to better identify those patients who benefit most from new treatment modalities, thus improving the management of elderly patients with AML.

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