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Outcome of acute myeloid leukaemia following myelodysplastic syndrome after azacitidine treatment failure

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Keywords

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Between 30% and 40% of myelodysplastic syndrome (MDS) patients progress to acute myeloid leukaemia (AML). The prognosis of these secondary AML (sAML) cases is poor with frequent resistance to conventional chemotherapy and an overall survival of <1 year (Nimer, 2008). Epigenetic deregulation has recently been demonstrated as one of the driving phenomena during disease progression (Jiang *et al*, 2009). Demethylating agents lead to significant clinical benefit for both MDS and AML patients (Fenaux *et al*, 2009) and represent an attractive option for AML arising after MDS. Nevertheless, a majority of patients fail to respond to azacitidine (AZA) and most responders progress within 2 years (Fenaux *et al*, 2010). There is no standard of care for salvage therapy after AZA failure and investigational agents have been extensively studied. We recently showed that the outcome of high risk MDS after AZA failure was poor (Prebet *et al*, 2011), with a median overall survival (OS) of 5-6 months but, to date, the outcome of sAML after AZA failure has not been described, representing a potential limitation for the design and interpretation of clinical studies. We therefore analysed the outcome of 74 patients with sAML after AZA treatment failure, collected from two Johns Hopkins University trials (J9950 and J0443, $n = 14$) (Gore *et al*, 2006; Fandy *et al*, 2009) and the French AZA compassionate programme ($n = 60$) (Itzykson *et al*, 2011). Inclusion criteria were: (i) diagnosis of AML arising from MDS according to the French-American-British classification; (ii) 30% or more bone marrow blasts before AZA onset; (iii) having received at least one cycle of AZA. Details of the methodology and AZA regimens have been previously described (Prebet *et al*, 2011). A minimum of four cycles was planned for each patient. Cytogenetic risk was assessed according to the European Leukaemia Net classification. Response had been assessed with

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Authors Contribution

TP treated patients, conceived research, collected data, analysed the data and wrote the manuscript. NV PF SG FD treated patients, analysed the data and participated in the writing of the manuscript. BQ, CG, ST, and OBR treated patients and collected data. BE analysed the data and participated in the writing of the manuscript.

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the International Working Group 2003 criteria (Cheson *et al*, 2003) and haematological improvements (HI) were also classified as response. Survival was calculated from the date of AZA failure. Disease status at the end of AZA was categorized as primary failure in the absence of any response to AZA (including HI), secondary failure if disease progressed after a first response (loss of HI or bone marrow progression) or AZA intolerance (if AZA was stopped because of adverse events regardless of clinical response). Statistical methods were as previously described (Prébet *et al*, 2011) and statistical analysis was performed using the R.2.3.0. software (R Development Core Team, Vienna, Austria). Patient characteristics are presented in Table I. Overall, patients had advanced disease, with 70% of the cases having a prior duration of MDS of more than 1 year and high-risk cytogenetics in 27% of the patients (including 14 complex cytogenetics). Fifty-two percent of the patients had received prior therapy before AZA: chemotherapy in 37 patients (low dose cytarabine $n = 7$, AML-like induction chemotherapy $n = 30$), and immunomodulatory drugs ($n = 2$). Thirty-two patients had received another drug in addition to AZA [histone deacetylase (HDAC)] inhibitors ($n = 25$, valproic acid, phenylbutyrate or entinostat) and chemotherapy ($n = 7$, anthracyclines and hydroxycarbamide given for cytoreduction on cycle 1). The median number of cycles of AZA was 4; 11 patients (15%) achieved a significant response (including six complete responses) and 12 patients (16%) achieved an HI without significant marrow response. At last follow-up, 66 patients had died, and eight remained alive. Median OS was 3.4 months with a 1-year survival probability of 8% [95% confidence interval (2.3–12.1%), Fig 1A]. There was no impact of age, cytogenetic stratification, bone marrow blast count or AZA treatment-related variables (schedule or duration of exposure). There was a trend for a better OS for patients that were not treated with intensive chemotherapy prior to AZA (median OS 4 months vs. 2.8 months, $P = 0.12$). Only complex cytogenetics ($n = 14$) were associated with significantly poorer outcome (median OS 1.9 months vs. 3.9 months for non complex cytogenetics ($P = 0.05$)). Survival of the present sAML patients following AZA failure was significantly shorter than that of higher risk MDS (median OS = 7.5 months, $P = 0.001$), but similar to that of refractory anaemia with excess blasts in transformation (i.e. bone marrow blast count between 20% and 29% median OS: 4.1 months, $P = \text{NS}$) we previously reported (Prébet *et al*, 2011). Information regarding treatment given after AZA failure was available in 39 patients (Fig 1B). Most of the patients were treated with best supportive care (BSC, $n = 20$) or palliative chemotherapy ($n = 6$, hydroxycarbamide, 6-mercaptopurine or low dose melphalan). Median survival was 2 months and was not influenced by the need for palliative chemotherapy (data not shown). Thirteen patients (33%) were treated with ‘active’ therapies: none of four patients treated with intensive AML-like chemotherapy responded or could bridge to transplantation (i.e. bone marrow blast count between 20% and 29% median OS 7.7 months). This is in line with a recent report regarding intensive chemotherapy for sAML (Bello *et al*, 2011), which showed that treatment with hypomethylating agents prior to induction chemotherapy was associated with a poorer outcome. Six patients were treated with other epigenetic agents (decitabine ($n = 4$) or HDAC inhibitors ($n = 2$)) but none responded (median survival 11 months). Finally, three patients were treated with allogeneic SCT. None of them received salvage regimens before transplantation. Two of them died of progressive disease after 10 and 11 months, respectively, and one patient was still alive after 14 months. There was a trend for improved survival in the group who received ‘active’ treatments as compared to palliative care (10 months vs. 2 months respectively, $P = 0.08$, Fig 1B). These results may possibly reflect patient selection bias but also stress the need for clinical trials in that subgroup of patients.

This report is the first to specifically address the issue of the outcome of sAML after primary or secondary AZA failure. The median OS of 3.6 months was even poorer than the survival of higher risk MDS in this situation, with a 1-year survival of only 8%. This even worse prognosis also indicates the need for closer monitoring of sAML during AZA treatment. Conventional treatment, such as BSC or cytotoxic drugs, appeared of little benefit

for such patients. Besides cytogenetics, no significant pretreatment variable was associated with OS, possibly due to the limited number of patients and/or the dismal outcome in all sub-groups. Our study gives the expected baseline for patients treated with conventional care and will be useful for the design of future clinical trials.

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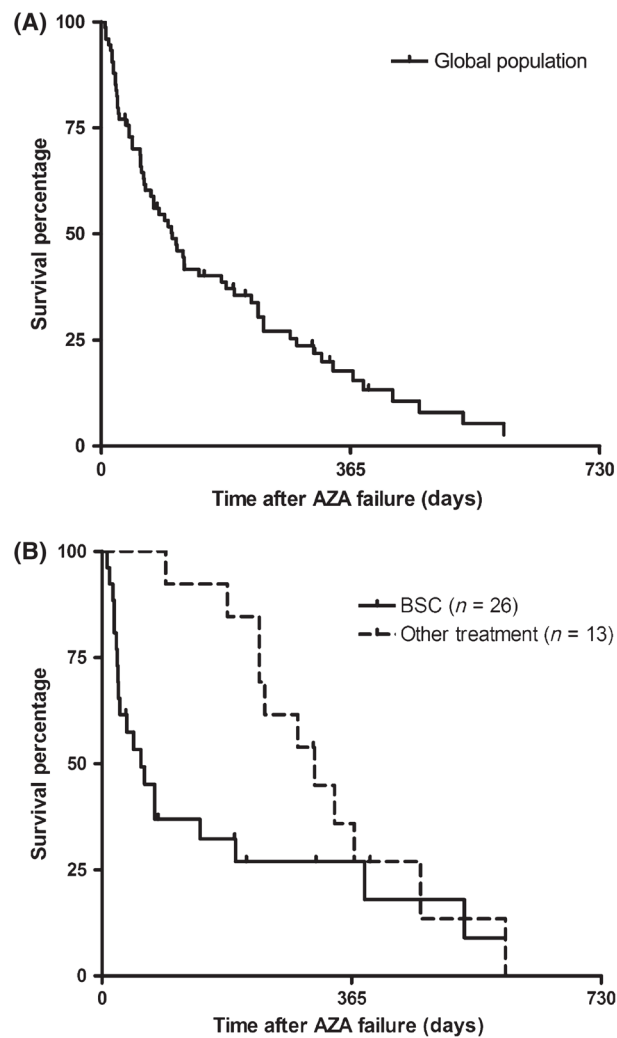


Fig 1. (A) Kaplan Meier estimates of the overall survival after azacitidine (AZA) failure for secondary acute myeloid leukaemia. (B) Survival analysis according to the salvage treatment regimen. The curves represent the survival estimates for the cohort of patients. Each tick mark represents a censored patient. Overall response rate for each treatment group is presented with the number of patients evaluable for response in each cohort. Best supportive care (BSC) included palliative chemotherapy; other treatments included allogeneic transplantation, epigenetic-targeted agents and intensive ‘acute myeloid leukaemia-like’ chemotherapy regimens.

Table I

Characteristics of the secondary AML patients who failed AZA treatment.

	Secondary AML (n = 74)
Median age (years)	70
Male/female	1·6 (46/28)
Therapy-related (Unknown = 8)	4/66 (6%)
Disease duration before AZA	
<1 year	22 (30%)
1–2 years	21 (29%)
More than 2 years	31 (41%)
Median bone marrow blast before AZA (%)	48% (30–74%)
Cytogenetics (AML stratification)	
Intermediate risk	47 (64%)
High risk	27 (36%)
Frontline AZA treatment	36 (49%)
AZA-based combination	27 (36%)
Cycle1 dose of AZA > 500 mg/m ²	59 (79%)
Median duration of AZA cycles	29 days
Number of AZA cycles	
6 or less	54 (73%)
7–12	13 (18%)
More than 12	7 (9%)
Type of failure	
Primary failure with SD	30 (42%)
Primary Failure with PD	21 (28%)
Secondary failure (after prior response)	21 (28%)
AZA intolerance	2 (2%)

AML, acute myeloid leukaemia; AZA, azacitidine; SD, stable disease; PD, progressive disease.

AZA courses are described with the total dose per cycle; 500 mg/m²/cycle (corresponding to 95% of the registered 75 mg/m²/day for 7 days schedule) was defined as the reference dose.