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Research paper

Impact of baseline cytogenetic findings and cytogenetic response on outcome of high-risk myelodysplastic syndromes and low blast count AML treated with azacitidine

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ABSTRACT

Karyotype according to the revised IPSS is a strong independent prognostic factor for overall survival (OS) in myelodysplastic syndromes (MDS), however established in untreated patients. The prognostic impact of cytogenetics and cytogenetic response (CyR) in MDS patients receiving azacitidine (AZA) remains uncertain. We examined the prognostic value of baseline cytogenetics and CyR for overall response rate (ORR) and OS in 702 AZA-treated higher risk MDS and low blast count acute myeloid leukemia (AML), including 493 (70%) with abnormal karyotype. None of the cytogenetic abnormalities had significant impact on ORR (43.9%) or complete response (15.35%), except 3q abnormalities and complex karyotypes, which were associated with a lower ORR. OS differed significantly across all R-IPSS cytogenetic subgroups ($p < 10^{-4}$) but patients with non complex del (7q) had similar survival as patients with normal cytogenetics. CyR was achieved in 32% of the 281 evaluable patients with abnormal cytogenetics, was complete (CCyR) in 71 (25.3%) patients. We found no correlation between hematological response and cytogenetic response and 21% of the patients with CCyR did not achieve morphological response. In the 281 patients, we found no impact of CyR on survival, but when restricting to MDS (ie: < 20% marrow blasts) achievement of CCyR was associated with better OS.

1. Introduction

Myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by ineffective hematopoiesis resulting in blood cytopenias, and by a high risk of progression to acute myeloid leukemia (AML) [1]. Cytogenetic abnormalities are found in about 50% of MDS patients, consisting mainly of complete or partial loss of chromosomes 5, 7, and 20 (del(5q), −7, del(7q), del(20q)), chromosome gains (especially +8), or complex karyotypes [11]. Cytogenetic findings were incorporated as prognostic markers in MDS in the classical International Prognostic Scoring System (IPSS) [9]. In the recent revised version of the IPSS (IPSS-R), based on 7012 patients, cytogenetic prognostic classification could be refined in five instead of three prognostic subgroups, and the prognostic "weight" of cytogenetics was increased compared to that of other parameters [10,18]. However, this IPSS-R cytogenetic classification was established in untreated patients.

The hypomethylating agent (HMA) azacitidine (AZA) improves survival, and has become a reference treatment of higher risk MDS and low blast count AML patients not candidates for intensive chemotherapy or allogeneic stem cell transplantation [7]. A feature of HMAs therapy is that a survival benefit may occur in the absence of complete or partial response (CR, PR), i.e. that patients who only

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improve their cytopenias (stable disease with hematological improvement or HI, according to IWG 2006 response criteria) also have a survival benefit [8]. Prognostic factors of response and survival with AZA treatment are still incompletely known. Regarding karyotype, it has been suggested in relatively small series that unfavorable karyotypes, including monosomy 7 and complex karyotype, were associated with good response rates, although survival remained shorter than in patients with more favorable cytogenetics [16,17]. Whether cytogenetic findings, and in particular IPSS-R cytogenetic classification, can predict outcome in large series of MDS patients receiving HMAs, remains to be determined. Moreover, while cytogenetic response is an important independent prognostic factor for outcome in chemotherapy-treated AML patients [5], only one paper evaluated cytogenetic response in AZA-treated MDS patients [12]. In that study evaluating low or high risk MDS patients treated with HMA (mainly Decitabine) achievement of complete cytogenetic response was associated with survival improvement [12].

In the present study, we analysed the prognostic value of baseline cytogenetic characteristics (including IPSS-R cytogenetic classification) on response to treatment and survival, and the prognostic impact of cytogenetic response, in 702 patients with higher risk MDS and low blast count AML (20–30% blasts) treated with Azacitidine in seven centers over an 11-year period.

2. Patients and methods

2.1. Patient selection

Patients with Higher Risk MDS, AML < 30% blasts or chronic myelomonocytic leukemia (CMML) having received at least one cycle of azacitidine, started between October 2002 and March 2013 in the seven participating centers, were eligible. Low blast count AML (with 20–30% marrow blasts) was included, as azacitidine is approved in this patient subset in most countries. Participating centers were the Lee Moffitt Cancer center Institute, Tampa; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Groupe francophone des myélodysplasies (GFM) including centers of hôpital Avicenne, Institut Paoli Calmettes, Marseille, university hospitals of Nice and Tours), and Universita di Firenze, Italy. This study was conducted in accordance with the Declaration of Helsinki.

A total of 702 Higher Risk MDS patients and low blast count AML were included in the analysis, excluding only AML patients with ≥30% marrow blasts and patients previously treated with intensive chemotherapy or allogeneic stem cell transplantation.

2.2. Cytogenetic analysis

Cytogenetic analysis was performed using standard chromosomes banding techniques and documented according to ISCN 2013 recommendations [19]. Twenty metaphases were required. When necessary, Fluorescent In Situ Hybridization (FISH) was made to assess a specific cytogenetic abnormality. Cytogenetic results were classified according to IPSS [9] and IPSS-R cytogenetic classifications [18]. Monosomal karyotype was defined as the presence of at least two autosomal monosomies or of a single monosomy associated with at least one structural abnormality [4].

2.3. Treatment

Azacitidine was generally administered as a single agent outside a clinical trial at the approved EMA/FDA approved schedule (75 mg/m^2/day for seven consecutive days or according to the 5-2-2 schedule, every 28 days) until disease progression, unacceptable toxicity, or patient decision. Patients older than 80 or with comorbidities, however, often received lower doses. Response was evaluated after four-six cycles by blood count, marrow aspirate and cytogenetic analysis.

2.4. Study endpoints

CR, PR, marrow CR (mCR), stable disease (SD), hematological improvement (HI), progression, were defined according to IWG 2006 criteria [6]. Complete cytogenetic response (CCyR) was defined as disappearance of a cytogenetic abnormality, requiring 20 analysable metaphases, and partial cytogenetic response (PCyR) as a 50% or more reduction of the number of abnormal metaphases [6]. Overall survival (OS) was measured from the onset of AZA.

2.5. Statistical analysis

Predictive factors for response were analysed using Fisher's exact test for univariate comparisons. Univariate analyses were performed with log-rank tests. Outcomes of patients with specific chromosomal abnormalities were compared with those of the normal karyotype group. All p values were 2-tailed. A landmark analysis on the impact of cytogenetic response was performed at three and six months, in all the patients with abnormal cytogenetics at the onset of the treatment and with evaluable cytogenetic analysis at treatment evaluation. All analyses were performed with Stata/SE Version 12.

3. Results

3.1. Baseline characteristics of the study population

The 702 MDS or low blast count AML patients included in the study had received AZA in the seven centers, started between October 2002 and March 2013. Their median age was 69 years (range 24–91), including 60% older than 65 years, and 37% were females. At onset of AZA (Table 1), WHO diagnosis was RAEB1 in 140 (19.9%) cases, RAEB2 in 338 (48.1%), AML with 20–30% blast in 123 (17.5%), RCMD in 62 (8.8%), RARS in 7 (1%), CMML in 20 (2.8%), unclassified MDS in seven and unknown MDS type (UK) in five patients. IPSS was Int-2 in 438 (62.66%), high in 261 (37.34%) and NA (but at least Int-2) in three patients. IPSS-R was very low in one (0.1%), low in 13 (2%), intermediate in 97 (14%), high in 243 (35%), very high in 320 (45%) and unknown in 28 patients.

3.2. Baseline cytogenetic characteristics

Among the 702 evaluable patients, 209 (29.8%) had a normal karyotype. According to IPSS-R cytogenetic categories, 10 (1.4%), 241 (34.3%), 130 (18.5%), 118 (16.8%) and 201 (28.6%) were classified as very good, good, intermediate, poor and very poor risk groups, respectively (two unclassified) (Table 1).

Two hundred and twenty seven patients had chromosome 7 abnormalities: 142 monosomy 7, including 29 isolated monosomy 7, 20 monosomy 7 with one additional abnormality (+1), and 93 monosomy 7 complex. Fifty one patients had del(7q), including 13 patients with isolated del(7q), nine del(7q) +1, and 29 complex with del(7q). The remaining 34 chromosome 7 abnormalities were mostly (72%) part of a complex karyotype.

Two hundred and six patients had chromosome 5 abnormalities: 126 had del(5q), including nine patients with isolated del(5q), 14 with del(5q) +1, and 103 complex. Thirty-nine had monosomy 5, all but one associated with a complex karyotype. The remaining 41 chromosome 5 abnormalities were mostly (97%) part of a complex karyotype.

One hundred and seven patients had trisomy 8, including 41 with isolated trisomy 8, 16 with trisomy 8 +1, and 50 complex.

Other frequent cytogenetic abnormalities included 17p abnormalities in 58 patients (51 being part of a complex karyotype), del(3q) in 26 patients (15 part of a complex karyotype), isolated del(20q) in 15 patients, del(11q) in 24 patients (15 being part of a complex karyotype), and isolated loss of chromosome Y in four patients. Finally, according to IPSS-R cytogenetic classification, other isolated and other double