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Treatment of myelodysplastic syndromes with 5q deletion before the lenalidomide era; the GFM experience with EPO and thalidomide

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Abstract

Anemia in MDS with 5q deletion was generally considered, until the advent of lenalidomide, unresponsive to available treatments. We analyzed erythroid response to erythropoetin (EPO) or darbepoetin (DAR) and thalidomide in MDS with 5q deletion treated by French centers (GFM) and in whom karyotype was successfully performed. Of 345 patients treated with EPO or DAR ± G-CSF, 48 had 5q deletion. The response rate was 46% (31% major, 15% minor) according to International Working Group (IWG) 2000 criteria versus 64% in patients without 5q deletion ($p = 0.03$). According to IWG 2006 criteria, the response rate in patients with 5q deletion was 39% versus 52% in patients without 5q deletion ($p = 0.10$). Mean duration of response was 14 months versus 25 months (IWG 2000) and 13 months versus 27 months (IWG 2006) in 5q deletion and non-5q deletion patients ($p = 0.019$ and 0.003, respectively). Of 120 MDS treated with thalidomide, all of whom had successful cytogenetic analysis, 37% of the 24 patients with 5q deletion responded (IWG 2000 criteria, 20% major, 17% minor) with a mean duration of 9.5 months, versus 32% (18% major, 14% minor) in MDS without 5q deletion and a mean response duration of 9 months (p = NS). Our results confirm that response rates to EPO or DAR and thalidomide are clearly inferior to those obtained with lenalidomide.

Keywords: Myelodysplastic syndromes; 5q deletion; EPO; Thalidomide

1. Introduction

Interstitial deletion of 5q (del 5q) is the most frequent chromosomal abnormality seen in myelodysplastic syndromes (MDS). MDS with del 5q include (i) the so called "5q-syndrome", defined by isolated del 5q and no excess of marrow blasts, and characterized by female predominance, typical dysmegakaryopoiesis, thrombocytosis, favorable outcome (ii) MDS with del 5q associated with an excess of marrow blasts and/or chromosomal abnormalities in addition to del 5q, that usually do not have the typical features of the 5q-syndrome and carry poorer prognosis [1–3]. Anemia is however a constant finding in MDS with del 5q which, until the recent introduction of lenalidomide, was considered generally unresponsive to available treatments. We tried to reevaluate the outcome of anemia in those patients in the pre-lenalidomide era by reviewing cases of MDS with del 5q treated with EPO or darbepoetin (DAR) ± granulocyte-colony stimulating factor (G-CSF) or thalidomide by centers of the Groupe Francophone des Myélodysplasies (GFM).

2. Patients and methods

Between 1998 and May 2006, 403 generally low or int-1 risk MDS were treated with EPO or DAR ± G-CSF by 25

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centers of the GFM, in 3 prospective clinical trials ($n = 158$) or according to guidelines of the GFM and the French Society of Hematology for the use of EPO (or darbepoetin alfa) in MDS with anemia (hemoglobin <10 g/dL, with or without transfusion requirement). Patients received at least 60,000 U/w of EPO (alpha or beta) or 300 μg/w of DAR, with or without G-CSF, during at least 12 weeks. Results obtained in the 403 patients have been published as full paper [4–6] or in abstract form [7], but without individualizing patients with del 5q. Successful cytogenetic analysis was obtained in 345 of the 403 cases and results in those 345 patients were used for the comparison between del 5q and non-del 5q patients.

In addition, between 1998 and 2006, 120 MDS were treated with thalidomide in two consecutive prospective clinical trials of the GFM where inclusion criteria were MDS with <10% marrow blasts and RBC transfusion-dependent anemia. Patients received escalating dose of 200–800 mg/d of thalidomide in the first trial and of 50–400 mg in the second trial, during at least 12 weeks. Cytogenetic analysis was available in the 120 patients. Clinical results obtained have been published as full paper in 47 patients [8] and presented in abstract form in the remaining 73 [9], but also without individualizing patients with del 5q.

Erythroid responses were classified according to International Working Group (IWG) 2000 and 2006 criteria [10,11]. Treatment results obtained in del 5q and non-del 5q patients were compared by Fisher's exact test and chi square test for categorical data, and Student's *t*-test for numerical data. The Mantel Haenszel test was used to test interaction through the groups of patients with <5% and ≥5% blasts. Survival plots for response duration were compared by the log-rank test. Censoring data for analysis was 1 March 2007.

Table 1
Initial characteristics of patients with del 5q treated with erythropoetin (EPO) or darbepoetin (DAR) and thalidomide by centers of the GFM

	EPO or DAR	Thalidomide
No. of patients	48	24
Sex ratio (M/F)	1:2	1:2.3
Median age (range)	68 (23–92)	69 (51–83)
WHO classification		
5q-syndrome	35%	30%
RA	5%	26%
RCMD	16%	–
RARS	4%	–
RCMD-RS	–	–
RAEB-1	27%	31%
RAEB-2	12%	13%
% BM blasts		
<5%	56%	40%
5–10%	29%	50%
>10%	15%	10%
Karyotype		
Isolated del 5q	62%	65%
Del 5q + 1 additional abn	19%	25%
Del 5q and >1 additional abn	19%	10%
IPSS		
Low	32%	18%
Int-1	41%	52%
Int-2	17%	30%
High	10%	0
% RBC transfusion requirement	62%	100%
Mean no. of RBC units/month	1.81	3.3
EPO		
≤200 UI/L	39%	NA
Median (range)	287 (12–5665)	

3. Results

3.1. Treatment with EPO or DAR

3.1.1. Treatment results in del 5q patients

48 MDS with del 5q received EPO (or DAR) ± G-CSF including 18, 10, 11 and 9 patients treated by EPO (alfa or beta) alone, EPO + G-CSF, DAR alone and DAR + G-CSF, respectively. Of the 48 patients, 30 had del 5q alone, 17 of them with <5% marrow blasts fulfilling WHO criteria of the "5q-syndrome" (Table 1).

22/48 patients (46%) had erythroid response to EPO or DAR, including 15 major and 7 minor responses according to IWG 2000 criteria (Table 2). The response rate was 52%, 55%, 22% and 33%, respectively in del 5q patients with the 5q-syndrome, one additional cytogenetic abnormality, >1 additional cytogenetic abnormality, and marrow blasts ≥5% Addition of G-CSF to EPO (or DAR) in del 5q did not significantly influence the response rate (42% with vs. 57% without G-CSF, p = NS). According to IWG 2006 criteria, the overall response rate was 39%, 52%, 44%, 11% and 19%, respectively in patients with the 5q-syndrome, one additional cytogenetic abnormality, >1 additional cytogenetic abnormality, and marrow blasts ≥5%. The response rate and response duration according to IWG 2000 and IWG 2006 did not significantly differ between the 5q-syndrome and other MDS with del 5q but major responses according to IWG 2000 tended to be more frequent in the 5q-syndrome than in other MDS with del 5q. Endogenous EPO level, and RBC transfusion requirement did not predict response in MDS with del 5q (not shown).

3.1.2. Comparison with MDS without del 5q

297 non-del 5q patients received EPO or DAR ± G-CSF. The non-del 5q MDS group included 47 RA, 49 RCMD, 59 PSA, 51 RCMD-RS, 8 unclassified MDS, 65 RAEB-1 and 18 RAEB-2. 73% of MDS with del 5q were IPSS low or int-1 risk versus 88% of MDS without del 5q. Baseline EPO was more elevated in del 5q patients than in non-del 5q patients (mean 570 UI/L vs. 168 UI/L, $p < 0.0001$). Pretreatment transfusion requirement was not different between del 5q MDS and non-del 5q MDS (percentage of transfused patients 62% vs. 54%, p = NS; mean number of RBC/month 1.8 vs. 1.3, p = NS). Response rates according to IWG 2000 criteria were 48% and 64% in patients with and without del 5q, respectively ($p = 0.03$) with major responses accounting