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Research paper

Lenalidomide treatment in lower risk myelodysplastic syndromes—The experience of a Czech hematology center. (Positive effect of erythropoietin ± prednisone addition to lenalidomide in refractory or relapsed patients)

Anna Jonasova[a,*,1], Radana Neuwirtova[a], Helena Polackova[a], Magda Siskova[a], Tomas Stopka[a], Eduard Cmunt[a], Monika Belickova[b], Alena Moudra[c], Lubomir Minarik[a], Ota Fuchs[b], Kyra Michalova[d], Zuzana Zemanova[d]

[a] 1st Department of Medicine and Biocev, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, U Nemocnice 2, Prague 2, 128 08, Czech Republic
[b] Institute of Hematology and Blood Transfusion, U Nemocnice 1, 128 00 Prague, Czech Republic
[c] Department of Genome Integrity, Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, 14220 Prague, Czech Republic
[d] Center of Oncocytogenetic, Institute of Medical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University and General University Hospital, U Nemocnice 2, 128 00 Prague, Czech Republic

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ABSTRACT

Lenalidomide therapy represents meaningful progress in the treatment of anemic patients with myelodysplastic syndromes with del(5q). We present our initial lenalidomide experience and the positive effect of combining erythropoietin and steroids with lenalidomide in refractory and relapsed patients. We treated by lenalidomide 55 (42 female; 13 male; median age 69) chronically transfused lower risk MDS patients with del(5q) (45) and non-del(5q) (10). Response, meaning transfusion independence (TI) lasting ≥ eight weeks, was achieved in 38 (90%) of analyzed patients with del(5q), of whom three achieved TI only by adding erythropoietin ± prednisone. Another five patients responded well to this combination when their anemia relapsed later during the treatment. In the non-del(5q) group only one patient with RARS-T reached TI. Cytogenetic response was reached in 64% (32% complete, 32% partial response). The *TP53* mutation was detected in 7 (18%) patients; four patients progressed to higher grade MDS or acute myeloid leukemia (AML). All seven RAEB-1 patients cleared bone marrow blasts during lenalidomide treatment and reached complete remission (CR); however, three later progressed to higher grade MDS or AML. Lenalidomide represents effective treatment for del(5q) group and combination with prednisone and erythropoietin may be used for non-responders or therapy failures.

1. Introduction

The most common cytogenetic abnormality of MDS is the deletion of the long arm of chromosome 5 (del(5q)), which occurs in nearly 30% of MDS patients [1]. The group of patients with this aberration is relatively heterogeneous with regard to clinical manifestation, although this depends on other factors such as bone marrow myeloblast count, additional cytogenetic aberrations, and the presence of mutations and cytopenias (especially thrombocytopenia) [2–5]. A special categorization is reserved among the subgroups of MDS for patients with isolated del(5q) without increased blasts. In this group, patients are predominantly those with 5q- syndrome, which, with regard to survival, is one of the most prognosticly favorable syndromes of MDS [6,7]. Unfortunately, within a few years the majority of these patients develop transfusion dependency, along with all its negative consequences, such as the organ siderosis, deterioration of quality of life, worsening morbidity, and decrease overall survival (OS). For these patients, the primary therapeutic aims consist of reaching a normalized blood count and eliminating transfusion dependency. In recent years, new therapeutic approach, immunomodulation therapy, represented by lenalidomide have been instituted in MDS treatment [8,9]. Lenalidomide have a significant effect, specifically in MDS patients with del(5q)

* Corresponding author at: 1st Department of Medicine, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, U Nemocnice 2, Prague 2, 128 08, Czech Republic.
E-mail address: anna.jonasova@vfn.cz (A. Jonasova).
[1] http://int1.lf1.cuni.cz/

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[10,11]. Lenalidomide treatment leads to normalized blood count and, in some patients, to the minimization (or, less often, the disappearance) of the pathological clone, which is detectable by standard cytogenetic examination. Response to lenalidomide therapy occurs in about 60–70% lower-risk MDS patients with del(5q) and in about 90% of patients that meet the criteria of typical 5q- syndrome [11,12]. Particular caution needs to be taken with patients who have other cytogenetic aberrations, higher blast counts, the *TP53* mutation, and thrombocytopenia. These patients are at greater risk of earlier disease progression, and thus it is necessary, in their cases, to consider more aggressive therapy [13,14,3]. However, only about 25–27% of non-del (5q) patients treated by lenalidomide reach red blood cell transfusion independence (RBC-TI) [15,16]. The response rate in these non-del(5q) patients could be increased by combining EPO with lenalidomide. A randomized phase III study in 131 RBC transfusion-dependent (RBC-TD) lower-risk erythropoietin (EPO)-refractory non-del(5q) MDS patients who were treated by lenalidomide alone or in combination with EPO showed positive effect of adding EPO [17]. RBC-TI was reached in 13.8 and 24.2% of the patients in the lenalidomide versus lenalidomide + EPO arm. Low baseline serum EPO level and a G polymorphism of CRBN gene in this study predicted erythroid response. Nevertheless, additional clinical research is further required to determine who might be the potential lenalidomide responder within the non-del(5q) group. In our recent study, we have analyzed the mRNA level of Cereblon (CRBN) in MDS patients with del(5q), non-del (5q) MDS patients, and controls and found statistically significant higher levels in del(5q) patients, as well as amongst the lenalidomide responders [18].

In our work, we herein present one Czech University center's experience with lenalidomide treatment in lower risk del(5q) and non-del (5q) MDS patients and point to some specific clinical observations, namely the positive effect of the erythropoietin and prednisone addition to lenalidomide therapy in refractory and relapsed patients.

2. Patients and methods

Since 2007 we have provided lenalidomide treatment for 55 (42F/13M) MDS patients, median age 69 (range 51–83 years). The patients' characteristics are summarized in the Table 1. All patients belong to the International Prognostic Scoring System (IPSS) low or intermediate group 1. They represent two groups: 45 patients with del(5q) [36 cases (82%) with isolated del(5q), nine cases (18%) with del(5q) and one additional cytogenetic aberration] with classic sex distribution 39F/6M, and 10 non-del(5q) patients (3F/7M). Six out of these 10 patients were treated with lenalidomide when accepted into MDS 005 trial, which was approved by the Institutional Review Board and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrollment.

WHO 2008 (World Health Organization) diagnoses are listed in Table 1. All patients were examined by conventional G-banding and by FISH with appropriate Vysis locus-specific DNA probes (Abbott Molecular). Six out of nine patients with a single additional aberration to del (5q) had an unrelated clone with trisomy of chromosome 8 and represent a specific group. We have repeatedly collected bone marrow samples for cytogenetic analysis and for other studies every six months of therapy, then at 12 months, and then every other 12 months thereafter. Thirty-nine patients (70%) were tested for *TP53* mutations before lenalidomide treatment. In order to determine the mutational status of the *TP53* gene, we analyzed the patients' DNA isolated from the bone marrow mononuclear cells, and applied the method of new generation sequencing (454 GS Junior, Roche).

All studied MDS patients were red blood cell transfusion dependent (RBC-TD), with a median hemoglobin (Hb) level 80 g/l (51–100) at the beginning of treatment. RBC-TD was defined as the requirement of at least two transfusions per month for at least eight weeks prior to the initiation of therapy. Forty-four patients received erythropoietin (EPO) prior to lenalidomide treatment (34 del(5q)), 10 non-del(5q) with just one intermittent responder. One of our patients also presented an interesting case, which following the diagnosis of RAEB2 with isolated del (5q) was treated by azacitidine (18 cycles, 7-day regime, 75 mg/m^2/day) and reached bone marrow complete response with just transient transfusion independency (TI). This patient was switched to lenalidomide upon RBC-TD and reached until now more than 2 years lasting TI without any signs of disease progression.

Table 1
Characteristics of lenalidomide treated patients.

Patients characteristics (No = 55)	Value
Age (years)	
median	69
range	51–83
Sex	
F	42
M	13
WHO 2008 in 5q- group	
Isolated del(5q) (true 5q- syndrome)	28
RCMD	9
RAEB 1	7
MDS/MPN-U	1
WHO 2008 in non 5q- group	
RCMD	7
RARS	1
RARS-T	2
IPSS (both groups)	
ISPP low	36
IPSS int I	16
Unclassified	3
Cytogenetic findings in 5q- group	
Isolated del(5q)	36
two unrelated clones with del(5q) and +8	6
del(5q),del(20q)	1
del(5q)der(19)t(1,19)	1
del(5q), t(2;11)	1
Cytogenetic findings in non 5q- group	
Normal karyotype	10
***TP53*mutation (39 tested)**	
5q- group	7 (18%)
Non 5q- group	0
Previous treatment	
EPO	44 (80%)
CyA + prednisone	1
Azacitidine	1
Transfusion dependency	55 (100%)
Hbg/l (median, range)	80 (51–100)
Thrombocytopenia($< 100 \times 10^9$/l)	1
Time from diagnosis to lenalidomide start (months)	
Median (range)	15 (2–199)

Abbreviations: CyA, cyclosporine, EPO, erythropoietin, Hb, hemoglobin F, female, IPSS, MDS/MPD-U, myelodysplastic/myeloproliferative neoplasm, M, male, unclassifiable international prognostic scoring system, RARS, refractory anemia with ring sideroblasts, RAEB-1, refractory anemia with excess of blasts, RARS-T refractory anemia with ring sideroblasts and thrombocytosis, RCMD, refractory cytopenia with multilineage dysplasia.

The median time from diagnosis to the beginning of lenalidomide therapy was 15 months, with a range of 2–199 months. Lenalidomide was administered at a dose of 5 mg from the beginning of treatment in 26 patients, and at a dose of 10 mg in 29 patients (including all non-del (5q) patients). The median duration of lenalidomide therapy was 15.5 months, with a range of 2–70 months.

Nine patients, six with del(5q) and three non-del(5q), were treated by EPO or by EPO plus prednisone in addition to lenalidomide when the initial response to lenalidomide was inadequate. In seven patients, all with del(5q), EPO ± prednisone was administered in addition to the lenalidomide therapy when their anemia relapsed during the lenalidomide treatment. Prednisone was added to EPO only when the response to EPO was not satisfactory within two months. All these patients received EPO before lenalidomide initiation, and all were primarily refractory patients. Median serum EPO level of these patients before