Treatment of Patients With Myelodysplastic Syndrome With Lenalidomide in Clinical Routine in Austria

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Abstract

Since the MDS-004 trial, a double-blind, phase 3 study, published in 2011, lenalidomide has shown efficacy in lower-risk myelodysplastic syndrome (MDS) patients with the del(5q) cytogenetic abnormality. We here show the results of 50 Austrian MDS patients who received lenalidomide, and the data support its use in lower-risk MDS patients in clinical practice.

Background: Lenalidomide has demonstrated remarkable efficacy for therapy of lower-risk myelodysplastic syndromes (MDS) associated with $5q^-$. The present evaluation aimed to describe the characteristics and outcomes of low-risk MDS patients treated with lenalidomide in Austria. **Patients and Methods:** For this retrospective, multicenter, observational analysis of MDS patients who received lenalidomide, data were collected at various hospitals in Austria over a period of 3 years. MDS classification, previous and current MDS therapies, and outcome and safety of lenalidomide were evaluated. **Results:** Forty-six percent of the patients (n = 23) had a $5q^-$ syndrome, while 12% (n = 6) exhibited $5q^-$ plus additional aberrations or isolated $5q^-$ but $\geq$ 5% blasts in the bone marrow (10%, n = 5). The remaining 32% of patients (n = 16) had MDS with other World Health Organization classifications. Seventy percent belonged to lower International Prognostic Scoring System risk classes. Sixteen centers participated, involving a total of 50 patients. Most frequently used lenalidomide doses were 10 mg and 5 mg on days 1 to 21 of a 28-day cycle. Seventy-five percent of the patients received 11 months of treatment, with a median therapy period of 3.5 months; median follow-up was 3.9 months (range, 0-26 months). Response rate, defined as transfusion independence during the 2 months after lenalidomide therapy, was 64%. Median overall survival was not reached. **Conclusion:** Lenalidomide was well tolerated and is an effective and well-tolerated option for therapy of patients with $5q^-$ syndrome but also lower-risk MDS patients with other World Health Organization classifications in clinical practice.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 11, e143-9
Keywords: 5q deletion, Lenalidomide, MDS clinical practice, Myelodysplastic syndromes

Introduction

The immunomodulating drug lenalidomide exerts its therapeutic effect in patients with myelodysplastic syndromes (MDS) via a dual mechanism: it suppresses $5q^-$ progenitors and supports effective erythropoiesis in MDS clones without a 5q deletion.[1-3] Erythroid response rates of up to 67% and cytogenetic response rates of up to 73% have been reported, as well as sustained transfusion independence in patients with complete cytogenetic remission.[4,5]

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Submitted: Jun 12, 2015; Revised: Jul 16, 2015; Accepted: Jul 28, 2015; Epub: Aug 05, 2015

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.07.645

Despite these facts and the promising outcome data, lenalidomide was not approved for therapy of these patients in Austria and most other European countries until June 2013. Reasons that accounted for the decision of the European Medicines Agency (EMA) against immediate approval were that (1) the pivotal study for product approval in the United States was a single-arm phase 2 study,[6] (2) there was concern regarding progression to acute myeloid leukemia (AML) in the absence of a comparator arm, and (3) long-term data on the use of lenalidomide in this group of patients were not available at that time. In 2011 a randomized controlled trial on lower-risk MDS patients with a 5q deletion has been published fulfilling most of these requirements, including longer-term follow-up data.[5]

The aim of the present study was to evaluate the characteristics of MDS patients who had actually received lenalidomide. By means of a questionnaire, general patient characteristics, cytogenetic status, and risk class according to International Prognostic Scoring System (IPSS) as well as treatment modalities were evaluated to identify the principles guiding Austrian physicians in their decision to use lenalidomide for treatment of MDS. A special focus of the analysis was on the safety of lenalidomide in terms of progression to AML. Finally, we wanted to investigate whether high response rates comparable to those reported in clinical studies could also be achieved with lenalidomide in a real-life situation in clinical practice.

Patients and Methods

Study Design and Patients

REALM (REtrospective Analysis of Local treatment in MDS) was a retrospective, multicenter, observational analysis of patients receiving lenalidomide for therapy of MDS in clinical practice in Austria. All general and teaching hospitals in Austria were invited to participate. Medical records of consecutive MDS patients that had received at least 1 cycle of lenalidomide between Q3/2006 and Q2/2009 were obtained and used for data collection. No other inclusion or exclusion criteria had to be taken into account. The observational period was the time of treatment with lenalidomide; the follow-up period was at the discretion of the treating physicians. The study was approved by local ethics committees. Data collection was in accordance with privacy law requirements.

Data Collection

A questionnaire was sent out to all general hospitals and university hospitals in the country (n = 30) that used lenalidomide for therapy of MDS. Sixteen centers participated, and a total of 50 questionnaires were returned. Baseline details collected included patient characteristics: age, weight, height, sex, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities and Charlson comorbidity index (CCI), ferritin serum levels, and iron chelation therapy; MDS diagnosis and classification: date of diagnosis, cytogenetic parameters, classification according to French–American–British (FAB)[7] and World Health Organization (WHO) classification,[8] and IPSS at diagnosis[9]; previous MDS therapies: antineoplastic therapies, red blood cell transfusions (RBCT), erythropoiesis-stimulating agents, and stem cell transplantation. During lenalidomide treatment, data collection per cycle included MDS and concomitant therapies (dose, frequency, dose delay and/or reduction, duration): lenalidomide, RBCT, antithrombotic prophylaxis, antibiotics, erythropoiesis-stimulating agents, granulocyte-colony stimulating factors, and iron chelation therapy; laboratory parameters (weekly): complete blood count including minimal absolute neutrophil count (ANC), serum creatinine and erythropoietin, urea, and C-reactive protein. In addition, ECOG performance status and adverse events per cycle had to be documented. If data were incomplete, these parameters were excluded from the analysis. Because our analyses were initiated in 2006, the WHO classification for MDS of 2001[8] was used in the present study. In contrast to the current classification[10], the 2001 WHO classification recognized the $5q^-$ syndrome as a separate entity that was defined by the following parameters: primary MDS, $5q^-$ as the only karyotypic abnormality, and < 5% blasts in blood and marrow.

Study Objectives and Outcome Parameters

The primary aim of the study was to evaluate patterns of use of lenalidomide in MDS patients in the clinical routine in Austria. Relevant information was derived from the parameters listed above in MDS and concomitant therapies. In addition, effectiveness and safety of lenalidomide were evaluated. Outcome and safety parameters assessed were direct parameters such as clinical response in terms of transfusion independence, cytogenetic response (if performed), overall survival (OS), and hematologic toxicities. Furthermore, surrogate parameters such as dosing and duration of lenalidomide therapy including number of cycles and reasons for discontinuation of therapy were documented. In addition, patients were divided into 4 subgroups according to the WHO classification from 2001[8] to determine the impact of the underlying type of MDS on the above-listed parameters: (1) $5q^-$ syndrome, (2) MDS with a deletion of 5q and additional aberrations, (3) MDS with a deletion of 5q as a single aberration (but ≥ 5% blasts in the bone marrow [BM]), and (4) all other MDS.

Statistical Analysis

Statistical analysis was descriptive in nature.

Results

Baseline Characteristics

Of the 30 invited centers, 16 participated involving a total of 50 patients in the study. Baseline characteristics are listed in Table 1. In general, the performance status of patients was good (73% of all patients, ECOG performance status 0 to 1) and the CCI score was low (90% of all patients, CCI 0 to 3). Most commonly specified comorbidities were congestive heart failure (n = 9), renal insufficiency (n = 8), venous thromboembolism (n = 8), diabetes (n = 7), and solid tumors (n = 6).

About half of the patients had a $5q^-$ syndrome (46%), while only minor proportions exhibited $5q^-$ plus additional aberrations (12%) or isolated $5q^-$ but ≥ 5% blasts in the BM (10%) (Table 2). The remaining patients had MDS with other WHO classifications. The disease had already progressed to AML in 2 patients at study entry, one with $5q^-$ plus additional aberrations and the other with isolated $5q^-$. This distribution pattern was reflected in the IPSS distribution: low risk and intermediate-1 patients accounted for 70% of the patients, while only 22% were graded as intermediate-2 or high risk (Table 2). In 4 patients (8%), the IPSS was not evaluable.

Eight patients had received previous hematologic or specific MDS therapies involving azacitidine, cytarabine, HAM (high-dose ara-C,