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ORIGINAL ARTICLE

Single-agent daratumumab in very advanced relapsed and refractory multiple myeloma patients: a real-life single-center retrospective study

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Abstract

The anti-CD38 monoclonal antibody daratumumab is approved as a single agent for the treatment of patients with relapsed and refractory multiple myeloma (RRMM) who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMID), or who are double refractory to a PI and an IMID. To date, no real-life data on the efficacy and tolerance of daratumumab in this setting are available. We report here the results of a single-center series of 41 RRMM patients treated with single-agent daratumumab outside clinical trials. Patients received a median number of 4 prior therapies. All patients were previously exposed to PI and IMID and all patients were refractory to the last line of therapy. Most patients presented with high-risk characteristics, including 24% adverse cytogenetics (del17p/t(4,14)), 31% extramedullary disease and 12% circulating plasmacytosis at time of daratumumab therapy. The overall response rate was 24%, including 5% very good partial response or better. After a median follow-up of 6.5 months, all patients experienced disease relapse. The median progression-free survival was 1.9 months. At the time of disease progression, 44% of patients did not receive subsequent therapy. The median overall survival was 6.5 months. No new safety signal was identified. These real-life results revealed modest efficacy of single-agent daratumumab in advanced patients with RRMM in comparison with data from clinical trials.

Keywords Daratumumab · Multiple myeloma · Real life

Introduction

The outcome of myeloma patients has been dramatically improved over the past decades [1]. This outstanding improvement is predominantly due to the widespread use of novel agents, including proteasome inhibitors (PI) and immunomodulatory drugs (IMID). However, the outcome of patients whose disease became refractory to PI and IMID remains poor, with a median overall survival (OS) of nearly 1 year [2]. In the past years, immunotherapy emerged as a major class for the treatment of multiple myeloma patients [3]. Daratumumab, a fully human monoclonal IgGk antibody targeting CD38, was the first monoclonal antibody that demonstrated single agent clinical activity in myeloma patients [4, 5]. Daratumumab was approved by the American Food and Drug Agency (FDA) in 2015 for the treatment of patients with

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relapsed and refractory multiple myeloma (RRMM) who have received at least three prior lines of therapy, including a PI and an IMID, or who are double refractory to a PI and an IMID. This approval was based on the results of phase I/II GEN501 and phase II SIRIUS trials [4, 6]. The pooled analysis of these two studies showed an overall response rate (ORR) of 31%, including very good partial response (VGPR) in 8.8% and complete response (CR) or better in 4.7% [7]. The median progression-free survival (PFS) and overall survival (OS) were 4.0 months and 20.1 months, respectively. To the best of our knowledge, no real-life data reported the efficacy and safety of single-agent daratumumab in relapsed myeloma patients. We report here a single-center experience on 41 consecutive RRMM patients who have received at least three prior lines of therapy, including a PI and an IMID, or double refractory to PI and IMID, treated with single-agent daratumumab.

Material and methods

Patients

We conducted a retrospective institutional review board approved analysis of all consecutive patients that fulfilled the following criteria: (i) diagnosis of multiple myeloma according to international criteria [8]; (ii) who have received at least three prior lines of therapy, including a PI and an IMID, or who were double refractory to a PI and an IMID; and (iii) treated with single-agent daratumumab outside clinical trial. All patients were treated in our institution (Hematology Department, University Hospital of Nantes, France). For each patient, we collected baseline data at the time of daratumumab therapy initiation including age, sex, ECOG PS, isotype, renal function, cytogenetic by FISH (i.e., t(4,14) and 17p deletion), the presence of extramedullary disease, and prior therapies. Circulating plasmacytosis was detected by blood smear. Cytogenetic anomalies were considered to be significant if detected in more than 30% of the cells analyzed.

Treatment

Daratumumab was administered intravenously, at the dose of 16 mg/kg once per week for 8 weeks, once every 2 weeks for 16 weeks, then once every 4 weeks according to the approved label, after a premedication comprising dexamethasone (20 mg before each infusion), acetaminophen, diphenhydramine, or equivalent. Montelukast was administered to patients with a history of chronic obstructive pulmonary disease. No post-infusion medication was given in the absence of infusion-related reactions (IRR). Daratumumab was given until disease progression or unacceptable toxicity.

Statistical analysis

The response categories were defined according to the International Myeloma Working Group consensus criteria [9]. The ORR was defined as the proportion of patients achieving at least a partial response (PR). The clinical benefit rate was defined as the proportion of patients achieving at least a minimal response (MR) [7]. OS was defined as the time from the first daratumumab infusion to death from any cause. PFS was defined as the time from the first daratumumab infusion to disease progression or death. Patients who did not have a recorded death date or a documented progression were censored at the time of the last follow-up (January 20, 2019). OS and PFS were estimated using the Kaplan-Meier method. Safety was evaluated through the rate of IRR and adverse events (AE) occurring during the treatment interval. Statistical analysis was performed using XLSTAT2018 software.

Results

Patients characteristics

From April 2016 to April 2018, 41 consecutive patients with relapsed multiple myeloma who had received at least three prior lines of therapy, including a PI and an IMID, or who were double refractory to a PI and an IMID, were treated with daratumumab at our institution. The characteristics of the patients are listed in Table 1. The median age was 68 years and 7 patients (17%) were older than 75 years. Ten patients (24%) had high-risk cytogenetic (17p deletion or t(4,14) translocation). Eight patients (20%) were ECOG 3 or 4, 13 (32%) had extra-medullary disease, and 5 (12%) had circulating plasmacytosis (mean 0.12 G/l, range 0.1–4.1). Fifteen patients had a renal impairment (37%). The median number of prior therapies was 4 (range 2–9). All patients were previously exposed to PI and IMID, including 59% refractory to both PI and IMID. Thirty-nine patients (95%) were refractory to IMID. All patients were refractory to the last line of therapy.

Efficacy

Patients received a median number of 3 cycles (range 1–19). The ORR was 24.4% (10/41). Responses included 2 very good partial responses (VGPR, 4.9%) and 8 PR (19.5%). The clinical benefit rate was 39%, and 63.4% of patients achieved stable disease (SD) or better. Responses are summarized in Table 2. One patient was not evaluable (NE) for efficacy because of a serious IRR, which occurred during the first infusion despite premedication and required permanent discontinuation of daratumumab. The median follow-up since daratumumab treatment initiation was 6.5 months. At the time of analysis, all patients discontinued daratumumab because of

Table 1 Patients characteristics at the time of daratumumab therapy

	$n = 41$
Median age, years (range)	68 (47–83)
Age > 75	7 (17.1%)
Immunoglobulin isotype	
Ig G	8 (19.5%)
Ig A	25 (61.0%)
Light chains	7 (17.1%)
International system staging	
I	10 (24.4%)
II	20 (48.8%)
III	7 (17.1%)
ECOG	
0–2	33 (80.5%)
3–4	8 (19.5%)
Cockcroft clearance < 60 ml/min	15 (36.6%)
High-risk characteristics	
FISH (del17p/t(4,14)): pos/neg/not known	10 (24.4%)/24 (58.5%)/7 (17.1%)
Extramedullary disease	13 (31.7%)
Circulating plasmacytosis	5 (12.2%)
≥ 1 high-risk characteristic	21 (51.2%)
Prior therapies	
Median numbers of prior therapies (range)	4 (2–9)
Refractory to last therapy	41 (100%)
Prior ASCT	30 (73.2%)
Prior Btz/refractory to PI	40 (97.6%)/24 (58.5%)
Prior Len/prior Pom/refractory to IMID	40 (97.6%)/39 (95.1%)/39 (95.1%)
Double refractory to IMID and PI	24 (58.5%)

Data shown as *n* (%) of patients unless otherwise specified. *ASCT*, autologous stem cell transplantation; *PI*, proteasome inhibitor; *IMID*, immunomodulatory agent; *Btz*, bortezomib; *Len*, lenalidomide; *Pom*, pomalidomide

disease progression. The median PFS was 1.9 months (95% CI, 1.4–2.5 months). The median PFS for patients achieving at least a PR was 10.1 months (95% CI, 8.3–11.6 months). Median time to response for those patients was 1.2 months (95% CI, 1.0–1.8 months), and median response duration was 9.0 months (95% CI, 4.6–10.6 months). Kaplan-Meier curves of PFS and PFS according to response are displayed in Fig. 1. The median OS was 6.5 months (95% CI, 3.1–10.0 months). Median OS for patients achieving PR or better was not reached. Kaplan-Meier curves of OS and OS according to response are displayed in Fig. 2.

Safety

IRR occurred in 29.3% (12/41) of patients. The majority of IRR was grade 1–2 (11/12), included pyrexia or respiratory symptoms, and was safely managed with post-infusion medication. Only one grade 4 IRR occurred and consisted of acute cardiac insufficiency due to malignant hypertension needing treatment in an intensive care unit and permanent discontinuation of daratumumab. Details of the IRR are summarized in Table 3. The other AE are reported in Table 3. They mostly (> 20%) consisted of infections, anemia, and thrombocytopenia. Two grade 5 infections occurred: one case of herpetic encephalitis in a patient non-compliant for his antiviral prophylaxis and one case of sinus mucormycosis in a patient with a history of allogeneic stem cell transplantation, neither were thought to be related to the treatment.

Table 2 Responses according to IMWG consensus criteria

Median number of cycles (range)	3 (1–19)
Best response to therapy	
ORR	10 (24.4%)
Clinical benefit	16 (39%)
CR	0 (0%)
VGPR	2 (4.9%)
PR	8 (19.5%)
MR	6 (14.6%)
SD	10 (24.4%)
PD	14 (34.1%)
NE	1 (2.4%)

Data shown as *n* (%) of patients. *ORR*, overall response rate; *CR*, complete response; *VGPR*, very good partial response; *PR*, partial response; *MR*, minimal response; *SD*, stable disease; *PD*, progressive disease; *NE*, not evaluable

Subsequent therapy after daratumumab discontinuation

Among the 41 patients who progressed on daratumumab, 23 patients (56%) received subsequent therapy. Subsequent therapies consisted of bendamustine (7/23), low-dose cyclophosphamide (6/23), carfilzomib (4/23), other anti-CD38 antibody (2/23), and CAR-T-cells (1/23). Six patients (26%) obtained PR and 1 patient achieved CR (CAR-T therapy). No response was obtained using another anti-CD38 after daratumumab failure.

Discussion

This single-center retrospective study investigated the efficacy of daratumumab single agent in 41 RRMM patients who have received at least three prior lines of therapy, including a PI and an IMID. Patients had advanced myeloma with a median number of 4 prior therapies. The majority of patients (59%) had double refractory (IMID and PI) disease and all patients were refractory to their last therapy. These disease characteristics are

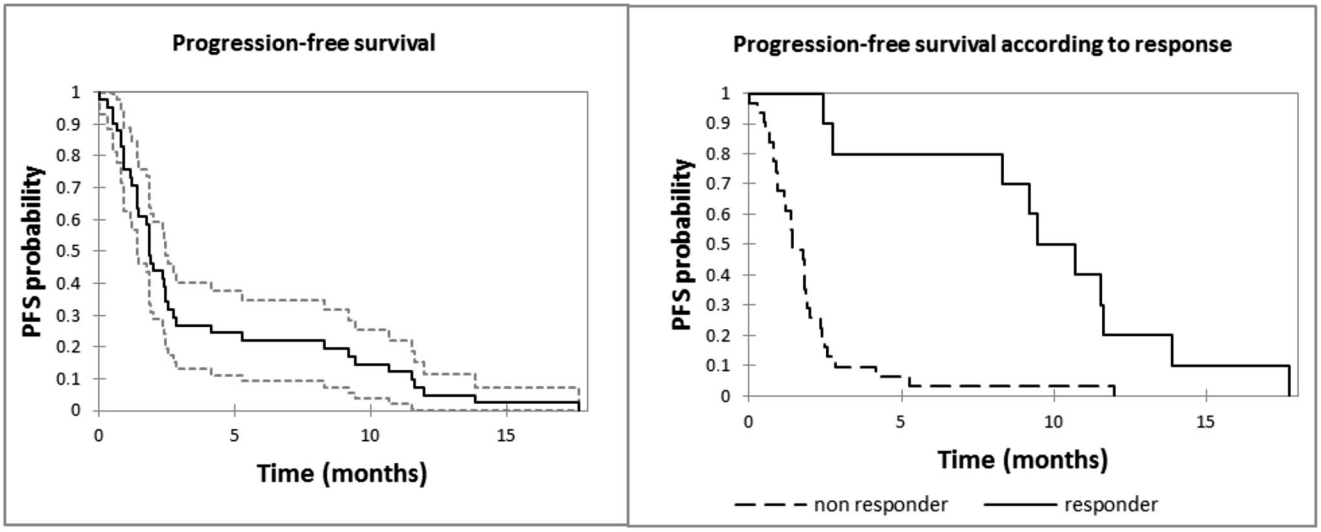

Fig. 1 Kaplan-Meier curves of progression-free survival

similar to phase 2 SIRIUS study [6]. In our study, daratumumab therapy resulted in an ORR of 24.4%, including 5% VGPR. No complete response was confirmed. Response rates were therefore found to be very similar to those obtained in the GEN501 and SIRIUS study [7]. However, the median PFS in our study was 1.9 months and the median overall survival was only 6.5 months. These outcome results are clearly inferior to those obtained in patients from the GEN501 and SIRIUS, with a median PFS of 4 months and median overall survival of 20.1 months [7]. Chari and colleagues recently reported the results of the early access treatment protocol of daratumumab in US patients with advanced RRMM ($n = 348$) [10]. In this report, the overall response rate was 23% and patients received daratumumab for a median of 1.9 months (range 0.03–6.0 months). It is well known that clinical trials induce biases in patient selection, especially for patients with advanced and/or aggressive diseases which are more difficult to include in clinical trials. In our real-life study, patients were older in comparison with patients from GEN501 and SIRIUS studies, including more patients aged over 75 (17% vs 11%) [7]. Patients in the present study also presented with a lower functional status (ECOG PS 3–4 19.5% vs 0%) and with a higher proportion of severe renal impairment (10% vs 3%) in comparison with patients from GEN501 and SIRIUS studies [7]. Disease presentation at the time of study entry was also more aggressive with one-third of patients presenting extramedullary disease and 12% patients presenting with circulating plasmacytosis at baseline. The advanced state of those RRMM is illustrated by the fact that only 56% of patients were able to receive subsequent therapy after progression on daratumumab. This study therefore revealed modest efficacy of daratumumab monotherapy in very advanced MM patients. Recently, two large phase 3 studies confirmed the strong efficacy of daratumumab in combination with lenalidomide or bortezomib for the treatment of

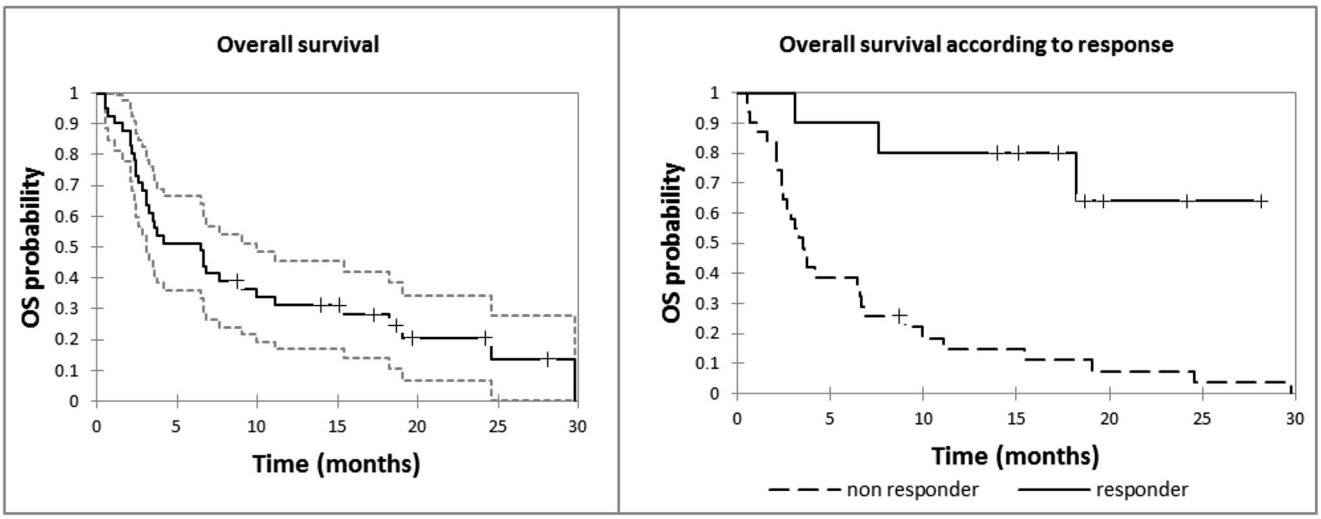

Fig. 2 Kaplan-Meier curves of overall survival

Table 3 Details of reported infusion-related reactions and other adverse events

Infusion-related reactions	12 (29.3%)	
Grades 1–2	11 (26.8%)	
Nausea	1 (2.4%)	
Cough	1 (2.4%)	
Dyspnea	4 (9.8%)	
Grade 3–4	1 (2.4%)	
Dyspnea	1 (2.4%)	
Permanent discontinuation for IRR	1 (2.4%)	
Adverse events	All grade	Grades 3–5
Fatigue	7 (17.1%)	0 (0%)
Infection	14 (34.1%)	4 (9.75%)
Anemia	10 (24.4%)	5 (12.2%)
Thrombocytopenia	12 (29.3%)	5 (12.2%)
Neutropenia	2 (4.9%)	2 (4.9%)

Data shown as *n* (%). *IRR*, infusion-related reactions; *AE*, adverse events

MM patients with less advanced disease (1 to 3 prior lines) [11, 12]. The addition of daratumumab to the standard of care of bortezomib, melphalan, and prednisone also greatly improved the outcome of previously untreated transplant ineligible MM patients [13]. Recently, Facon et al. reported the interim result of the MAIA trial, showing the strong efficacy of daratumumab in combination with lenalidomide and dexamethasone in the same setting [14]. Regarding toxicity, our real-life data confirm the favorable safety profile of single-agent daratumumab. Interestingly, fewer IRR occurred in our retrospective study compared to published clinical studies. The pro-active IRR management with the standardization of pre- and post-medication may be an explanation for this lower rate. Overall, this real-life study demonstrated favorable safety profile but modest clinical efficacy of daratumumab monotherapy in very advanced RRMM patients and highlights the importance of real-life data to complement published clinical trial data.

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Authorship CT PM and MJ designed the study. MJ collected data. MJ performed statistical analysis. CT and MJ wrote the manuscript. All authors treated patients and critically reviewed the manuscript and gave final approval.

Compliance with ethical standards

Conflict of interest CT and PM are advisory board member and received honoraria from Janssen. Other authors have no conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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