Elotuzumab, lenalidomide, and dexamethasone as salvage therapy for patients with multiple myeloma: Italian, multicenter, retrospective clinical experience with 300 cases outside of controlled clinical trials

Recently, monoclonal antibodies (mAb) directed to antigens expressed by plasma cells demonstrated major clinical activity in multiple myeloma (MM), thus gaining a relevant role in the treatment of MM patients.[1] Two mAb targeting signaling lymphocytic activation, molecule F7 (SLAMF7/CS1) and CD38, have been increasingly included in relapse/refractory (RR) MM (RRMM) therapeutic regimens.[2] Among them, elotuzumab (Elo), targets the glycoprotein receptor SLAMF7 causing, on the one side, activation of natural killer cells, and on the other, myeloma cell death through antibody-dependent cellular cytotoxicity (ADCC).[3,4] Surprisingly, Elo failed to demonstrate significant anti-tumor activity as single-agent,[5] ultimately refining its anti-myeloma action in combination with immunomodulatory drugs (IMiD) such as lenalidomide (R). A randomized phase III clinical trial comparing the clinical benefits of R plus dexamethasone (Rd) *versus* Rd plus Elo (EloRd) resulted in a longer progression-free survival (PFS) in patients allocated to the experimental arm.[6] Moreover, extended assessments at 3-year,[7] 4-year,[8] and 5-year[9] follow-ups showed a significantly higher overall response rate (ORR) for EloRd as compared to the Rd regimen. Accordingly, the addition of Elo to Rd significantly reduced the risk of death by 27%.[8]

Here we report data of an Italian 'real-life' experience on EloRd as therapy for RRMM patients treated outside of controlled clinical trials, after receiving marketing approval in Italy in April 2017.

Overall, 300 RRMM patients treated with EloRd according to the marketing approved schedule between April 2017 and April 2019 at 40 Italian centers entered this study (*Online Supplementary Methods*). Baseline characteristics are shown in Table 1. Approximately one quarter of patients (24.3%) had resistance to their most recent line of therapy, symptomatic relapse was observed in 171 patients (57%), and a biochemical relapse in 56 (18.7%). Over one-third (38.3%) received autologous stem cell transplant (ASCT), while 26% of patients had received prior lenalidomide treatment. Fluorescence *in situ* hybridization (FISH) data were available in only 64 patients; ten patients showed high-risk abnormalities. Thirty patients with mild renal impairment received R at the starting dose of 10 mg, while 24 with severe renal impairment received the starting dose of 15 mg every other day; 123 elderly patients (>75 years) received a weekly dose of 20 mg.

At the time of last database update, the median number of courses administered was 12 (range, 1-43). A total of 188 (62.7%) patients stopped EloRd treatment at the time of the cut-off date (median follow-up: 19 months [range 1–36 months]) mainly owing to disease progression (151 cases), 13 patients for toxicity (9 infections, 2 lenalidomide-related severe skin rash, one dexamethasone-related psychosis, and one lenalidomide-related hepatotoxicity), 22 patients due to therapy-unrelated deaths, while two patients underwent ASCT. Infusion reactions occurred in 19 patients (6.3%, all grade 1-2) and were promptly resolved in all patients (no discontinuation reported). Major adverse events (AE) are shown in Table 2 and included grade 3/4 neutropenia (19%), anemia (15.7%), lymphocytopenia (12.7%), and thrombocytopenia (10%) while infection rates and pneumonia were approximately 34% and 16%, respectively. Notably, there was no significant difference in incidence of AE between younger (≤75 years) and elderly patients (*data not shown*).

Age is an important factor in the treatment decision-making process for MM patients because of its association with frailty, increased comorbidities, poor tolerability, and higher risk of complications.[10] In our series, approximately 41% of patients were aged ≥75 years, and

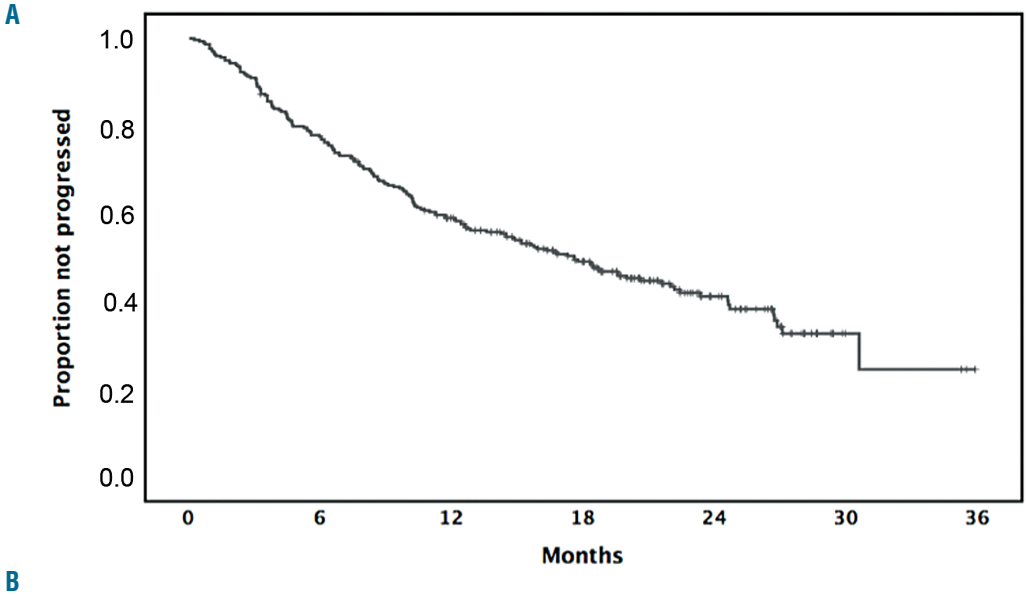
Table 1. Main characteristics of patients at baseline.

	N. of patients (%)
Age, (years)	
<75	177 (59)
≥75	123 (41)
Sex	
Male	157 (52.3)
Female	143 (47.7)
Paraproteins (isotype)	
Immunoglobulin G	188 (62.7)
Immunoglobulin A	55 (18.2)
Immunoglobulin D	2 (0.7)
Light chain only	53 (17.7)
Non-secretory	2 (0.7)
Creatinine clearance (mL/min)	
≥60	214 (71.3)
<60	86 (28.7)
Stage ISS, (n=238)	
I	91 (38.3)
II	95 (39.9)
III	52 (21.8)
Number of previous lines of therapy	
1	186 (62)
2	70 (23.3)
3	20 (6.7)
³4	24(8)
Previous ASCT	
No	185 (61.7)
Yes	115 (38.3)
Previous therapies	
Bortezomib	282 (94)
Lenalidomide	78 (26)
Cytogenetic profile	
Standard risk	49 (16.3)
High risk*	10 (3.3)
Not evaluated	241 (80.4)
Disease status	
Biochemical relapse	56 (18.7)
Symptomatic relapse	171 (57)
Refractory to last treatment	73 (24.3)
Time from diagnosis to EloRd treatment (years)	
≥3.5	154 (51.3)
<3.5	146 (48.7)

N: number; ISS: International Staging System; ASCT: autologous stem cell transplant; EloRd: lenalidomide plus dexamethasone (Rd) plus elotuzumab. *Patients harboring a t(4;14), t(14;16), or del(17p) were classified as having high-risk disease and all other cases as being at standard risk.

of these about 29% presented with renal impairment. In addition, the Eloquent-2 phase III trial[6] and subsequent updates[7-9] have suggested that this triplet drug regimen is safe. Although these results should be treated with some caution given the retrospective nature of the present study and the different clinical features of patients included in the two series (i.e., the median number of previous lines of therapies, 2 in the Eloquent-2 trial and one in our retrospective series), our real-world cohort documented similar AE profiles, except lymphopenia incidence, possibly due to the above mentioned median number of previous lines of therapies and the reduced dexamethasone dose for patients >75 years. Of note, no significant differences in terms of incidence of AE were documented between younger (<75 years) and elderly patients. Thus, the choice of adding elotuzumab to Rd seems to have been rewarded by the clinical benefit observed in our 'real-world' cohort, and as previously described, in the Eloquent-2 phase III trial[6-9] across key subgroups including elderly patients, as well as in individuals with a reduced renal function, thus offering a paradigm for case selection.[11]

The ORR was 77%, with 23 complete remissions (CR) (7.6%) and 88 very good partial remissions (VGPR) (29.3%). The median time to first response was 1.7 months, while the median time to best response was 3.5



B

Variable	HR (95% CI)	*P*-value
β2M, ≥3.5 <5.5 mg/L	0.968 (0.6 - 1.561)	0.893
Age, >75 years	0.949 (0.651 - 1.384	0.786
Sex, Male	1.17 (0.807 - 1.696)	0.408
ASCT, yes	1.182 (0.814 - 1.717)	0.379
CrCl, <60 ml/min	1.291 (0.874 - 1.907)	0.2
Prior lenalidomide, yes	1.444 (0.969 - 2.152)	0.071
β2M, ≥5.5 mg/L	1.519 (0.93 - 2.479)	0.095
Type of relapse, CRAB	1.375 (0.856 - 2.209)	0.188
Prior bortezomib, yes	1.277 (0.561 - 2.908)	0.56
Disease status at EloRd initiation, refractory	1.572 (1.054 - 2.345)	0.027
Time to EloRd start, <3.5 years	1.505 (1.036 - 2.187)	0.032
No. of previous lines of therapies, >2	1.777 (1.227 - 2.571)	0.002
Albumin, <35 g/L	1.849 (1.241 - 2.757)	0.003

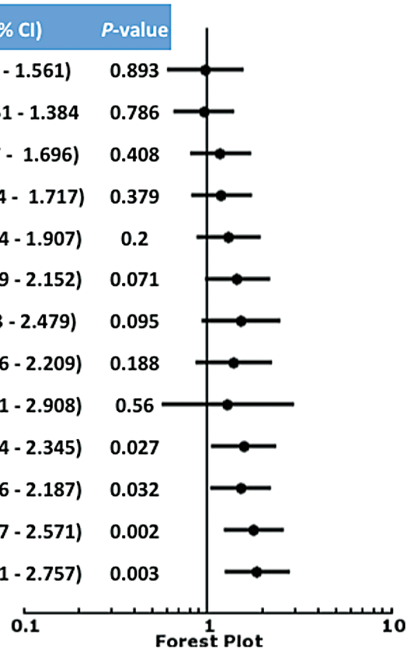


Figure 1. Progression-free survival (PFS) of the retrospective cohort of relapse/refractory (RR) multiple myeloma patients treated with lenalidomide plus dexamethasone (Rd) plus elotuzumab (EloRd). Kaplan-Meier curve of PFS of the entire cohort (A). Forest plot of Cox univariate analysis for PFS according to clinical laboratory variables (B). β2M: beta-2-microglobulin; ASCT: autologous stem cell transplant; CrCl: creatinine clearance; CRAB: hypercalcemia, renal failure, anemia, and bone disease; N: number.

Table 2. Incidence of serious adverse events.

	EloRd (n=300)
Grade 3/4 adverse events	N. of cases (%)
Hematologic toxicities	
Lymphocytopenia	38 (12.7)
Anemia	47 (15.7)
Thrombocytopenia	30 (10)
Neutropenia	57 (19)
Non-hematologic toxicities	
Infections	103 (34.3)
Pneumonia	50 (16.7)
Fatigue	62 (20.7)
Diarrhea	22 (7.3)

months (*Online Supplementary Figure S1*) with approximately 73% and 91% of patients reaching the best response at 6 and 12 months, respectively. The ORR of our 'real-world' cohort was comparable with that of the Eloquent-2 trial (77% *vs.* 79%),[6] with a similar number of patients reaching good quality responses. Moreover, the median time to achieve the best response was 3.5 months as compared to 2.8 months according to the Eloquent-2 independent review and 3.8 months based on the investigators' assessment.[6]

Among the variables analyzed, a significantly worse treatment response was observed among patients previously exposed to lenalidomide and those with refractory disease status at EloRd start (*Online Supplementary Table S1*). However, the association between response and disease status at EloRd was no longer significant after Bonferroni correction. Nevertheless, in the light of the etiological nature of our study, multivariate ordinal regression analysis was still performed, showing prior lenalidomide exposure as the unique variable adversely and independently associated with the best response (odds ratio: 2.04, 95%CI: 1.2-3.3; *P*=0.005). Thus, prior lenalidomide exposure should be considered to be an additional concern when choosing EloRd treatment.

During the follow-up period, 173 patients out of 300 experienced disease progression or died; 94 patients died. Median PFS was 17.6 months (95%CI: 14.1-21.0), and the 1-year PFS was 59.1% (Figure 1A), both results were very similar to the 19.4 months and 68% determined in the Eloquent-2 trial.[6] Univariate Cox analyses showed that refractory disease status at EloRd initiation (HR:1.572, 95%CI: 1.054-2.345; *P*=0.027), a shorter time (i.e., <3.5 years) from diagnosis to EloRd start (HR:1.505, 95%CI: 1.036-2.187; *P*=0.032), more than two previous lines of therapy (HR:1.777, 95%CI: 1.227-2.572; *P*=0.002), and serum albumin level below 35 g/L (HR:1.849, 95%CI: 1.241-2.757; *P*=0.003) were associated with a significantly higher risk to progress or of death (Figure 1B). Notably, in the multivariate Cox model, albumin <35 g/L (HR:1.721, 95%CI: 1.147-2.581; *P*=0.009), time from diagnosis to EloRd start <3.5 years (HR:1.811, 95%CI: 1.179-2.781; *P*=0.007), and >2 lines of previous therapy (HR:2.116, 95%CI: 1.39-3.22; *P*<0.0001) maintained an independent prognostic impact on PFS.

This multivariate model confirmed the Eloquent-2 trial results,[6] demonstrating that those cases with a short disease history could be more prone to progress. Notably, a precocious EloRd treatment in MM patients with asymptomatic biochemical relapse failed to improve PFS in our series, strengthening the concept that only patients with recurrence of the most typical clinical manifestations of MM (hypercalcemia, renal failure, anemia, and bone disease; CRAB) should start treatment.

Moreover, ten cases with high-risk cytogenetic abnormalities showed a significantly shorter PFS than 54 cases with standard risk (*Online Supplementary Figure S2*). Nevertheless, the low number of evaluated cases (19.6%) does not allow any conclusions to be drawn regarding efficacy of EloRd in high-risk patients.

Another objective of this analysis was to determine the relationship between the quality of response and PFS. EloRd-treated patients who achieved ≥VGPR were associated with higher PFS rates compared with EloRd-treated patients who achieved a partial response (PR) or less (*Online Supplementary Figure S3*). The results of Cox regression are detailed in the inbox in *Online Supplementary Figure S3*. Specifically, PFS rates at one year were approximately 80.1% (HR:1, reference group), 59% (HR: 2.15, 95%CI: 1.46-3.16; *P*<0.0001), and 23.8% (HR: 6.74, 95%CI: 4.47-10.15; *P*<0.0001) for cases achieving ≥VGPR, partial response (PR), and <PR, respectively (*Online Supplementary Figure S3*). Interestingly, no difference was demonstrated between complete remission (CR)/near CR (nCR) cases as compared with those achieving VGPR.

The median time-to-next-treatment (TTNT) (25.3 months ([95%CI: 22.1-28.3]) (*Online Supplementary Figure S4*) of our 'real-world' cohort was comparable to that of the Eloquent-2 trial (25.3 *vs.* 33.4 months).[7]

Finally, median overall survival (OS) was not reached and 1-year OS was 65.5% (*Online Supplementary Figure S5*).

To our knowledge, our survey is one of the largest EloRd series in terms of number of patients evaluated. This regimen represents one example of five triple schedules that have received high-level evidence and uniform consensus as a preferred treatment regimen for patients with RRMM.[12,13]

In conclusion, our 'real-world' cohort clearly showed that EloRd was a safe and effective regimen for RRMM patients, confirming the results obtained in the Eloquent-2 controlled clinical trial.[6-9] Based on both studies, we suggest incorporating EloRd as a first salvage regimen in lenalidomide naïve patients and in patients with relatively longer disease duration. New ongoing trials will assess the efficacy of elotuzumab either in combination or with other IMiD[14] in the context of an intensified treatment algorithm.[15]

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