EUROPEAN JOURNAL OF CANCER 47 (2011) 814–818

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Short Communication

Previous thalidomide therapy may not affect lenalidomide response and outcome in relapse or refractory multiple myeloma patients

T. Guglielmelli [a,*], S. Bringhen [b], S. Rrodhe [a], F. Gay [b], F. Cavallo [b], A. Berruti [a], V. Montefusco [c], E. Piro [d], G. Benevolo [e], M.T. Petrucci [f], T. Caravita [g], M. Offidani [h], P. Corradini [c], M. Boccadoro [b], G. Saglio [a], A. Palumbo [b]

[a] Department of Clinical and Biological Sciences, University of Turin and San Luigi Hospital, Orbassano, Turin, Italy
[b] Myeloma Unit, University of Turin and San Giovanni Battista Hospital, Turin, Italy
[c] Division of Haematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[d] Division of Haematology, Pugliese Ciaccio Hospital, Catanzaro, Italy
[e] Division of Haematology 2, San Giovanni Battista Hospital, Turin, Italy
[f] Department of Cellular Biotechnology ad Haematology, La Sapienza University, Rome, Italy
[g] Haematology Department, St Eugenio Hospital, Rome, Italy
[h] Division of Haematology, Ospedali Riuniti di Ancona, Ancona, Italy

ARTICLE INFO

Article history:
Received 19 October 2010
Received in revised form 23 December 2010
Accepted 23 December 2010
Available online 18 February 2011

Keywords:
Multiple myeloma
IMIDs
Relapse
Refractory
Lenalidomide

ABSTRACT

Introduction: Lenalidomide is a thalidomide analogue, designed to have improved efficacy and tolerability over the parent drug. The aim of this retrospective analysis is to evaluate the impact of thalidomide therapy on lenalidomide response and outcome in relapse or refractory multiple myeloma patients.

Patients and methods*Patients and methods:* A total of 106 relapsed or refractory multiple myeloma patients received lenalidomide 25 mg plus dexamethasone as salvage therapy; 80 patients progressed on thalidomide treatment (thalidomide-resistant) and 26 patients discontinued thalidomide in at least partial remission (thalidomide-sensitive). Median time from diagnosis to lenalidomide treatment was 57 months. Median prior lines of therapies were 3, range 1–6. 62% of patients were previously treated with autologous stem cell transplantation, and 71% with bortezomib-based regimens.

Results: In the thalidomide-resistant and -sensitive groups, the at least partial response rates were 56.2% and 61.5% ($P = .45$), including at least VGPR rates of 16.2% and 11.5%; the median progression free survival was 10 and 12 months ($P = .12$) and the median overall survival was 17 and 18.5 months ($P = .50$), respectively.

* *Corresponding author*: Adress: Department of Clinical and Biological Sciences, University of Turin and San Luigi Hospital, Regione Gonzole 10, 10043 Orbassano, Italy. Tel.: +39119026712; fax: +39119038636.

E-mail addresses: tguglielmelli@libero.it (T. Guglielmelli), sarabringhen@yahoo.com (S. Bringhen), sokolrrodhe@yahoo.it (S. Rrodhe), francescam_gay@yahoo.it (F. Gay), cavfed@hotmail.it (F. Cavallo), alfredo.berruti@gmail.com (A. Berruti), vittorio.montefusco@istitutotumori.mi.it (V. Montefusco), piroeugenio@libero.it (E. Piro), gbenevolo@molinette.piemonte.it (G. Benevolo), petrucci@bce.uniroma1.it (M.T. Petrucci), tcaravita@yahoo.it (T. Caravita), m.offidani@ospedaliriuniti.marche.it (M. Offidani), paolo.corradini@unimi.it (P. Corradini), mario.boccadoro@unito.it (M. Boccadoro), giuseppe.saglio@unito.it (G. Saglio), appalumbo@yahoo.com (A. Palumbo).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.12.026

Conclusion: Lenalidomide may be equally effective in heavily pre-treated multiple myeloma patients who are thalidomide-resistant or thalidomide-sensitive to a previous therapy.

1. Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 15,000 new diagnoses and causes nearly 19,000 deaths each year in Europe.[1] Despite significant advances in the knowledge of the biological mechanisms leading to the disease, MM remains incurable and relapse occurs in almost all patients. The development of biological-based treatment, such as thalidomide, lenalidomide and bortezomib has significantly improved the outcomes of MM patients both at diagnoses as well as at relapse.[2] These new drugs have shown to be effective in overcoming drug resistance and prolonging response duration.[3–7]

Lenalidomide (Revlimd®; Celgene, NJ, USA) is an oral immunomodulatory analogue of thalidomide. Although both immunomodulatory drugs (IMIDs) have a similar immunomodulatory profile, lenalidomide inhibits IL-6 and TNF-alpha production more potently than thalidomide. Lenalidomide has also been shown to have a different safety profile when compared to thalidomide with fewer neurological symptoms (particularly peripheral neuropathy), but more myelosuppression.[8,9] In this study we evaluated the response and the outcome of 80 heavily pre-treated MM patients who progressed on thalidomide and received lenalidomide–dexamethasone as salvage therapy. The results were also compared with the response and the outcome of 26 patients who discontinued thalidomide in at least partial remission.

2. Patients and methods

We recruited 106 MM patients from 8 Italian Haematology Divisions. These patients received salvage therapy with lenalidomide–dexamethasone from March 2007 to March 2010; all patients were previously treated with thalidomide-based regimens (from January 2001 to May 2009).

Eighty patients progressed on thalidomide (thalidomide-resistant, TR) and 26 discontinued thalidomide in at least partial remission (PR) (thalidomide-sensitive, TS). All patients provided written informed consent for the use of thalidomide and lenalidomide therapy.

Thalidomide was administered at the maximum tolerated doses (median thalidomide dose 100 mg in both groups). In the TR group, 47 patients (58.8%) received thalidomide–dexamethasone and 33 (41.2%) thalidomide plus chemotherapy combinations. In the TS group, all patients discontinued thalidomide in at least partial remission. Eleven patients (42.3%) received thalidomide–dexamethasone and 15 (57.7%) thalidomide plus chemotherapy combinations. Twenty-two of the twenty-six patients discontinued treatment due to serious adverse events: peripheral neuropathy ($n = 12$), neutropenia ($n = 3$), thrombosis (1), infections (2), thrombocytopenia (1), rush (1), fatigue (1) and bradycardia (1). The remaining 4 patients discontinued thalidomide on the basis of medical decisions (induction with thalidomide-based regimens before transplantation).

As salvage therapy, lenalidomide was administered at the dose of 25 mg/day, day 1–21 on a 28-day cycle. All patients received dexamethasone, either at high dose (40 mg orally on days 1–4, 9–12 and 17–20) or at low dose (40 mg orally on days 1–4 or on days 1, 8, 15 and 22). Relapse, progressive disease and response to treatment were assessed according to the International Myeloma Working Group Uniform Response Criteria.[10] Progression free survival (PFS) was defined as time from therapy to the date of progression, relapse or death from any cause. Overall survival (OS) was defined as time from therapy until the date of death or the date that patient was last known to be alive. Toxicities were defined using the National Cancer Institute's Common Toxicity Criteria (version 3.0).[11] Time-to-event analysis was performed using the Kaplan-Meier method.[12] The analyses were performed using the SPSS for Windows software (version 14.0).

3. Results

3.1. *Patient characteristics*

Table 1 shows patients' characteristics. Median age was similar in both groups (63 and 65 years, respectively $P = .24$). A similar proportion of TR and TS patients demonstrated International Staging System (ISS) stage I (38.8% versus 38.5%), II (35% versus 26.9%) and III (13.8% versus 7.7%), ($P = .09$). TR patients had more prior lines of therapy than TS (median 3 versus 2.5, $P = .051$). Median time from diagnosis (TFD) to thalidomide treatment was 24 versus 31 months in the TR and TS groups, respectively, ($P = .57$) with a median duration of therapy of 12 and 10 months ($P = .15$). Time from diagnosis to lenalidomide was similar in the groups (median, 56 versus 58 months, P0 .40). Overall, 58.7% and 65.4% ($P = .55$) of TR and TS patients underwent autologous bone marrow transplantation and 72.5% and 69.2% ($P = .8$) received bortezomib-based regimens before lenalidomide therapy.

3.2. *Outcomes*

Table 2 shows outcomes of lenalidomide treatment. Overall response rate (ORR) was similar among TR and TS patients (56.2% versus 61.5%, $P = .45$) including no difference in the proportion of complete remission (CR) (10% versus 7.7%), very good partial remission (VGPR) (6.2% versus 3.8%) and PR (40% versus 50%). Similarly, there was no difference in PFS (median, 10 versus 12 months, $P = .12$) and OS (median, 17 versus 18.5 months, $P = .50$) among the TR and TS groups, respectively. Logistic regression analysis demonstrated that ISS stage ($P = .34$; ODD ratio = .81; 95% CI .53–1.2), number of prior lines of therapy ($P = .96$; ODD ratio = 1; 95% CI .73–1.38) and response to previous bortezomib-based regimens treatment

Table 1 – Patients' characteristics.

Patients' characteristics	Thalidomide sensitive $n = 26$	Thalidomide resistant $n = 80$
Median age, y (range)	63 (54–82)	65 (43–86)
International staging system,% (*n*)		
1	38.5 (10)	38.8 (31)
2	26.9 (7)	35 (28)
3	7.7 (2)	13.8 (11)
Missing	26.9 (7)	12.4 (10)
Isotype,% (*n*)		
IgG	61.5 (16)	58.7 (47)
IgA	26.9 (7)	21.2 (17)
Light chain	11.6 (3)	16.2 (13)
NS	0	3.9 (3)
k	77 (20)	67.5 (54)
λ	23 (6)	30 (24)
Median prior lines of therapy, *n* (range)	2.5 (1–5)	3 (1–6)
1,2 lines,% (*n*)	50 (13)	22.6 (18)
3 lines	15.4 (4)	38.7 (31)
>3 lines	34.6 (9)	38.7 (31)
Previous tranplantation,% (*n*)	65.4 (17)	58.7 (47)
Previous bortezomib,% (*n*)	69.2 (18)	72.5 (58)
Thalidomide combination regimen,% (*n*)	57.7 (15)[a]	441.2 (33)[b]
ThalDex,% (*n*)	42.3 (11)	558.8 (47)
Median dose of thalidomide, mg (range)	100 (50–100)	100 (50–400)
Median duration of prior thalidomide treatment, mo	10	12
Median time from diagnosis to thalidomide, mo	31	24
Median time from diagnosis to lenalidomide, mo	58	56

[a] 3 patients, bortezomib thalidomide dexamethasone; 3 patients, thalidomide doxorubicin dexamethasone; 3 patients, melphalan prednisone thalidomide; 5 patients, bortezomib melphalan prednisone thalidomide; 1 patient dexamethasone thalidomide cisplatin doxorubicin cyclophosphamide etoposide.

[b] 3 patients, cyclophosphamide thalidomide dexamethasone; 8 patients, bortezomib thalidomide dexamethasone; 3 patients, thalidomide doxorubicin dexamethasone; 8 patients, melphalan prednisone thalidomide; 9 patients, bortezomib melphalan prednisone thalidomide; 2 patients, dexamethasone thalidomide cisplatin doxorubicin cyclophosphamide etoposide.

Table 2 – Outcomes of lenalidomide after thalidomide treated patients.

Response% (*n*)	Thalidomide sensitive, $n = 26$	*P*	Thalidomide resistant, $n = 80$
CR	7.7 (2)		10 (8)
VGPR	3.8 (1)		6.2 (5)
PR	50 (13)		40 (32)
Overall response,% (95% CI)	61.5 (42.3–80.7)	.45	56.2 (45.2–67.2)
Median PFS, mo (95% CI)	12 (2.8–19.1)	.12	10 (6.5–11.5)
Median OS, mo (95% CI)	18.5 (2.7–31.3)	.50	17 (12.6–21.4)

CR complete response, PR partial response, VGPR very good partial response, PFS progression free survival, OS overall survival.

(ORR = 75%, $P = .22$; ODD ratio = 1.9; 95% CI .68–5.4) are not predictive factors for being lenalidomide responsive or refractory.

3.3. *Toxicity*

Discontinuation of lenalidomide therapy due to adverse events was observed in 10 (12.2%) and 2 (7.7%) of TR and TS patients, respectively, and was mainly haematologic toxicity. Neutropenia and thrombocytopenia were more common in TS than in TR patients and occurred in 23% ($n = 6$) versus 16.2% ($n = 13$) and 19.2% ($n = 4$) versus 3.7%, ($n = 3$), respectively. Venous thromboembolism was also more common in TS patients (7.7%, $n = 2$ versus 1.2%, $n = 1$), despite the use of aspirin or low-molecular-weight heparin prophylaxis. The incidence of anaemia was not significantly different among the 2 groups (7.7%, $n = 2$ versus 8.7%, $n = 7$). Similar rate of dermatologic toxicity, mainly rush, was reported (3.8%, $n = 1$ versus 1.2%, $n = 1$). Infections and peripheral neuropathy occurred in 6.2% ($n = 5$) and 2.5% ($n = 2$) of TR patients, but not in TS patients.

4. Discussion

In this study, lenalidomide–dexamethasone is an effective salvage treatment for relapsed or refractory MM patients who progressed on thalidomide. TR and TS patients had similar ORR (56.2% versus 61.5%, $P = .45$), PFS (median 10 versus 12 months, $P = .12$) and OS (median 17 versus 18, 5 months, $P = .50$). The MM-009 and MM-010 trials compared lenalido-

mide plus high dose dexamethasone to high dose dexamethasone and placebo in previously-treated MM patients.[13,14] Of the 704 patients enrolled, 39% had previously received thalidomide therapy. These studies demonstrated that lenalidomide–dexamethasone led to higher ORR, longer time to progression (TTP) and PFS in comparison with dexamethasone despite prior thalidomide exposure. Patients without thalidomide exposure had a significant higher ORR and PFS than patients previously exposed but the OS did not differ. Specifically, treatment with lenalidomide–dexamethasone results in an ORR of 50%, 41% and 64.8% in thalidomide refractory (no response to thalidomide, $n = 20$), relapsed (progression after at least a partial response to thalidomide, $n = 31$) and sensitive (no progression after at least a partial response to thalidomide, $n = 54$) patients, with a median PFS of 7, 7,8 and 9,3 months, respectively.[15] Patients included in the MM-009 and MM-010 trials had received fewer than 3 prior lines of therapy and had a median TFD of 48 months; 61% of the thalidomide-exposed patients underwent autologous transplantation and only 9% received bortezomib-based regimens before lenalidomide therapy. Our cohort of patients was heavily pre-treated with prior lines of therapy ranging from 1 to 6 and a median TFD of 57 months. In our study, 62% of the thalidomide-exposed patients underwent autologous bone marrow transplantation and 71% received bortezomib-based regimens before lenalidomide therapy.

The toxicity profile of lenalidomide was similar to that previously reported.[13–16] Neutropenia and thrombocytopenia were the major toxicities. Venous thromboembolism was present despite the use of aspirin or low-molecular-weight heparin prophylaxis. The TS group had more toxicity than the TR. This may be due to the selection of fragile patients that discontinued thalidomide for toxicity. Peripheral neuropathy occurred exclusively in thalidomide-resistant patients. As expected, no worsening or serious de novo peripheral neuropathy was reported in TS patients, confirming the absence of severe peripheral neuropathy during lenalidomide therapy. The major limitations to this study were that it was not a randomised trial and that thalidomide-based regimens were heterogeneous and not administered contemporaneously. In contrast our study was carried out on a larger population sample of MM patients who progressed on thalidomide. Patients had received from one to six previous lines of therapy and a large proportion were already exposed to bortezomib. In our study, ORR was 56.2% and PFS was 10 months. In the MM-009 and MM-010 trials ORR was 60% and median PFS was 11,1 months.[13,14,17] Another subset analysis of the MM-009 and MM-010 trials showed that lenalidomide–dexamethasone conferred a significant improvement of benefit after first relapse when compared with a later use.[18] It should be very interesting to evaluate response rate and outcome of relapsed or refractory MM patients treated with thalidomide combination regimens at diagnoses and lenalidomide–dexamethasone at first relapse.

We concluded that lenalidomide may be equally effective in heavily pre-treated multiple myeloma patients who are thalidomide-resistant or -sensitive to a previous therapy. Lenalidomide may overcome thalidomide resistance in previously thalidomide-exposed MM patients.

Conflict of interest statement

Honoraria Celgene and Janseen for everybody with the exception of A Berruti.

Acknowledgements

The authors would like to thank Federica Leotta for her effort in collecting data.

REFERENCES

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005;**16**:481–8.
2. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;**111**(5):2516–20.
3. APEX (Assessment of Proteasome inhibition for Extending remissions) trial: phase III randomized, multi-center, placebo-controlled trial to evaluate the efficacy and safety of bortezomib versus dexamethasone in patients with recurrent or treatment-resistant multiple myeloma. Clin Adv Hematol Oncol 2003;1(3):190.
4. Richardson PG, Sonneveld P, Schuster MW, et al. Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed multiple myeloma. *Br J Haematol* 2007;**137**(5):429–35.
5. Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* 2007;**110**(10):3557–60.
6. Kumar S, Rajkumar SV. Thalidomide and lenalidomide in the treatment of multiple myeloma. *Eur J Cancer* 2006;**42**:1612–22.
7. Kastritis E, Dimopoulos MA. The evolving role of lenalidomide in the treatment of haematologic malignancies. *Expert Opin Pharmacother* 2007;**8**:497–509.
8. Anderson KC. Lenalidomide and thalidomide: mechanisms of action-similarities and differences. *Semin Hematole* 2005;**42**(4):S3–8.
9. Vallet S, Palumbo A, Raje N, Boccadoro M, Anderson CK. Thalidomide and lenalidomide mechanism-based potential drug combinations. *Leukemia and Lymphoma* 2008;**49**(7):1238–45.
10. Durie BG, Harousseau JL S, Miguel J, et alInternational Myeloma Working Group. International uniform response criteria. *Leukemia* 2006;**20**:73–1476.
11. Cancer Therapy Evaluation Program: Common terminology criteria for adverse events, version 3.0 DCTD, NCI, NIH, DHHS March 31, 2003. http://ctep.cancer.gov.
12. Kaplan EL, Meir P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958;**53**:457–81.
13. Weber DM, Chen C, Niesvizky R, Wang M, et al. Multiple Myeloma (009) Study Investigator. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;**357**:2123–32.
14. Dimopoulos M, Spencer A, Attal M, et al. Multiple Myeloma (010) Study Investigator. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;**357**:2133–42.
15. Wang M, Dimopoulos MA, Chen C, et al. Lenalidomide plus dexamethasone is more effective than dexamethasone alone in patients with relapsed or refractory multiple myeloma

regardless of prior thalidomide exposure. *Blood* 2008;**112**:4445–51.
16. Gay F, Hayman SR, Lacy MQ, et al. Lenalidomide plus dexamethasone versus thalidomide plus dexamathasone in newly-diagnosed multiple myeloma: a comparative analysis of 411 patients. *Blood* 2010;**115**(7):1343–50.
17. Dimopoulos MA, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase 3 trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia* 2009;**23**:2147–52.
18. Stadmauer EA, Weber DM, Niesvizky R, et al. Lenalidomide in combination with dexamethasne at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. *Eur J Haem* 2009:1–7.