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A Phase II Clinical Trial of Lenalidomide Intensification in Patients with Serologic/Asymptomatic Progression of Multiple Myeloma While on Lenalidomide Maintenance. A Tri-State Transplant Consortium Study.

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Lenalidomide; Myeloma; Transplant; Relapse

Introduction

The standard first line therapy for patients with multiple myeloma includes 3 phases: An initial induction therapy followed by consolidation with autologous hematopoietic cell transplantation (HCT) using high dose melphalan (HDM) followed by maintenance therapy usually with the immune modulatory drug lenalidomide.(1,2) Multiple randomized trials have now demonstrated that post HCT maintenance therapy with lenalidomide at doses ranging from 5 to 15 mg daily or 21 of 28 days is associated with prolongation of progression free survival (PFS) and in a recently published meta-analysis overall survival (OS) (3–6).

Post HCT lenalidomide has been widely adopted in the United States with more than 50% of patients now receiving this type of therapy. (7) Notwithstanding, most patients on lenalidomide therapy will still have relapse of their disease (6). Patients with “symptomatic progression of disease (POD)” defined by new symptomatic bone lesions, progressive anemia, hypercalcemia, or progressive renal failure attributable to the multiple myeloma, usually in association with a rise in the serum or urine paraprotein, will require re-induction therapy with combination chemotherapy to prevent further organ deterioration. The optimal approach for these patients have been extensively studied in multiple randomized trials as well as extensively reviewed.(reviewed in 8) However, there is a subset of patients with “serologic or asymptomatic POD”, i.e. whose only evidence of disease progression is an increase in the paraprotein level by > 25% above plateau baseline, whose natural history may be extremely variable with many patients not showing symptomatic progression for months or years. (9–11)

We hypothesized that in patients relapsing on lenalidomide maintenance at doses of 5–15 mg orally daily, the disease could be brought under control by increasing the dose of lenalidomide (intensification) to 25 mg daily with or without dexamethasone. However, the response rates and tolerance of lenalidomide dose intensification in the setting of lenalidomide maintenance is unknown and therefore we embarked on a prospective phase II clinical trial whose primary objective was to determine the overall response rate (ORR) at 6 months and the toxicity of lenalidomide administered at a dose of 25 mg orally, days 1 to 21 of a 28 day-cycle, in patients with multiple myeloma found to have asymptomatic POD. The trial was designed to estimate the overall response rate of lenalidomide intensification that would show a increase in response rates from 15% to 30% based on lenalidomide responses in thalidomide failures. A total of 53 patients were planned for accrual with a type I and type II errors of 0.10 respectively with no planned interim analysis. The trial was closed

after 11 patients were accrued over a period of three years due to slow accrual and low overall response rate. Herein are the results of these patients treated on trial.

Patients and Methods

Patients with multiple myeloma with evidence of asymptomatic POD while on lenalidomide maintenance post HCT or on continuous/maintenance therapy as part of first line therapy were eligible to participate in this trial. Asymptomatic POD was defined as progression of disease documented by modified International Myeloma Working Group criteria without evidence of progression of organ damage (progression of severe anemia, renal failure, hypercalcemia, or bone disease). Other eligibility criteria included:

1. Measurable disease as defined by one or more of the following: serum M-protein > 0.5 g/dl, urine M-protein > 200 mg/24 h, and/or serum FLC assay: involved FLC level > 10 mg/dL with abnormal serum FLC ratio.
2. Karnofsky performance status (KPS) of 70% or greater.
3. No evidence of myeloma progression using advanced imaging strategies (i.e PET CT scan or MRI)
4. Adequate organ function and peripheral blood counts.

The trial was initially approved by the institutional review board at Memorial Sloan Kettering Cancer Center and submitted for approval to the Institutional Review Boards of the other participating centers. Trial was managed through the Tristate Transplant Consortium (TSTC). The trial was originally opened in 2011 and closed in 2014 due to slow patient accrual with a total of 11 patients accrued. The primary reason for slow accrual was screen failure due to lesions seen on advanced imaging and competing trials with new agents.

Patient Characteristics

Patient characteristics are summarized in Table 1. In brief, median age was 65 (range, 47–75) with a median number of prior therapies of 4 (range, 2–5) with all patients being registered at time of first progression post HCT. Median time to progression was 20.5 months (range, 10–68).

Treatment Characteristics

After registration patients began therapy with lenalidomide 25 mg daily, 21 days out of a 28-day schedule. All patients were evaluated monthly after every cycle. The dose was adjusted downward in response to side effects and according to specific guidelines. Symptomatic POD occurring at any time during the study resulted in removal of the patient from the study. After 2 cycles of lenalidomide, patients with at least stable disease (SD) continued lenalidomide indefinitely unless they had asymptomatic disease progression at which time dexamethasone was added at a dose of 40mg weekly.

Results

The primary objective of this study was to estimate overall response rate (> PR) to lenalidomide intensification with or without dexamethasone at 6 months. A total of 10 patients were evaluable for the primary endpoint of response. One patient achieved a PR, 1 patient achieved a MR and 7 patients had stable disease. The median PFS was 9.7 months (95% CI: 1.8 to Not Reached [NR]). The median number of cycles received were 6 cycles (range 1–22). At the time of this report 7 patients were alive at a median OS of 60 months (95% CI: 34.2 to NR). Three patients received dexamethasone for asymptomatic progression and failed to have an improvement of response with the addition of dexamethasone, and all relapsing patients went on to receive subsequent treatment that was not captured. Lenalidomide intensification was well tolerated with the most common toxicity being hematologic.

Discussion

The two largest reports of clinical characteristics of myeloma relapse post autograft in myeloma were both published prior to the advent of lenalidomide and bortezomib. (9,10) Both series described that asymptomatic elevations of the blood or urine protein occurred in about 20–30% of patients and was associated with better outcomes. Our single institution experience in a more modern cohort of patients showed that most patients being followed prospectively have asymptomatic elevations of their paraprotein peak, but that a proportion of these patients if carefully evaluated with imaging and marrow would have signs of clinically active disease. Patients with overtly symptomatic disease had a higher risk of death than those without overtly symptomatic disease (hazard ratio: 3.43 (2.09, 5.63), $P < 0.001$). (11)

Based on this experience and since most patients relapsing after primary therapy are on maintenance lenalidomide we hypothesized that increasing the dose could re control the disease in a proportion of patients without undue toxicity and allow further use of the drug for a longer period. The patients on this study represented a potentially high risk group based on the median PFS of 20 months which is significantly less than what has been reported in the randomized trials. (1,3–6) Despite the early closure due to slow accrual the data suggests that disease stability can be reached with lenalidomide dose intensification for a clinically significant period (median 6 months) but that all patients will eventually progress. We did not explore in this study whether addition of dexamethasone would enhance responses. With the number of effective agents and combination regimens available for patients with relapsing myeloma we would only recommend this approach for patients with low risk disease and isolated chemical relapse as a potential strategy to bridge to protocol therapy or delay the need for therapeutic changes.

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References

1. Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orłowski R, Blade J et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood* 2011; 117: 6063–6073. [PubMed: 21447828]
2. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma Version 1.2020 9 6, 2019
3. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma *N Engl J Med*, 366 (2012), pp. 1770–1781 [PubMed: 22571201]
4. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma *N Engl J Med*, 366 (2012), pp. 1782–1791 [PubMed: 22571202]
5. Palumbo A, Cavallo A, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma *N Engl J Med*, 371 (2014), pp. 895–905 [PubMed: 25184862]
6. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. *J Clin Oncol*. 2017 10 10;35(29):3279–3289. doi: 10.1200/JCO.2017.72.6679. Epub 2017 [PubMed: 28742454]
7. D'Souza A, Zhang MJ, Huang J, et al. Trends in pre- and post-transplant therapies with first autologous hematopoietic cell transplantation among patients with multiple myeloma in the United States, 2004–2014. *Leukemia*. 2017 9;31(9):1998–2000. doi: 10.1038/leu.2017.185. Epub 2017 Jun 13. [PubMed: 28663578]
8. Chim CS, Kumar SK, Orłowski RZ, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. *Leukemia*. 2017 1 16. doi: 10.1038/leu.2017.329. [Epub ahead of print] Review
9. Alegre A, Granda A, Martinez-Chamorro C, et al.: Different patterns of relapse after autologous peripheral blood stem cell transplantation in multiple myeloma: clinical results of 280 cases from the Spanish Registry. *Haematologica* 87:609–14, 2002 [PubMed: 12031917]
10. Lenhoff S, Hjorth M, Turesson I, et al.: Intensive therapy for multiple myeloma in patients younger than 60 years. Long-term results focusing on the effect of the degree of response on survival and relapse pattern after transplantation. *Haematologica* 91:1228–33, 2006 [PubMed: 16956822]
11. Zamarin D, Giral S, Landay H, et al. Patterns of relapse and progression in multiple myeloma patients after auto-SCT: implications for patients' monitoring after transplantation. *Bone Marrow Transplant*. 2013 3;48(3):419–24. doi: 10.1038/bmt.2012.151. Epub 2012 Aug 13 [PubMed: 22890289]

Table 1.

Characteristics of registered patients.

N	11
Median Age (range)	65 (47– 75)
Sex Female/Male	Female= 2
	Male= 9
Myeloma Subtype	
IgG	7
IgA	3
IgD	0
Light chain only	1
Number of Prior Therapies	Median= 4 Range= 2–5
Time from HCT to Progression	Avg= 30.2 months
	Median= 20.5 months
Lenalidomide Dose at Progression	Median= 5 mg
Cytogenetic Risk Category	2 high risk
	1 t(4,14)
	1 del17
	2 unknown

N: number; HCT: hematopoietic cell transplantation.