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Original Research Article

A prospective comparative study of efficacy of lenalidomide plus dexamethasone combination therapy versus VAD (vincristine, doxorubicin and dexamethasone) regimen in the treatment of multiple myeloma

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ABSTRACT

Background: Lenalidomide plus Dexamethasone (Len-Dex) and VAD (Vincristine, Doxorubicin and Dexamethasone) regimen are the two common drug therapies employed in the treatment of Multiple myeloma.
Objectives: To compare the efficacy of Len-Dex versus VAD regimen based on complete remission achieved with treatment in newly diagnosed cases of multiple myeloma in a tertiary care hospital in Kerala.
Methods: Eighty patients (forty in each group) of newly diagnosed cases of multiple myeloma, who were willing to give the informed consent, were included in the study. Patients were allocated by the treating physician to two groups; one group was given Len-Dex (lenalidomide + dexamethasone) regimen and the other VAD (Vincristine, Adriamycin, Dexamethasone) regimen. A total of six cycles were given for both groups. Their baseline investigations and follow up investigations were collected at regular intervals, based on these values, the outcome was classified as partial remission and complete remission and the results were compared and analyzed.
Results: Among the forty patients in each group, 17 (38%) on VAD regimen and 28 (62%) on Len-Dex regimen achieved complete remission. The statistical analysis was done using chi square test (χ^2= 6.13, df= 1, p= 0.01) which showed statistically significant difference.
Conclusions: The study showed that the efficacy of Lenalidomide-Dexamethasone (Len-Dex) combination therapy is clearly higher than that of VAD regimen among the study population. The overall efficacy of Len-Dex combination is 70% and that of VAD regimen is only 42.5%.

Keywords: Complete remission, Efficacy, Lenalidomide plus Dexamethasone (Len-Dex) regimen, Multiple myeloma, VAD (Vincristine, Doxorubicin and Dexamethasone) regimen

INTRODUCTION

Multiple myeloma is a plasma cell proliferative disorder that accounts for over 11000 deaths every year in the world.[1,2] Multiple myeloma is the second most common among hematological malignancies. It is responsible for 15-20% of deaths from hematological malignancies and about 2% of all deaths from cancer.[3] The incidence of multiple myeloma in India ranges from 0.5 to 1.2 per 100,000.[4,5] and there are about 16,000 newly diagnosed cases each year in India.[6]

Multiple myeloma usually affects the terminally differentiated B-cell, i.e. plasma cells. The disease proceeds through different phases. In the inactive phase, the mature plasma cells are non-proliferative. In the active phase, there is only a small percentage (1%) of

proliferating plasmablastic cells. There is a fulminant phase in which there are large amount of plasmablastic cells along with frequent occurrence of extra medullary proliferation.[7] Multiple myeloma is a disease of old age, the usual age of presentation being above 55 years. The disease is more common in males with a male: female ratio of 3:2. The survival rate after diagnosis is usually 5 years.[5]

The common clinical presentations of the disease are bone pain, fatigue, hypercalcemia, anemia, renal impairment, recurrent bacterial infections etc.[8] There are different treatment modalities for multiple myeloma. The management of multiple myeloma includes medical treatment using drugs, bone marrow transplantation, supportive measures and treatment of complications.[9] Medical management is by use of cytotoxic drugs. Melphalan with prednisolone is the time-tested treatment of multiple myeloma but this combination is not currently because of the bone marrow suppression.[10] With the advent of newer agents, the popularity of melphalan has come down. The most popular regimen used nowadays being Vincristine, Adriyamycin, Dexamethasone (VAD) regimen.[11] However, cytotoxic drugs have their own toxicities which limit their usefulness. Hence, research into other areas led to the emergence of immunomodulatory drugs like thalidomide and lenalidomide. Thalidomide along with dexamethasone (Thal-Dex) proved to be a good alternative in the treatment of multiple myeloma, but its analogue lenalidomide was found to be more efficacious than thalidomide.[12,13] Lenalidomide along with dexamethasone (Len-Dex) also causes less adverse effects than Thal-Dex.[14] A newer analogue of this group pomalidomide is under trial for the treatment of multiple myeloma.[15] Other group of drugs that are tried in the treatment of multiple myeloma includes bisphosphonates, interferons, the proteosome inhibitor bortezomib, the monoclonal antibody carfilzomib etc.[16]

Bone marrow transplantation is a very effective modality of treatment of multiple myeloma, but its main limitation is the cost involved. Bone marrow ablative regimens are becoming popular nowadays. Complications like anemia, fractures, infections, spinal cord compression need close monitoring and management.[5] Once the patients attain remission, the follow up and maintenance treatment are important factors that determine the quality of life and survival of the patients. Even though multiple myeloma is a common hematological malignancy, it is usually diagnosed late.[17]

The objective of the study was to compare the efficacy of Lenalidomide plus Dexamethasone (Len-Dex) and VAD (Vincristine, Doxorubicin and Dexamethasone) in the treatment of multiple myeloma.

METHODS

This prospective study was carried out in a tertiary care hospital after obtaining approval of the Institutional Review Board.

Inclusion criteria

- Both male and female patients above 18 years of age
- Newly diagnosed cases of multiple myeloma, who have not received any treatment and satisfying the following criteria
- Patients with bone marrow plasma cells 20% or more
- Patients with measurable disease defined as serum monoclonal protein level >10g/L
- Patients with Hb >8 mg/L
- Patients with platelet count >100 x109/L
- Patients with absolute neutrophil count >1.5 x109/L
- Patients with urine creatinine level <2.5mg/dL.
- Patient with lytic bone lesions.
- Patients with 'M' band on electrophoresis.

Exclusion criteria

Severely ill patients, patients with deep vein thrombosis, uncontrolled infections and other co-existing malignancies were excluded from the study.

The sample size (n) was calculated using the data obtained from similar study by using formula.[18,19]

$$n = \frac{2(Z\alpha+Z_{1-\beta})^2 pq}{d^2}$$

'p' is calculated from similar study from literature, i.e. p = p1+p2

p_1= efficacy of Len-Dex (lenalidomide-dexamethasone) regimen in multiple myeloma i.e. about 91%
p_2 = efficacy of VAD regimen in multiple myeloma i.e. about 63%
q=100-p
d=p1-p2

At 5% significance level, Zα is 1.96.

At 80% power, $Z_{1-\beta}$ is 0.842.

$$n = \frac{2\times(7.85)\times77\times23}{(91-63.7)^2} \approx 38$$

So the minimum sample size required in each treatment group was fixed as 40.

The study was started after obtaining written informed consent from the patients. Information regarding patients' demographics, family history, education and occupation

were obtained by asking leading questions and was recorded in the proforma.

On the first visit, a detailed history was taken and clinical examination was performed before initiation of treatment. Baseline investigation reports like haemoglobin, TC, DC, ESR, platelet count, bleeding time, clotting time, serum levels of calcium, phosphorus, and M protein, LFT, RFT, ECG, X-Ray skull and bone marrow examination were recorded. Clinical examination of the patient was carried out and these parameters were noted: height, weight, pallor, icterus, cyanosis, pulse, blood pressure, system wise examinations like CVS, Respiratory system, nervous system and gastrointestinal system examination.

Patients were allocated by the treating physician and one group was given Len-Dex (lenalidomide+ dexamethasone) regimen and the other VAD (Vincristine, Adriamycin, Dexamethasone) regimen. A total of six cycles were given for both groups. The dosing schedule of each cycle is as follows:

- Patients put on Len-Dex regimen were administered Lenalidomide in the dose of 25 mg orally four times daily from day 1 to 21. The same patients received dexamethasone 40 mg orally daily on days 1, 8, 15, 22 of chemotherapy.[20]
- Patients on VAD regimen received Vincristine in the dose of 0.4mg i.v bolus and doxorubicin 9mg/m^2 i.v infusion over 2 hours, daily from day 1 to 4 and dexamethasone in the dose of 40mg orally daily on days 1 to 4, 9 to 12 and 17 to 20.

There was an interval of four weeks in between the cycles of both regimens. The patients reported to the physician before starting each cycle with all the baseline investigations repeated except bone marrow study, which was done only before and after completion of the treatment. All data were entered in the proforma before treatment, after each cycle and after completion of treatment which include:

- Detailed history including that of any adverse effects
- Detailed clinical examination
- Laboratory investigation reports

Evaluation of efficacy of the treatment regimens (End point of the study).

The efficacy of the treatment regimens were compared by using following parameters (Table 1).

- Serum M protein: In multiple myeloma, the plasma cells produce an abnormal protein called monoclonal protein, or M protein. Absence of M protein in the serum is considered as complete remission.
- Plasma cells: Large number of plasma cells in the bone marrow is a diagnostic feature of multiple myeloma. If this value decreases to <5%, it is indicative of complete remission, 5-10% as partial remission and >10% as failure.
- Lytic punched out bone lesions: Another diagnostic criterion of multiple myeloma, if absent after treatment is considered as complete remission. If the lesions persist after treatment, but with no fresh lesions it is classified as partial remission and appearance of fresh lesions indicate failure of treatment.
- Elevation of ESR to very high values is a diagnostic feature of multiple myeloma. A patient who's ESR becomes 20 or less after treatment, is considered to have achieved complete remission. ESR above 20 is classified as partial remission or failure.

Table 1: Working definition of partial and complete remission.

	Investigations	Partial remission	Complete remission
1	Serum monoclonal protein	At least 50% reduction from pre-treatment value	Complete disappearance
2	ESR	>20mm/hr	<20mm/hr
3	Lytic bone lesions	No increase in the number or size of lytic bone lesion	Disappearance of lytic bone lesions
4	Bone marrow plasma cells	In between 5%-10%	<5% of plasma cells

All data was tabulated and analysis was done using Statistical Package for Social Sciences (SPSS) software version 17.

RESULTS

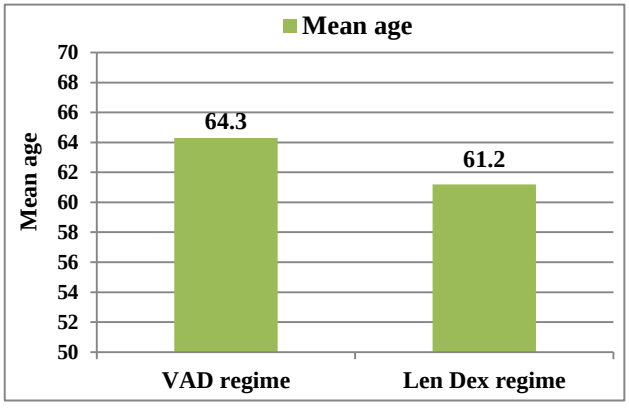

Figure 1: Mean age of patients receiving VAD and Len-Dex regimens (n=40 in each group).

Eighty patients were recruited into the study with 40 in each group. One group received VAD regimen and the other Len-Dex regimen. The age range of the study

population was between 40 and 80 years. As shown in Figure 1, the mean age of patients is 62.8 years, while that of VAD regimen is 64.3 years and Len-Dex regime is 61.2 years. Out of 80 patients, 48 (60%) were males and 32 (40%) were females. Among patients put on VAD regimen 27 (67.5%) were males and 13 (32.5%) were females. In Len-Dex regimen group, there were 21 males (52.5%) and 19 females (47.5%).

Evaluation of efficacy

Overall efficacy

Comparison of the overall efficacy of the regimens was done based on complete remission achieved. A total of 45 (56.25%) patients (out of 80) achieved complete remission. Figure 2 depicts, among the 45 patients, 17 (38%) were on VAD regimen and 28 (62%) on Len-Dex regimen. The statistical analysis was done using chi square test (χ^2= 6.13, df= 1, p= 0.01) which shows statistically significant difference.

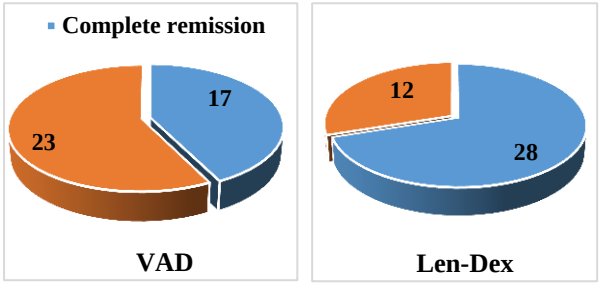

Figure 2: Overall efficacy - Comparison of VAD and Len-Dex regimens, n= 40 in each group (χ^2= 6.13, df= 1 and p= 0.046).

Serum myeloma protein

All patients recruited in the study had Myeloma proteins in their serum. After treatment, M proteins in serum were not detected in serum in 17 (42.5%) patients on VAD regimen and 28 (70%) patients on Len Dex regimen (Figure 3). Statistical comparison was done using chi square test (χ^2= 6.146, df = 1, p= 0.013).

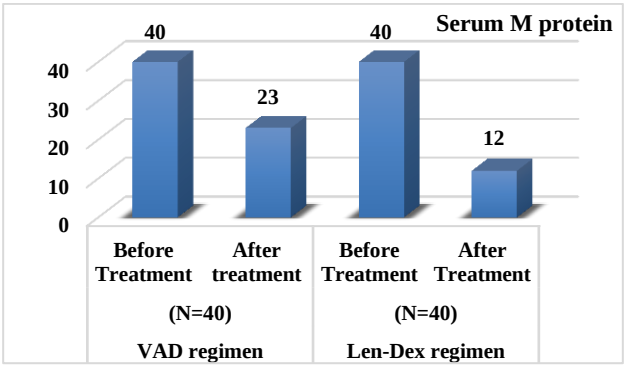

Figure 3: Recovery profiles indicated by serum M protein (χ2 = 6.14, df =1 and p = 0.013).

Plasma cells in bone marrow

Presence of plasma cell in bone marrow is another diagnostic criterion of multiple myeloma. It has been found that all patients recruited to both the regimens had more than 10% of plasma cells in their bone marrow. A count of < 5% after treatment is considered as complete remission whereas 5-10% indicates partial remission and all values above 10% are considered as failure of treatment. 17 (42.5%) patients on VAD regimen and 28 (70%) on Len-Dex achieved complete remission (Table 2). Partial remission was seen in 7 (17.5%) patients on VAD regimen and 4 (10%) on Len-dex regimen. 16 (40%) patients on VAD regimen and 8 (20%) patients on Len-dex regimen failed to attain remission. Analysis was done using chi square test (χ^2= 6.472, df= 2, p= 0.091).

Table 2: Bone marrow plasma cells after treatment with VAD and Len-Dex regimens (χ^2= 6.47; df= 2; p= 0.091).

Bone marrow plasma cells	VAD regimen (N=40)	Len-Dex regimen (N=40)
<5%	17 (42.5%)	28 (70%)
5-10%	7 (17.5%)	4 (10%)
>10%	16 (40%)	8 (20%)

Complete remission was seen with 42.5% of patients on VAD regimen and 70% on Len-Dex regimen (Figure 4). 17.5% on VAD regimen and 10% on Len-Dex regimen showed partial emission while 40% on VAD regimen and 20% on Len-Dex failed to respond.

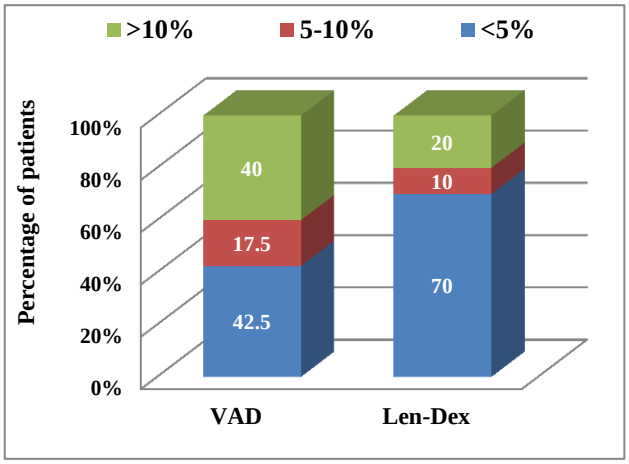

Figure 4: Recovery profiles indicated by bone marrow plasma cells, n= 40 in each group.

Lytic bone lesions

Lytic punched out lesions seen in X-ray of the skull is diagnostic of multiple myeloma. In this study all patients had such lesions. Disappearance of lytic lesions indicates complete remission. If it persists after treatment, it is considered as partial remission and appearance of new lesions as failure of treatment.

After treatment lytic lesions disappeared in 17 (42.5%) on VAD regimen and 28 (70%) patients on Len-Dex regimen, while in 13 (32.5%) on VAD regimen and 7 (17.5%) on Len-Dex regimen it persisted (figure 5). New lesions appeared in 10 (25%) on VAD regimen and 5 (12.5%) on Len-Dex regimen indicating failure of treatment. Analysis was done using chi square test (χ^2= 5.165, df= 3, p= 0.023) which shows that the results obtained are statistically significant.

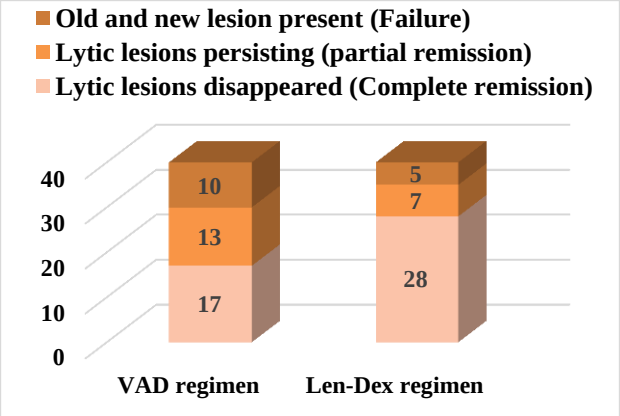

Figure 5: Lytic bone lesions after treatment - comparison of VAD and Len-Dex regimens (χ^2= 5.16; df= 3 and p= 0.023).

Erythrocyte sedimentation rate (ESR)

The ESR values of all patients were high in all patients recruited in both regimens, being one of the diagnostic criteria. A fall in ESR values to less than 20 is considered as complete remission while those above 20 as partial remission or failure. After treatment with VAD regimen the ESR values fell to less than 20 in 17 (42.5%) patients indicating complete remission. Patients on Len-Dex regimen showed that 28 (70%) had an ESR value less than 20. 42.5% of patients went into complete remission with VAD regimen and 70% with Len-Dex regimen (Figure 6).

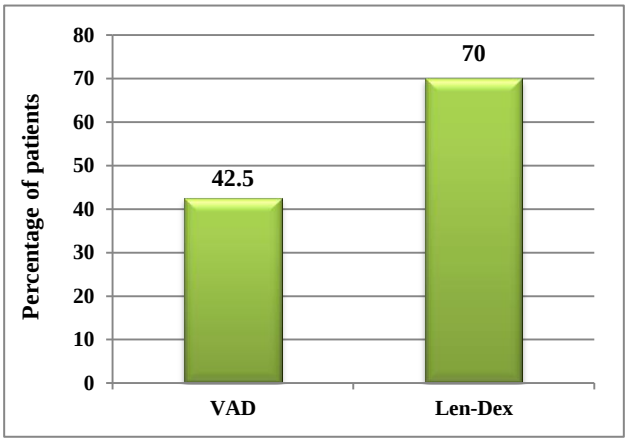

Figure 6: Recovery profile of VAD and Len-Dex regimens according to ESR values.

DISCUSSION

As thalidomide usage is teratogenic, its active analogues have been tried with varying success. In many of the preclinical studies lenalidomide has shown promising results.[14] Few multicentric studies have also shown improved remission rates.[18,19,24] These newer congeners are slowly replacing time tested Melphalan-prednisone (MP) combination in multiple myeloma patients older than 65 years.[25] Combination of a derivatives of thalidomide is reported to improve progression-free survival.[26] Such combination is considered the new standards of care for elderly patients with newly diagnosed multiple myeloma.[25]

Comparison of demographic profiles like age and sex showed that the mean age of patients included in Len-Dex regimen was less than that of VAD regimen. The maximum number of patients belonged to the age interval of 51 to 70 years, and majority received Len-Dex regimen.

The efficacies of the two regimens were compared by using the parameters like, serum M Protein, bone marrow plasma cells, lytic bone lesions and ESR. Comparison of overall efficacy based on the above criteria, showed that out of the 45 patients who achieved complete remission, majority of them received Len-Dex (62%). This shows that the efficacy of Len-Dex regimen is superior to VAD regimen which is statistically significant. This finding is consistent with the study done by Rajkumar SV et al and Gay F et al. The response rates of VAD in our study appeared comparable to previous studies.[22,23] The previous studies with lenalidomide and dexamethasone (both in higher and lower doses) has shown better short term overall survival in newly diagnosed myeloma patients.[27] This study evaluates the efficacy of medical management of multiple myeloma and effect of bone marrow transplantation or chemotherapy is not studied. In the current study, all patients responded to the drug treatment.

Adverse effect profile, though not reported here, shows that some adverse effects like nausea, vomiting are significantly less with Len-Dex regimen whereas others like constipation, leucopenia, thrombocytopenia, slow wound healing, sedation, renal toxicity and hepatotoxicity are high. VAD regimen produce higher incidence of nausea, vomiting, diarrhoea, anemia and peripheral neuropathy. Both regimens showed almost equal incidence of frequent upper respiratory infections, loss of weight, fever, pedal oedema, palpitations etc. The better tolerability of Len-Dex regimen offers a better quality of life to the patients. Long term study should be undertaken to assess disease progression and longevity. The performance status of the study population accessed using Karnofsky performance score evaluation showed that the overall improvement of performance status was higher in Len-Dex regimen compared to VAD regimen.

CONCLUSION

The efficacy of Lenalidomide-Dexamethasone combination therapy is clearly higher than that of VAD regimen among the study population. The overall efficacy of Len-Dex combination is 70% and that of VAD regimen is only 42.5%. Long term study should be undertaken to assess disease progression and longevity.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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