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Prospective Study of DCEP Chemotherapy in Patients with Relapsed or Refractory Multiple Myeloma

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Abstract: Multiple myeloma (MM) is the 2nd most common haematological malignancy among the elderly. Majority of MM patients develop refractoriness/relapse to conventional agents and in such patients, chemotherapy is one of the treatment options. However, prospective data on DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) chemotherapy is limited. This phase II prospective study intends to find out the response rate, toxicity and survival outcomes of DCEP infusional chemotherapy in relapsed or refractory MM patients (RRMM) who failed ≥ 2 conventional lines of treatment (including bortezomib and one of the IMiDs). The study period was from January 2012 to December 2013. Twenty one patients were recruited into the study. The median age was 48 years (range 38-63y). Male:female ratio was 12:9. ISS stage I, II and III were equally distributed. Of the 21 patients, 15 completed 6 cycles of DCEP chemotherapy, 4 discontinued and 2 expired after 1st cycle (cause being pneumonia and dengue haemorrhagic fever). Eight (53.3%) had an overall response (complete, very good partial and partial response). The 2 yr and 5 yr progression free survival (PFS) was 10.5% and 5.3% respectively. The 2 yr and 5 yr overall survival (OS) was 46.4% and 37.2% respectively. At a median follow up of 29.1 months, the median PFS was 9.3 months [95% CI 5.2-13.4m] and the median OS was 21.4 months [95% CI 0-46.0m]. There were 5 grade 3/4 haematological toxicities which was managed with prophylactic growth factors and appropriate supportive care. At 5 yr follow up, 4 patients are alive, of whom 3 are on subsequent novel agents and one continues to be in remission. DCEP chemotherapy has good response rate with manageable toxicity and should be considered as a salvage option in RRMM patients. Molecular studies in RRMM are needed to find patients who may get durable benefit with infusional chemotherapy regimens.
Keywords: Relapsed refractory multiple myeloma, Salvage therapy, DCEP.

INTRODUCTION

Multiple myeloma (MM) is a clonal proliferative disorder of malignant plasma cells, which predominantly manifests as anaemia, hypercalcemia, renal failure, repeated infections and skeletal related events. MM is essentially incurable and majority of the patients will experience relapse and/or refractoriness in their due course, a state known as Relapse Refractory Multiple Myeloma (RRMM). With the better insight into the biology and molecular pathogenesis of MM, there has been a paradigm shift in the treatment options for MM over the past few decades [1-3]. Novel agents like proteasome Inhibitors (PI), immunomodulatory drugs (IMiDs), monoclonal antibodies (Mab) and histone – deacetylase inhibitors (HiDAC inhibitors) are currently the novel treatment options for RRMM. These agents have shown to not only prolong the survival, but also to maintain good quality of life with acceptable toxicity profile [4-6]. The chemotherapy drugs like cyclophosphamide, doxorubicin, etoposide and cisplatin are accepted agents in combination or along with novel agents for RRMM. In patients who relapse after multiple lines of treatment, effective treatment options are very limited. The available data on combination chemotherapy with cyclophosphamide, dexamethasone, etoposide, and cisplatin (DCEP) infusional chemotherapy in RRMM is limited to retrospective series. Hence we conducted a prospective study (phase II design) to study the toxicity and efficacy of DCEP infusional chemotherapy in RRMM patients who failed at least two lines of conventional treatment.

MATERIALS AND METHODS

The study was conducted by the Department of Medical Oncology, Regional Cancer Centre, Trivandrum from January 2012 to December 2013, in patients with MM who relapsed after or refractory to at least two prior systemic treatments with conventional agents including bortezomib/ lenalidomide/ thalidomide/ combination chemotherapy of vincristine + adriamycin + dexamethasone (VAD)/ high dose chemotherapy and autologous peripheral blood stem cell transplant (HDC + auto PBSCT).

Inclusion / exclusion criteria

Eligibility criteria included age ≥18yrs, Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2, Absolute Neutrophil Count of >1500/cmm, Platelet count >50,000/cmm with adequate renal and hepatic reserve. Patients with deranged renal function (S.Creatinine>1.8 mg%), S.Bilirubin / transamines ≥ 2 x upper limit of normal and uncontrolled diabetes were excluded from the study. The protocol was approved by the Institute Review Board and the patients were enrolled after obtaining informed consent.

Study protocol

Baseline investigations included haemoglobin (Hb), total WBC count (TC), platelet count (PLC), blood urea (B. Urea), serum creatinine (S.Cr), serum bilirubin (S.Br), aspartate aminotransferase/ alanine aminotransferase (SGOT/SGPT), serum calcium (S. Ca), magnesium (S. Mg), sodium (S. Na), potassium (S.K), quantitative Immunoglobulin assay IgG, IgA, IgM, free light chain (FLC) assay and ratio, serum protein electrophoresis (SPE), 24 hour urine protein, bone marrow study, skeletal survey and MRI (if clinically indicated). Immunofixation (serum/urine) facility was not available at our centre during the study period. Before each cycle, adequate haematological and organ function reserve were ensured. Each cycle consisted of cyclophosphamide 300mg/m^2/day, etoposide 30mg/m^2/day, cisplatin 15mg/m^2/day as continuous i.v infusion over 24 hrs (D1-4), and dexamethasone 40 mg daily as i.v (D1-4). Cycles were repeated every 4 weeks for a total of 6 cycles. Appropriate anti-emetic measures and hydration status were ensured. Prophylactic G-CSF (granulocyte-colony stimulating factor) were given to all patients from day +4 till hematopoietic recovery. Response assessment, based on International Myeloma Working Group (IMWG) Response Criteria was done after 3rd and 6th cycle with Hb, TC, PLC, B. Urea, S.Cr, S.Br , SGOT / SGPT, S. Ca, S. Mg, S. Na, S. K, quantitative IgG, IgA, IgM, FLC ratio and SPE. Bone marrow study and skeletal survey were done after the 6th cycle. At each cycle visit, patients were examined for any signs or symptoms of clinical relapse and toxicity. Toxicity was graded as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In the event of grade 1 or 2 haematological toxicity, next cycle was given after its complete recovery. In patients with grade 3 or 4 haematological toxicity, 20% dose reduction for further cycles was done.

Endpoints

The primary endpoint of the study was overall survival (OS) defined as the time from the initiation of DCEP to the last follow up. The secondary endpoints were i) progression- free survival (PFS) defined as the initiation of DCEP to the start of subsequent therapy at progression ii) response assessment as per IMWG response criteria and iii) toxicity profile (graded as per CTCAE v 4.0). Overall response was defined as CR (complete response) plus VGPR (very good partial response) plus PR (partial response).

STATISTICAL ANALYSIS

The baseline patient characteristics, treatment characteristics, response assessment and toxicity profile were analysed using descriptive statistics. OS and PFS were analysed by Kaplan – Meier method, using SPSS v. 17.

RESULTS

Baseline patient characteristics: (shown in Table 1)

Twenty one patients met the eligibility criteria and were enrolled into the study. The median age was 48 yrs (range 38-63 yrs). Twelve were males and nine were females. Eight patients had Hb <10 g/ dL. ISS stage I, II and III were equally distributed among the study subjects. Out of 21 patients considered for the study, 11 had IgG myeloma, 4 had IgA, 1 had IgM and 5 had light chain myeloma. The median number of prior treatment lines was 3 (range 2-5). Regarding prior treatment lines, 21 (100%) had received bortezomib based regimen, 18 (86%) received one of the IMiDs (Len / Thal) also and 8 (38%) received VAD. 4 (19%) had undergone high dose melphalan and autologous peripheral stem cell transplantation (HDC + Auto PBSCT) as consolidation following primary treatment.

Treatment characteristics

All chemotherapy cycles were administered as inpatient. Of the 21 patients, 15 completed the planned 6 cycles of chemotherapy. 4 discontinued after 2nd cycle (due to logistic reasons) and 2 patients died after the 1st cycle of chemotherapy (1 – due to pneumonia, 1 – due to dengue haemorrhagic fever, NS1Ag+). Five patients had grade 3/4 haematological toxicities and 20 % dose reduction was given for further cycles. None of the patients needed a 2nd dose reduction.

Table-1: Baseline patient characteristics

Baseline patient characteristics *(n=21)*	n (%)
Median age (yrs)	48 (range 38-63)
M : F ratio	12:9
Hb < 10 g/ dL	8 (38)
Platelet count • 1,00,000/ cmm • 1,00,000 – 50,000 / cmm	 20 (95) 1 (5)
ISS Stage (n) • I • II • III	 7 (33.3) 7 (33.3) 7 (33.3)
Myeloma – subtype • IgG • IgA • IgM • Light chain myeloma ○ Kappa light chain ○ Lambda light chain	 11 (52.4) 4 (19) 1 (4.8) 5 (23.8) 4 1
Prior therapies (n, %) No. of lines , median (range) • Bortezomib • Thal / Len • VAD • HDC+ Auto PBSCT	 3 (2-5) 21 (100%) 18 (86%) 8 (38 %) 4 (19%)

Response assessment: (shown in Table 2)

Fifteen patients completed the planned 6 cycles of chemotherapy. After 3 cycles of chemotherapy, 1 patient achieved VGPR (very good partial response), 5 achieved PR (partial response) and 9 had SD (stable disease). At the end of 6 cycles, 4 attained CR (complete response), 1 attained VGPR, 3 attained PR, 2 were in SD and 5 had PD (progressive disease). Overall response [CR + VGPR + PR] to DCEP chemotherapy was seen in 8 patients (53.3%).

Among the 4 patients who achieved CR, 3 relapsed at 14, 22 and 39 months respectively and received next line of treatment. One patient continues to be in complete remission after DCEP chemotherapy at 5 year follow up.

Table-2: Response assessment

Status	After 3 cycles *(n,%)*	After 6 cycles *(n,%)*
CR	0 (0)	4 (26.7)
VGPR	1 (6.7)	1 (6.7)
PR	5 (33.3)	3 (20)
SD	9 (60)	2 (13.3)
PD	0 (0)	5 (33.3)

Survival analysis

The 2 yr and 5 yr OS was 46.4% and 37.2% respectively. The 2 yr and 5 yr PFS was 10.5% and 5.3% respectively. At a median follow up of 29.1 months, the median progression free survival was 9.3 months [95% CI 5.2-13.4] (figure 1) and the median overall survival was 21.4 months [95% CI 0-46.0months] (figure 2). At 5 year follow up, 4 patients are alive, 6 patients were lost to follow up and 11 expired (9 due to progression, 1 due to pneumonia, 1 due to dengue haemorrhagic fever).

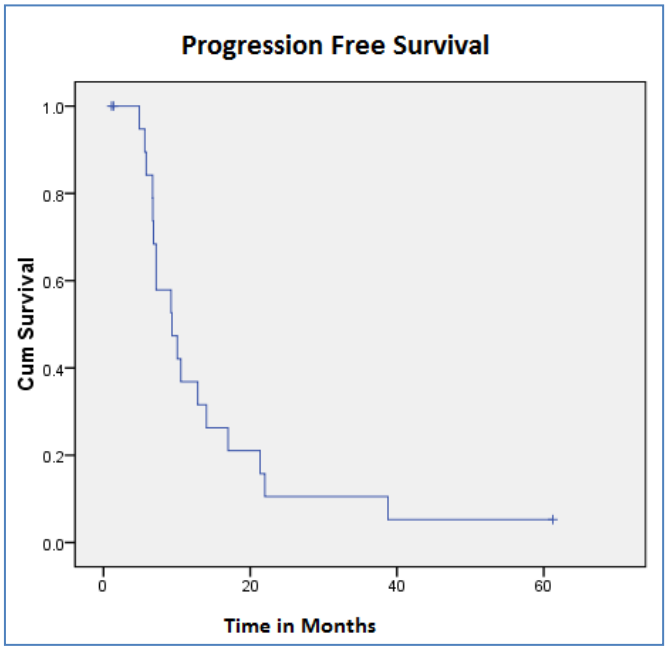

Fig-1: Progression free survival

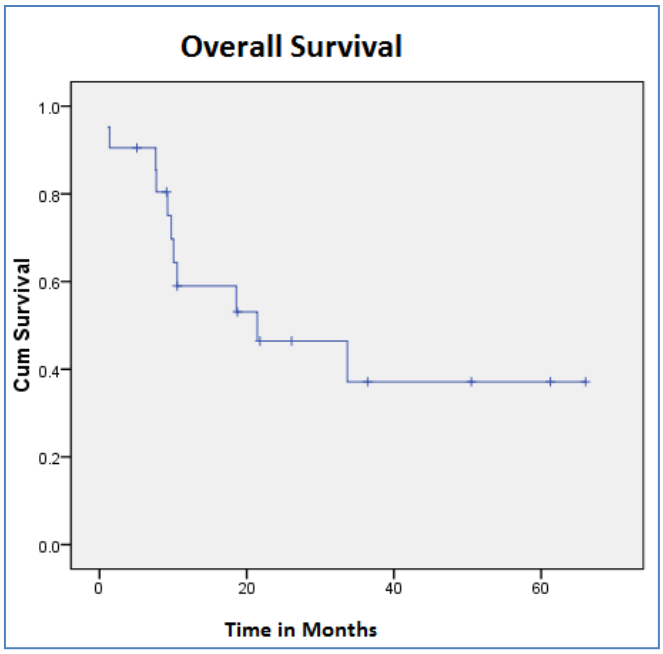

Fig-2: Overall survival

Toxicity profile: (shown in Table 3)

The majority of the toxicities were haematological. Grade 1-2 haematological toxicities were managed on an out-patient basis with hematopoietic growth factor support and antibiotics for febrile neutropenia. Grade 3/4 haematological toxicities were mainly seen in the 1st and 2nd cycles which were managed as in-patients with appropriate supportive care. There were no deaths due to haematological toxicity.

The non-haematological toxicities were of grade 1-2 severity, namely fatigue, vomiting, diarrhoea and mucositis; none had grade 3-4 adverse events. All the non-haematological toxicities were manageable on conservative lines. While on chemotherapy, 2 patients expired after the 1st cycle of chemo – 1st, due to pneumonia; 2nd - dengue haemorrhagic fever, NS1Ag+ve.

In our study, DCEP chemotherapy is a well-tolerated regimen and the toxicity profile seems to be manageable with appropriate and timely supportive care.

Table-3: Toxicity profile

	Grade 1-2 (n-21)	Grade 3-4 (n-21)	Grade 5 (n-21)
Haematological toxicity			
• Anaemia	8	5	0
• Thrombocytopenia	7	3	0
• Neutropenia	9	5	0
Non haematological toxicity			
• Fatigue	10	0	-
• Vomiting	5	0	0
• Diarrhoea	3	0	0
• Mucositis	2	0	0
• Pneumonia			1
• Unrelated cause (dengue haemorrhagic fever)			1

DISCUSSION

The novel/targeted agents like proteasome inhibitors, immunomodulatory agents, monoclonal antibodies and histone deacetylase inhibitors has widened the overall survival of myeloma patients including primary and relapsed refractory [7]. Chemotherapy has been the mainstay of treatment in RRMM before the advent of these novel agents, the main ones being melphalan (oral), low dose oral cyclophosphamide with steroids, VAD (Vincristine, Adriamycin, Dexona) regimen, etoposide high dose melphalan for auto PBSCT etc [8]. Pegylated liposomal doxorubicin is a renal friendly agent used for RRMM. Orlowski etal, in a randomised phase III study has evaluated bortezomib with or without pegylated liposomal doxorubicin in RRMM and had shown that the combination therapy was superior in terms of time to progression and survival rate [9]. The NCCN guidelines v 1.2019 includes chemotherapy regimens like DCEP, DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide), VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide) and high dose cyclophosphamide as options for aggressive RRMM patients. However there is paucity of prospective data on DCEP chemotherapy in RRMM patients. We could not find prospective data on DCEP chemotherapy in relapsed / refractory myeloma after extensive literature search. Our prospective study evaluated the efficacy and toxicity profile of DCEP infusional chemotherapy in multiple myeloma patients who relapsed after/refractory to at least two prior systemic treatments with conventional agents.

Dadacaridou M *et al*. evaluated DCEP regimen as 2nd salvage in 12 patients with RRMM and reported an overall response rate of 52% with manageable toxicity [10]. A retrospective study by Griffin etal has published the comparison data of 3 salvage infusional chemo regimens (DCEP, VTD-PACE, CVAD) [11]. According to the study, the ORR for DCEP, VTD-PACE and CVAD regimens were 52%, 73% and 49% respectively and it was also noted that the more intense VTD-PACE regimen was more toxic and not superior to DCEP in terms of survival. No correlation was noted between refractoriness to PI/IMiDs and response to infusional chemotherapy. In a recently published retrospective study by Park etal, 59 patients with RRMM received DCEP and the ORR was 45% with a median PFS and OS of 3.7m and 8m respectively [12]. All patients in the study had prior exposure to either an IMiD or a PI and the median number of prior therapies was 3 (range 1-7). However the reported treatment related mortality (TRM) was 14.8% which is probably due to the fact that prophylactic G-CSF was not mandatory in their protocol.

In our study, all patients were exposed to bortezomib previously and either one among IMiD or conventional chemo agents. 4 had undergone HDC and autologous PBSCT as consolidation after primary systemic treatment. The median number of prior treatment lines in our study was 3 (range 2-5). 15 patients completed the planned 6 cycles of DCEP infusional chemo and at the end of 6 cycles, 4 attained CR (complete response), 1 attained VGPR, 3 attained PR, 2 were in SD and 5 had PD (progressive disease). Overall response (CR + VGPR + PR) to DCEP chemotherapy was seen in 8 patients (53.3%) which is in similar tunes with other studies [10]. The median PFS and OS at 5 year follow up are 9.3 m [95% CI 5.2-13.4] and 21.4 m [95% CI 0-46.0 months] respectively. Among the 4 patients who achieved CR, 3 received the next line of treatment after an average of 37 months and 1 patient is maintaining his CR status at 5 yr follow up. This observation shows that there might be a subgroup of patients among RRMM who get durable responses with DCEP infusional chemotherapy. Further prospective molecular studies are indicated to understand the disease biology of these subset of patients.

The study regimen was well tolerated by our patients and they could complete the chemotherapy. The majority of the side effects were haematological, all of which were manageable with prophylactic G-CSF and antibiotics. None of the patients died due to

haematological toxicity, however 5 patients needed chemotherapy dose reduction in view of grade 3/4 hematologic toxicity. We recommend prophylactic G-CSF along with DCEP infusional chemotherapy, as was also shown in another study by Agnes Yuen *et al*. [13]. In our study, one patient died during the chemo due to dengue haemorrhagic fever and one died due to pneumonia. The pulmonary toxicity syndrome in the form of drug – induced pneumonitis following DCEP chemotherapy was reported by Fassan *et al*. [14]. In our observation, DCEP infusional chemo is a well-tolerated regimen for RRMM when used along with appropriate supportive care (including prophylactic G-CSF and antibiotics) and the side effects are manageable.

The limitation of our study is the small sample size. Although DCEP chemotherapy has been first evaluated as a mobilising regimen for peripheral blood stem cell harvest in multiple myeloma, recent reports suggest that in heavily pre-treated disease, DCEP chemo is an effective bridge therapy to auto SCT [15]. In a recently published retrospective study on DCEP chemo by Agnes Yuen etal, the ORR was 55% (total 65 patients) and those who were bridged to autologous stem cell transplant had significantly better OS compared to those who were not (median 32.8 vs 10.7m, p=.0004) [13].

CONCLUSION

DCEP infusional chemotherapy is a relatively safe and effective salvage regimen for RRMM. Further prospective molecular studies are needed to identify the subset of RRMM patients who would benefit with infusional chemotherapy regimens.

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