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Cyclophosphamide, Etoposide, Vincristine, Adriamycin, and Dexamethasone (CEVAD) Regimen in Refractory Multiple Myeloma: An International Oncology Study Group (IOSG) Phase II Protocol

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A 4- day continuous intravenous (CIV) infusion of vincristine and doxorubicin with high-dose dexamethasone (VAD) regimen is a standard refractory multiple myeloma (MM) regimen. A Phase II study of a CEVAD regimen, i.e., VAD plus etoposide administered as a 96-hr continuous infusion, was carried out with IV bolus cyclophosphamide. Thirty-six patients were treated on study and received a total of 114 cycles of CEVAD: median 2 cycles (range 1–8). No patient achieved a CR. The overall rate of PR was 15/36 (42%). Patients achieved maximal response after a median of 4 (range 3–6) courses. PR rates were 40% (4/10) in patients with primary refractory disease, 48% (11/23) in patients with secondary refractory disease, 31% (6/19) in patients who had failed previous VAD therapy, and 50% (7/14) in patients receiving 2nd or subsequent relapse therapy. Three patients died during their initial cycle of therapy from rapidly progressive disease and sepsis. Overall median survival was 24 weeks with a 1-year survival of 33.3% {95% confidence interval of 20–46%}. Myelosuppression was the most frequent adverse event with NCI grade 2 neutropenia and/or thrombocytopenia in 15% of first cycles, grade 3 in 20%, and grade 4 in 65%. Two-thirds of patients had at least one episode of grade 3 or 4 sepsis. In 15% of septic episodes positive blood cultures were obtained. Overt cardiotoxicity was seen in two patients. CEVAD as used in this study was not more effective than VAD in terms of overall response rate or survival. Am. J. Hematol. 63:125–130, 2000.

Key words: myeloma; cyclophosphamide; etoposide; vincristine; adriamycin; dexamethasone

INTRODUCTION

Standard regimens induce an average objective response (OR) rate (SWOG Criteria) of 40–50% in patients with previously untreated multiple myeloma (MM) [1]. Most patients who initially achieve remission eventually relapse, with less than 20% being in ongoing remission at 5 years from time of initial therapy. At least 40% of MM patients fail to adequately respond to induction chemotherapy [2]. While a single autologous stem cell transplantation (ASCT) prolongs survival if performed within 1 year of diagnosis, the majority of patients will ultimately relapse following ASCT [3]. Prolongation of median survival beyond 1 year in refractory MM patients is rarely achieved [2]. Failure of current cytotoxic therapy has lead to attempts to improve treatment by the investigation of mechanisms of cytotoxic drug resistance, to either prevent or circumvent drug resistance, and the pursuit of novel anti-MM agents [4].

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A 4-day continuous intravenous (CIV) infusion of vincristine and doxorubicin with high-dose dexamethasone (VAD) regimen is a standard refractory MM therapy [5]. Attempts to modify this regimen by giving the vincristine and/or doxorubicin by bolus injection rather than infusion and/or by the addition or substitution of other agents have not proven any better than the VAD regimen as initially described [6–21]. In the initial description of the VAD regimen, Barlogie et al., when initially describing the VAD regimen emphasized the potential importance of prolonged tumor exposure to cytotoxic drugs given as CIV infusions in the therapy of MM, referred to the long generation time and low growth fraction of malignant plasma cells in most patients [5].

Wilson et al. developed the etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) regimen and showed it to be very effective in refractory lymphoma [22,23]. On the basis of in vitro evidence that lymphoma cells were less resistant to prolonged exposure to low concentrations of some anticancer agents, compared with brief higher concentration exposures, they conducted a Phase II study of etoposide, vincristine, and doxorubicin, administered as a 96-hr continuous infusion, with IV bolus cyclophosphamide and oral prednisone in 74 consecutive patients who relapsed from or failed to respond to most of the same drugs administered on a bolus schedule. Seventy-one percent had previously received all of the drugs contained in the EPOCH regimen, and 92% had received at least four of the drugs. Seventy patients were assessable for response, of whom 19 (27%) achieved a complete remission (CR) and 42 (60%) a partial remission (PR) [22]. As positive EPOCH data was reproduced by other groups and in order to test this approach in patients with refractory MM [24]. We thus developed the CEVAD regimen which also contains etoposide, vincristine, and doxorubicin, administered as a 96-hr continuous infusion, with IV bolus cyclophosphamide and oral dexamethasone. Recombinant human granulocyte-macrophage colony stimulating factor (GM-CSF) has been shown to be effective in reducing the toxicity of systemic therapy in MM [25,26]. It was thus added to the CEVAD regimen as used in this International Oncology Study Group (IOSG) international multicenter Phase II study in patients with refractory MM.

METHODS

Study Design

This was a single arm international multi-center Phase II study designed to assess the response rates and survival duration associated with the protocol regimen in patients with advanced MM. Pretreatment evaluation involved a complete history and physical examination with an assessment of weight, height, and performance status, a full blood count with white cell differential, serum creatinine and bilirubin, blood urea, serum transaminases, blood glucose, serum calcium, serum protein and albumin, serum immunoelectrophoresis, immunoglobulin assay, monoclonal protein (M-protein) quantitation, a bone marrow aspirate and/or biopsy, chest radiograph and full skeletal survey, an ECG and a 24-hr urine collection for total and Bence Jones protein quantitation. Follow-up tests and evaluations were performed and documented at four weekly intervals during the administration of chemotherapy. During the maintenance phase follow-up evaluations were performed every 12 weeks. In addition, evaluations were documented at disease relapse, and when a patient went off protocol. The protocol complied with the World Medical Association Declaration of Helsinki for biomedical research involving human subjects. Prior to patient recruitment, the protocol was reviewed and approved by the ethics committee (or its equivalent) of each participating institution. All patients were required to give informed consent according to institutional guidelines prior to commencing protocol treatment.

A complete remission (CR) was defined as a response to treatment with undetectable paraprotein by immunoelectrophoresis on two determinations at least 4 weeks apart without hypercalcemia or progression of bone lesions with a normal bone marrow with <5% plasma cells, normal peripheral blood values and no MM-related signs or symptoms. CR also required a normal serum calcium, serum proteins, normal levels of polyclonal immunoglobulins, and normal serum viscosity with resolution of all soft-tissue plasmacytomas. A PR was defined as a reduction in the serum M-protein concentration on two determinations at least 4 weeks to less than 50% of the base line value in serum with no evidence of progression of bone lesions (±25%) or hypercalcemia. PR also required that all baseline soft-tissue plasmacytomas must reduce by >50% the sum of the products of the cross diameters of each measurable lesion and that there be a decrease in bone pain from severe/moderate to mild/none. Stable disease was defined when the response was neither a response nor progressive disease. Progressive disease was defined as an increase of more then 25% in M-protein concentration in serum or appearance of new or progression (>25%) of bone lesions or plasmacytomas as measured serially by the sum of the products of the cross diameters of each measurable lesion. Collapse of bony structures from preceding disease did not constitute disease relapse or progression. Primary resistance to a regimen was defined as a >50% in the serum M-protein levels, measured on two determinations 2 weeks apart, when compared with baseline measurements, while the patient was still therapy with that regimen, having received 2 or more cycles of therapy. Results from recent studies involving systemic chemotherapy in relapsed or primary resistant MM indicate median survival durations

of 1 year. The desired outcome of this study was to achieve a survival duration of 2 years. Assuming *N* patients have been followed until death or at least for 1 year, a 95% confidence interval for an observed survival rate at 1 year of 75% would go no lower than 60% if *N* is >33. We thus proposed that 36 patients would be entered on protocol. Survival time was measured from day 1 of first CEVAD cycle to date of death. The survival analysis was calculated according to the method described by Kaplan and Meier.

Patients

Eligible patients with MM were registered centrally at the IOSG Data Office. Patients with previously treated Stage II or III MM were eligible if the patients had either (a) demonstrated primary refractoriness to at least two cycles of induction chemotherapy which includes an alkylating agent (e.g., MP) *and/or* a topoisomerase II inhibitor (e.g. VAD), or (b) achieved a response but relapsed while still on induction therapy or post remission. For entry on protocol patients were required to have an ECOG performance status of less than or equal to 3 and to be 18 years of age or older. Included patients had no active cardiac problems by history, examination, or investigation (ECG/ chest radiograph). Patients were ineligible for entry on protocol if they had a history of impaired cardiac status, myocardial infarction within 3 months, or angina requiring medication. For inclusion on protocol baseline bilirubin had to be less than or equal to 1.5 the upper limit of normal range (ULN) and SGOT or SGPT less than three times the ULN. Women who were pregnant or lactating at the time of diagnosis were not protocol eligible. Patients were advised that they should not plan on conceiving children during the treatment program and that women becoming pregnant on-protocol would be removed from protocol. Patients with a serious medical or psychiatric condition precluding protocol therapy, preventing informed consent, or potentially limiting survival to less than 6 months were not protocol eligible. Patients with nonsecretory or Bence Jones protein-only MM were not protocol eligible.

Treatment

Patients had insertion of a double-lumen central venous catheter prior to commencement of therapy. They then received the CEVAD regimen at 28-day intervals until maximum degree of response was documented plus one further consolidation cycle *or* until a maximum of eight cycles in total had been received. CEVAD was administered as follows cyclophosphamide 1,000 mg/m^2 IV day 6 only, etoposide 50 mg/m^2/day CIV days 1–4 (total 200 mg/m^2), vincristine 0.4 mg/day CIV days 1–4 (total 1.6 mg), doxorubicin 9 mg/m^2/day CIV days 1–4 (total 36 mg/m^2), and dexamethasone 40 mg PO daily days 1–4 (total 160 mg). H_2-blockers were administered together with dexamethasone. GM-CSF 250 mg/m^2 per day was added to each course on day 7 and continued until the absolute neutrophil count (ANC) was $>2 \times 10^9$/L or had returned to baseline ANC value if that value was $<2 \times 10^9$/L and felt to be attributable to active MM. GM-CSF was discontinued at least 48 hr prior to a subsequent CEVAD cycle. Radiation to local lesions as clinically indicated was allowed if such radiation in total was to less than 20% of the skeleton. Evaluation for response was performed before starting each CEVAD cycle. Patients were prescribed allopurinol 300 mg/day for the first 21 days of therapy and monitored following the initial cycles of CEVAD to detect and treat adverse effects of rapid tumor lysis.

Toxicity was graded per the NCI toxicity criteria, and dose adjustments were made on the basis of these grades. Dexamethasone was discontinued for active peptic ulcer disease, uncontrollable hyperglycemia, uncontrollable serious infection, steroid psychosis, severe thromboembolic disease, or any Grade 4 toxicity. Dexamethasone was tapered if steroid-withdrawal symptoms occurred. The dose of both doxorubicin and cyclophosphamide were reduced by 50% if the ANC was between 1 and 2 $\times 10^9$/L and/or the platelet count between 50 and 100 $\times 10^9$/L.

Doxorubicin was discontinued for any clinical evidence of cardiac failure, ECG changes, decrease in cardiac ejection fraction below baseline or normal as applicable, and bilirubin elevation to more than twice ULN. Vincristine dose was reduced by 50% for Grade 2 paresthesia or constipation, and was discontinued for any Grade 3 or 4 event.

Patients were removed from protocol for progressive or relapsing disease, intolerable toxicity, or if the constraints of the protocol were deemed to be detrimental to the patient's health and/or the patient no longer wished to continue protocol therapy. If the patient showed a stable disease response after the first two cycles of CEVAD, four further cycles, i.e., a total of six cycles, were given as long as the disease remained stable. All protocol patients were to be followed and reported on until death.

RESULTS

Patient and Treatment

Thirty-six patients were treated in this study. Table I shows the patient's baseline clinical characteristics. Patients received 114 cycles of CEVAD, and the median was 2 cycles (range 1–8) with 14 patients receiving 1 cycle, 4 patients receiving 2 or 3 cycles, 3 patients receiving 4 cycles, 2 patients receiving 5 cycles, 7 patients receiving 6 cycles, and 2 patients receiving 8 cycles.

Response and Survival

No patient achieved a CR. The overall rate of PR was 15/36 (42%). Patients achieved maximal response after a

TABLE I. Characteristics of Patients at Study Entry

Number of patients	36
Male/female	22/14
Age in years, median/range	61 (52–65)
Months from diagnosis to entry into study	22 (3–38)
Median/range	
Disease status	
Primary refractory	12
Secondary refractory	24
More than one prior relapse	14
Previous treatment with VAD	19
Durie-Salmon stage at study entry	
II	8
III	28
M-protein isotype	
IgG	30
IgA	6

TABLE II. Response Rates According to Patient Subgroups

Subgroup (evaluable patients)	Partial remission (%)	Progressive disease (%)	Stable disease (%)
All patients ($N = 33$)	15 (45)	12 (36)	6 (18)
Primary refractory ($N = 10$)	4 (40)	6 (60)	
Secondary refractory ($N = 23$)	11 (48)	6 (26)	6 (26)
Previous VAD ($N = 19$)	6 (31)	13 (69)	
≥2 relapse ($N = 14$)	7 (50)	7 (50)	

median of 4 (range 3–6) courses. Table II shows the response rates by patient subgroup. Three patients died during their initial cycle of therapy from rapidly progressive disease and sepsis and are not assessable as regards response. Figure 1 shows overall survival; median survival was 24 weeks with a 1 year survival of 33.3% {95% confidence interval of 20–46%}.

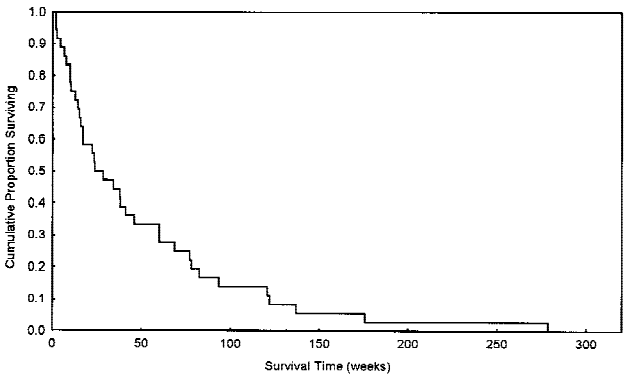

Fig. 1. Overall survival of all patients.

Toxicity

Fourteen patients received only one cycle of CEVAD therapy. One patient proceeded to ASCT after his initial cycle of therapy from which he had achieved a PR. Three patients died during their initial cycle of therapy from rapidly progressive disease and sepsis. One patient developed a grade 4 generalized itch skin rash which was possibly caused by GM-CSF during his initial CEVAD cycle and declined further protocol therapy. Two patients developed gram-negative septicemia during the first cycle and were taken off protocol by their physicians. Three patients, all of whom had normal baseline serum creatinine values, developed acute renal failure requiring dialysis after completing one CEVAD cycle. All three patients had biochemical signs of tumor lysis syndrome and did not receive further therapy on protocol. Four patients with rapidly progressive disease had no overt response to their first cycle of therapy and were removed from protocol by their physicians.

Myelosuppression was the most frequent adverse event with grade 2 neutropenia and/or thrombocytopenia in 15% of first cycles, grade 3 in 20%, and grade 4 in 65%. Two patients had overt gastrointestinal bleeding attributable to CEVAD-induced thrombocytopenia. Hematologic toxicity decreased with increasing number of treatment cycles per patient as non-responding patients were taken off therapy. No significant relationship between baseline ANC or platelet count and CEVAD-attributable myelosuppression was evident. Two-thirds of patients had at least one episode of grade 3 or 4 sepsis while on protocol. In 15% of septic episodes positive blood cultures were obtained—all in the first cycle of therapy. Overt cardiotoxicity was seen in two patients who experienced moderate left ventricular failure (NYHA grade II) after 2 courses each of CEVAD: both had received prior VAD therapy and a cumulative prior doxorubicin dose of over 300 mg/m^2 doxorubicin each. One patient each developed vincristine-attributed grade 2 constipation and grade 3 painful parasthesias. Two patients required dexamethasone dose-adjustment for hyperglycemia.

DISCUSSION

The VAD regimen has become a standard front-line and relapse regimen in MM [17,18,27–30]. Reported overall response rates vary from 50% to 80% in previously untreated patients depending on response criteria used, number of courses given, and the prognostic subgroups involved. In MM patients with advanced disease response rates of about 60% are attributable to VAD if patients are receiving this regimen for the first time; rates are much lower if patients have been previously treated with VAD [4].

A dual approach to potentially improving on VAD results was taken in this study: (1) the addition of cyclophosphamide and etoposide and (2) infusional administration of the etoposide. Cyclophosphamide and etoposide when used in combination with doxorubicin, and high-dose betamethasone (EACB) or with idarubicin and

dexamethasone (DC-IE) as MM salvage therapy, have given favorable results [31,32]. Dimopoulous et al. have previously documented the efficacy of a combination of cyclophosphamide, etoposide, and GM-CSF in VAD-resistant MM, reporting a 42% PR rate in 52 patients [33]. This group also documented a 40% PR rate in a cohort of 58 MM patients who had failed both prior melphalan and prednisone (MP) and VAD therapy with the hyperCVAD regimen which is cyclophosphamide 300 mg/m^2 IV over 3 hr every 12 hr for 6 doses plus a 48-hr CIV infusion of vincristine and doxorubicin and oral dexamethasone [34]. Thus it appeared reasonable to add both cyclophosphamide and etoposide for a potential additive or synergistic effect with VAD as originally described.

Wilson et al. in their development of the EPOCH regimen highlighted the potential importance of prolonged exposure of tumor cells to relatively low concentrations of cytotoxic agents [22,23]. Of 70 evaluable patients who relapsed from or failed to respond to most of the same drugs administered on a bolus schedule, 19 (27%) achieved a CR and 42 (60%) a PR. Among 21 patients who had no response to prior chemotherapy, 15 (71%) responded [22]. The IOSG thus developed the CEVAD regimen which is very similar to EPOCH and conducted an international multi-center Phase II study in refractory MM patients.

CEVAD proved to be a significantly toxic regime in this patient population. The overall results of CEVAD on this study showed no evidence that this regimen is more effective than VAD in terms of overall response rate (less than 50%) or survival (median survival 24 weeks). CEVAD appears to cause more myelosuppression than VAD although only a prospective comparison would allow this to be properly assessed. Although CEVAD was able to achieve PR in 31% of previously VAD-resistant patients, these responses were transient and not associated with long-term survival. Based on this data, the CEVAD regimen as used in this study does not have any clear advantage over the simpler VAD regimen. The IOSG is currently pursuing liposomal daunorubicin-based regimens in MM based on data that these preparations of anthracyclines may be less MDR modulated; initial positive data in MM have been reported [35].

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