Cancer Chemother Pharmacol (1995) 35: 343–344

CLINICAL TRIAL REPORT

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Vincristine and oral etoposide in refractory multiple myeloma

Received: 6 May 1993 / Accepted: 15 July 1994

Abstract A total of 15 patients with refractory multiple myeloma (MM; 4 primary unresponsive and 11 relapsed and resistant to re-induction/salvage therapy) received i.v. vincristine on day 1 and oral etoposide daily for 4 days, the treatment being repeated at 3-weekly intervals. The patients were re-assessed after three cycles of chemotherapy, and non-responders received no further therapy. There was no complete or partial response. A minimal response was seen in two patients, and two others showed stable disease. None of the responses was sustained, and all patients eventually had progressive disease. It is concluded that combination chemotherapy with vincristine and oral etoposide given by this schedule is unlikely to be of any value in refractory myeloma.

Key words Refractory multiple myeloma · Vincristine Etoposide

Introduction

The term "refractory multiple myeloma" (MM) can be applied to those cases where disease is either resistant to initial therapy (non-responders) or those where re-induction or salvage regimens are ineffective after relapse. The role of vincristine in combination chemotherapy regimens is well established in both the initial management and salvage therapy of myeloma [3, 9]. In myeloma resistant to VAD (vincristine, Adriamycin and dexamethasone), the use of etoposide (a semisynthetic podophyllotoxin derivative) as a single agent has produced no response; however, it has been reported to be effective in combination therapy [4]. Teniposide, an analogue of etoposide, has also been successfully used in combination with cyclophosphamide and dexamethasone for the treatment of refractory myeloma [8]. We investigated the combination of vincristine and etoposide, as this can be readily given on an out-patient basis, with minimal myelosuppression.

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Patients and methods

Patients with MM refractory either to melphalan and prednisolone (cyclophosphamide and prednisolone in those with associated renal impairment) or to VAMP (vincristine, Adriamycin, methyl prednisolone) were studied. All patients had a performance status of 2 or better on the Eastern Co-operative Oncology Group (ECOG) scale. Full blood count, estimation of renal and liver function, serum calcium, serum electrophoresis, estimation of monoclonal paraprotein ("M" band) and urinary light chains were performed before treatment and periodically thereafter.

Patients were treated with i.v. vincristine (2 mg by injection) on day 1 and with oral etoposide (200 mg daily) for 4 days. Cycles were repeated at 3- to 4-weekly intervals, depending on the blood counts. A complete response (CR) was defined as the complete disappearance of paraprotein from serum and urine, with $<5\%$ plasma cells in bone marrow [7]. A partial response (PR) was defined as a $>50\%$ reduction in serum paraprotein. A minimal response (MR) was defined as a $>25\%$ but $<50\%$ reduction in serum paraprotein with relief of symptoms. Stable disease (SD) was defined as either no change or a response smaller than an MR. Any remaining patients were classified as having progressive disease (PD). Patients were re-evaluated after three cycles, and those with either SD or PD received no further treatment. Responders received further cycles until they achieved a plateau of paraprotein or their disease progressed.

Results

A total of 15 patients were studied; their characteristics are summarised in Table 1. In all, 4 patients were resistant to induction therapy, and 11 who had previously responded were refractory to re-induction and/or salvage therapy. No patient achieved either a CR or a PR. One patient achieved a short-lived MR after three cycles, only to relapse with progressive disease after a fifth cycle of treatment. Another

Table 1 Patients' characteristics and treatment results

Number of patients	15
Median age (years)	58 (range, 43–67)
M:F	12:3
Monoclonal paraprotein type:	
IgG kappa	8
IgG lambda	3
IgA kappa	2
IgA lambda	1
Kappa light chain only	1
Stage:	
IIA	1
IIIA	13
IIIB	1
Primary resistance:	
Melphalan + prednisolone	1
Cyclophosphamide	1
VAMP	2
Relapsed refractory:	
Melphalan + prednisolone (M + P)	3
M + P and VAMP	4
High-dose melphalan	2
High-dose busulphan	1
Cyclophosphamide	1
Responses:	
CR	0
PR	0
MR	2
SD	2
PD	11

patient achieved an MR but relapsed within 4 weeks of completing therapy. Two patients achieved SD that was not sustained after treatment was stopped. The remaining 11 patients displayed PD. The toxicity of the regimen was negligible, and no patient developed leucopenia or thrombocytopenia to a degree that necessitated delays in treatment. Only two patients suffered grade 1 nausea (WHO) [10].

Discussion

The majority of patients with MM show an objective response to first-line chemotherapy. Those with 50%–75% tumour regression after induction therapy remain in remission for an average of 3 years [6]. However, ultimately, all patients relapse. Patients who fail initial chemotherapy are unlikely to respond to any subsequent treatment and achieve a median survival of only 15 months from the start of therapy [5]. Chemotherapy of relapse using single agents has proved disappointing, but response rates and survival are better with combination regimens [6], median survival being 16 months with the VAD protocol [2]. The outlook for those patients with refractory MM that fails first-line chemotherapy or re-induction/salvage therapy is dismal. Such patients are therefore often offered investigational drugs.

Vincristine, used as a single agent in patients with relapsed myeloma resistant to melphalan, elicits a response in 25% of cases [1]. Etoposide, used in the same way, produces no response. However, the addition of etoposide to dexamethasone, cytosine arabinoside (Ara-C) and cisplatin (EDAP regimen) is reported to have resulted in a 40% response rate with a median survival of 4.5 months, while its omission (DAP regimen) produced no response at all [4]. This study therefore suggests a possible role for etoposide in combination chemotherapy for resistant myeloma.

In the study reported herein, refractory MM was treated with a combination of vincristine and etoposide. Only two MRs were seen, and two patients achieved SD for the duration of treatment; none of these responses was sustained. The disease ultimately progressed in all 15 patients, necessitating alternative salvage therapy. From these results it is concluded that the combination of vincristine and etoposide given in this schedule and at these doses is inactive against refractory MM.

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