Leukemia (1997) 11, Suppl 5, S22–S26

Oral idarubicin, dexamethasone and vincristine (VID) in the treatment of multiple myeloma

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In order to replace the central venous line necessary for continuous infusion of vincristine and doxorubicin with high-dose dexamethasone (VAD) and to avoid hospitalization, we evaluated the efficacy and toxicity of oral idarubicin, vincristine and dexamethasone (VID) in patients with multiple myeloma. Vincristine (1.6 mg/m², max 2 mg) was given as a bolus injection on day 1. Idarubicin was given in capsules 10 mg/m²/day for days 1–4 with an intraindividual dose escalation, 40 mg dexamethasone were given on days 1–4, 9–12, 17–20. Treatment cycles were repeated every 28 days. At this interim analysis, 53 patients have been entered into the ongoing trial; 46 patients are evaluable for toxicity. The median age was 60 years (interquartile range, 52–65). 46% were primary or secondary refractory, 20% had previously been treated with VAD and 30% had previously untreated disease, 4% had two or more relapses. Four patients died within 2 months from entry and were considered as early deaths (8.7%). 45% of the 42 patients evaluable for efficacy achieved a partial remission and 26% a minor remission. The median reduction of the M-component was 43% (interquartile range, 25–64%). VID is an effective and convenient alternative to VAD even in relapsed or refractory patients.

Keywords: multiple myeloma; idarubicin; oral application; VAD; VID; therapeutic trial

Introduction

The continuous infusion of vincristine and doxorubicin (adriamycin) over 96 h combined with high-dose oral dexamethasone (VAD) is an established therapy for patients with relapsed or refractory multiple myeloma and may also be administered in high risk patients as first-line treatment.[1] The rationale for the protracted administration is based on the long generation time and the low growth fraction of myeloma cells in most patients.[2,3] As treatment with melphalan severely impairs the mobilization of autologous peripheral stem cells,[4] many patients are treated with VAD before high-dose chemotherapy.[5] The administration of VAD, however, necessitates a central venous catheter, which is complicated by infection, thrombosis and other problems in up to 24% of the cases.[6] Therefore a cytotoxic agent with oral administration is needed.

Idarubicin (4-demethoxy-daunorubicin) is an anthracycline with several properties not seen in other substances of this group.[7,8] Being highly lipophilic it is the only orally absorbed anthracycline.[9] Its main metabolite, idarubicinol, shows cytotoxicity comparable with the mother compound.[10] The terminal half-life of idarubicin is about 33 h and about 66 h for idarubicinol.[11] After oral administration of idarubicin the combined bioavailability of idarubicin and idarubicinol is about 41%.[11] Furthermore, it has been shown that the cytotoxicity of idarubicin is less influenced by P-glycoprotein-associated multiple drug resistance,[12] it has a 20% higher DNA-binding than daunorubicin[13] and it is clearly less cardiotoxic than doxorubicin.[14,15] Therefore, it seems feasible and much more convenient for the patient to replace the continuous infusion of doxorubicin through a central venous line by the oral administration of idarubicin.[16] Such a new regimen would be attractive even if its therapeutic efficacy is not superior to VAD.

In this interim analysis we report on 46 patients with different stages of multiple myeloma treated with oral idarubicin, dexamethasone and a bolus injection of vincristine (VID).

Patients and methods

The study was designed as a phase II study and approved by the appropriate ethical committees. Patients were included from 10 participating centers when written informed consent was obtained. For inclusion of a patient the diagnosis of multiple myeloma had to be confirmed according to the British Columbia Cancer Agency criteria[17] and one of the criteria shown in Table 1 had to be fulfilled. Patient accrual is continued.

Vincristine was administered as an intravenous bolus injection on day 1 (1.6 mg/m², max 2 mg). Idarubicin (Zavedos; Pharmacia and Upjohn, Erlangen, Germany) was given as capsule, 10 mg/m²/day p.o., on days 1–4 (total dose 40 mg/m²/course). If the leukocyte count at nadir was above 2.0 g/l and the platelet count at nadir above 75 g/l, the idarubicin dose could be augmented by 1 mg/m²/day each cycle to a maximum of 13 mg/m²/day on days 1–4 (total dose 52 mg/m²/course) after three courses of dose escalation. When leukocytes fell below 1 g/l or platelets below 50 g/l the last dose escalation was reversed and no further dose escalation was undertaken. Patients experiencing neutropenia in the first course of therapy received 8 mg/m²/day on days 1–4 (total dose 36 mg/m²/course). If neutropenia occurred at this dose level, the patient had to be withdrawn from the study. Dexamethasone was given 40 mg daily p.o. on days 1–4, 9–12, 17–20. Courses were repeated on day 29 for up to eight courses.

Patients received radiation to bone lesions if necessary. Pamidronate (90 mg) was given every 4 weeks and ranitidine (in some centers other H_2-blockers) was administered together with dexamethasone. A complete blood count, paraprotein concentrations, creatinine and serum calcium levels were assessed before each treatment course, bone lesions were examined every three courses or immediately if there were signs of progression

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Table 1 Inclusion criteria

Previously untreated patients
1 Patients with high-risk multiple myeloma in Durie–Salmon stage II or III (A/B) (eg with advanced osteolytic lesions or very high levels of M-component) who should be treated with VAD according to the institutions treatment guidelines.
2 Patients with multiple myeloma in any stage scheduled to receive high-dose chemotherapy with stem cell reinfusion.

Patients with relapsed or refractory disease.
3 Patients with multiple myeloma in Durie–Salmon stage II or III (A/B) not responding to melphalan and prednisone standard-dose induction therapy (primary refractory)
4 Patients with multiple myeloma in Durie–Salmon stage II or III (A/B) not responding to chemotherapy (either a repeated induction therapy or a different regimen) at relapse
5 Patients with multiple myeloma in Durie–Salmon stage II or III (A/B) with two or more relapses
6 Patients with multiple myeloma in Durie–Salmon stage II or III (A/B) previously treated with VAD

The disease stage was determined according to Durie and Salmon.[18] A complete remission was defined as a response to treatment with undetectable paraprotein by immunelectrophoresis without hypercalcemia or progression of bone lesions. A partial remission was assumed when the M-component concentration was reduced to less than 50% of the base line value in serum or to less than 10% of the baseline value in urine, in the case of light chain excretion only, with no evidence of progression of bone lesions (±25%) or hypercalcemia. A minor remission was assumed when the M-component concentration was reduced to 76–50% of the base line value in serum or 10–51% in urine and if there was no progression of bone lesions or hypercalcemia. A stable disease (no change) was assumed when the M-component change was ±25% in serum or ±50% in urine with no change in bone lesions and no hypercalcemia. Progressive disease was defined as an increase of more than 25% in M-component concentration in serum and more than 50% urine or a progression (>25%) of bone lesions. Response in nonsecretory myeloma was classified according to the reduction of bone marrow infiltration by atypical plasma cells (<50%: partial remission, 26–50% minor remission etc).

Median and interquartile ranges or 95% confidence intervals (95% CI) are given where appropriate. The survival analysis was calculated according to the method described by Kaplan and Meier.[19] All computations were performed with the Statistical Package for the Social Sciences (SPSS für Windows, Rel 6.1.2; Munich, Germany).

Table 2 Base line characteristics of evaluable patients at study entry

Number of patients	46
Male/female	26/20
Age (years)	60 (52–65)
Months from diagnosis to entry into study	17 (2–41)
Disease status	
Primary refractory	9
Secondary refractory	12
More than one relapse	2
Previous treatment with VAD	9
Previously untreated	
High-risk myeloma	10
Preparation for ASCT	4
Highest Durie–Salmon stage at or prior to entry into the study	
IA	1
IIA	9
IIIA	30
IIIB	6
M-component isotype	
IgG	30
IgA	13
Light chain	2
Non-secretory	1

ASCT, autologous peripheral stem cell transplantation.

Results

Fifty-three patients have been entered into the study until June 1997. Two patients were excluded after registration: one patient, who had already been treated with idarubicin and dexamethasone; another patient was excluded since she died after 2 days of chemotherapy in the first course from pneumonia acquired before the start of chemotherapy. Five patients are not yet evaluable. Forty-six patients are currently evaluable with respect to response and toxicity. Base line characteristics of these patients are shown in Table 2. Four patients (8.7%) died within 2 months from entry into the study. Forty-two patients were evaluable for response. At this interim analysis, data of 206 treatment courses were evaluable (median four courses per patient, range 1–8).

The overall rate of partial remission was 19/42 (45.2%; 95% CI 30–61%) (Table 3). Patients achieved maximal response after a median of four (3–6) courses. The median reduction of shows the response rates and the median M-component reduction rates for subgroups.

Two patients died due to hematological complications. One patient (age 60 years) succumbed to neutropenic sepsis in the first course which was clearly therapy-related. He had received intensive pre-treatment with 15 courses of melphalan before and had experienced several neutropenia episodes after the administration of melphalan. Another patient (age 70 years), also intensively pretreated with three lines of therapy and severely thrombocytopenic at entry into the study, died from intracerebral hemorrhage after the second course of VID while still thrombocytopenic.

The idarubicin dose was escalated in 15 patients. Two of the 27 other patients had a WHO grade IV leukocytopenia (WBC <1.0 g/l) and four patients a WHO grade III leukocytopenia (WBC 1.0–2.0 g/l) after the first course and were therefore not eligible for dose escalation. In the other 21 patients a dose escalation was not performed. Of the 15 patients with dose escalation, 11 have had at least four courses at this interim analysis and three (27%) of those patients did not reached the highest dose level due to hematological toxicity, whereas eight patients escalated to the highest dose level

Table 3 Response rates and M-component reduction rates according to patient subgroups

Subgroup (evaluable patients)	*Partial remission (%)*	*Minor remission (%)*	*No change (%)*	*Progressive disease (%)*	*M-component reduction (%)*
All patients ($n=42$)	19 (45.2)	11 (26.2)	6 (14.3)	6 (14.3)	42.8 (25–64)
Primary refractory ($n=8$)	4 (50.0)	1 (12.5)	3 (37.5)	0 (0)	41.7 (15–59)
Secondary refractory ($n=11$)	2 (18.2)	4 (36.4)	1 (9.1)	4 (36.4)	38.4 (0–49)
Previous VAD ($n=9$)	4 (44.4)	3 (33.3)	1 (11.1)	1 (11.1)	46.8 (27–63)
⩾2 relapse ($n=2$)	1			1	
De novo disease before ASCT ($n=4$)	2 (50.0)	2 (50.0)	0	0	43.9 (34–55)
De novo disease high-risk ($n=8$)	6 (75.0)	1 (12.5)	1 (12.5)	0	70.1 (31–83)

ASCT, autologous peripheral stem cell transplantation.

influence of dose escalation on the overall remission rate could be demonstrated (data not shown).

Complete data to evaluate the nadir was available for 146 courses. In all patients the percentage of courses with WHO grade IV leukocytopenia (WBC <1.0 g/l) was 9.6% and WHO grade III leukocytopenia (WBC 1.0–2.0 g/l) was 13.7%.

Clinically relevant cardiotoxicity was seen in one patient only who experienced moderate left ventricular failure (NYHA grade II) after 14 courses of VAD plus four courses of VID and a cumulative dose of approximately 504 mg/m^2 doxorubicin and 184 mg/m^2 oral idarubicin. Treatment was continued with dexamethasone and vincristine only and the patient recovered from clinical symptoms.

The survival from entry into the study is shown in Figure 1. As 75% of the patients have been observed for not more than 210 days it is expected that the plateau in the survival curve will not persist with further follow-up.

Discussion

This study demonstrates that the combination of oral idarubicin with an intravenous bolus injection of vincristine and oral high-dose dexamethasone (VID) is active in previously untreated, relapsed or refractory patients with multiple myeloma. Even 44% of patients who had been previously treated

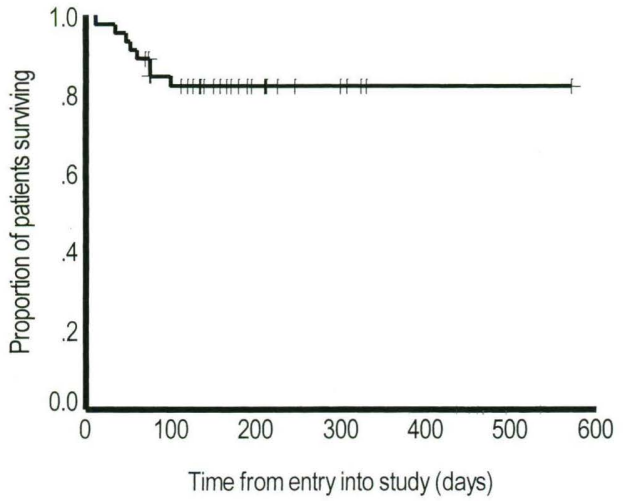

Figure 1 Survival of 46 evaluable patients with multiple myeloma from entry into the study. The median time of observation was 162

with VAD achieved a partial remission. Overall, the hematological and nonhematological toxicity was low, but patients with a significantly decreased bone marrow function (mostly after prolonged treatment with melphalan) are at risk for severe hematological toxicity and related infectious events.

The introduction of the VAD regimen by Barlogie, Smith and Alexanian in 1984[1] was a major advance in the therapy of multiple myeloma. Later, these investigators and several other groups have reported larger non-randomized trials with identical or hybrid forms of this combination therapy.[5,6,20–22] Response rates varied from 41% partial and complete remissions in previously untreated patients receiving three courses in preparation for high-dose chemotherapy and autologous stem-cell reinfusion[5] to 84% after six courses in previously untreated patients.[6] In patients with refractory disease response rates of about 40% were reported.[20–22] Relapsed patients achieved response in about 60%.[6] However, considerable inconvenience and a 24% complication rate is associated with the central venous line that is necessary for the continuous infusion of vincristine and doxorubicin.[6]

In a recent study patients were asked for their choices of palliative chemotherapy in a scenario-based questionnaire.[23] Ninety-two out of 103 patients clearly preferred an oral application of chemotherapy to an intravenous (bolus) chemotherapy if efficacy was not compromised. The evaluation of less demanding applications for palliative chemotherapy seems therefore an important goal.

A few smaller studies have previously demonstrated activity of oral idarubicin in multiple myeloma.[24–26] The pharmacokinetic properties of idarubicin make it possible to devise a regimen that could replace the continuous infusion of doxorubicin by an oral administration of idarubicin for several days. The first larger study of such a combination chemotherapy, the Z-Dex regimen, was reported by Cook *et al*[16] from the Glasgow Royal Infirmary. In the latest update of that study, 32 patients received oral idarubicin (10 mg/m^2/day for 4 days) and dexamethasone (40 mg/day, three blocks of 4 days in the first course and days 1–4 only in subsequent courses).[27] This treatment was repeated every 3 weeks for four courses. Thereafter the patients proceeded to mobilization of peripheral blood stem cells with one of four different regimens. In this group of mostly untreated patients an overall response rate of 75% was reached. Stem cell mobilization was satisfactory in 30 patients.[27]

The overall response rate in previously untreated patients in the Z-Dex study was 92% (22/24; 95% CI: 79–99%), which compares favorably with the 62% response rate (8/13; 95% CI: 32–86%) in our VID study. This may be due to variation

the two studies that should be considered. First, all patients in the Z-Dex study were selected for high-dose chemotherapy and autologous stem-cell transplantation, whereas in our study only four patients were considered for this therapeutic intensification which may have resulted in the selection of better risk patients in the Z-Dex study. Second, the duration of the treatment courses was 21 days in the Z-Dex and 28 days in the VID study, so that the dose intensity of idarubicin was 33% higher in the Z-Dex study. Furthermore, the administration of dexamethasone was different and vincristine was not used in the Z-Dex trial. However, the response and toxicity rates in our study compare well with those reported by Barlogie *et al*.[5]

With regard to refractory patients the VID regimen resulted in response rates that do not differ from those reported for VAD.[20–22] Surprisingly, however, patients previously treated with VAD responded to VID therapy in 44%. Similar results have been recently reported by Giles *et al*,[28] who used oral lomustine (CCNU), idarubicin and dexamethasone. This beneficial effect could be due to a superior cytotoxic action of oral idarubicin in comparison to doxorubicin as has been suggested by *in vitro* studies.[29] Further investigation in this patient subgroup seems warranted.

Only 14% of patients treated in this trial were progressive despite VID therapy. Four of the six patients were secondary refractory and three of six had received dexamethasone before VID. Four of these patients died from disease progression.

The majority of patients in the VID trial did not experience any major side-effects. However, considerable hematotoxicity and two treatment-related deaths occurred in intensively pretreated patients with a reduced bone marrow function. These patients, especially when pretreated with larger doses of melphalan, should not receive full dose VID. Therapeutic options for these patients are dose reductions in the first course (eg 8 mg/m^2/day idarubicin for 3 to 4 days) with subsequent adaptation to the hematological response or – in patients with severe cytopenia at entry – treatment with high-dose dexamethasone only should be considered.[30]

In summary, this phase I–II trial demonstrates that VID therapy – without the necessity for a central venous line – effectively induces responses in previously untreated, relapsed and refractory patients with multiple myeloma. VID therapy can easily be administered on an outpatient basis and toxicity was acceptable.

Acknowledgements

This study was supported by Leukämie-Initiative Bonn e.V. Furthermore, we thank Prof Dr T Sauerbruch, Bonn, and Priv-Doz Dr I Schmidt-Wolf for their review of the manuscript, as well as Dr R Derichs, Düsseldorf, and Dr B Meuter, Trier, for inclusion of patients and documentation of results.

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