British Journal of Haematology 2000, **109**, 571–575

CCNU (lomustine), idarubicin and dexamethasone (CIDEX): an effective oral regimen for the treatment of refractory or relapsed myeloma

R. Parameswaran,[1] Chrissy Giles,[2] M. Boots,[2] T. J. Littlewood,[2] M. J. Mills,[1] S. M. Kelsey[2] and Diana Samson[1] [1]*The East London and Essex Haematology Research Group, The Royal London Hospital, London, and* [2]*The Riverside Haematology Group, Hammersmith Hospital, London*

Received 5 November 1999; accepted for publication 2 February 2000

Summary. We report the results of a non-randomized pilot study of an oral regimen comprising CCNU (lomustine; 25 or 50 mg/m^2 on day 1), idarubicin (4-demethoxydaunorubicin) (10 mg/m^2 on days 1–3) and dexamethasone (10 mg b.d. on days 1–4) in patients with relapsed or refractory myeloma. Treatment was given every 28 d for a maximum of six courses. Sixty patients were entered of whom 57 were evaluable. Overall response rate (partial or minor response) was 49% with 30% of patients achieving a partial response (50% tumour reduction). Response rates were higher in patients with untested relapse than in those with refractory disease (overall response rates 56% vs. 31%). The major toxicity was neutropenia and the regimen was otherwise well tolerated. The median survival from entry of all patients was 15 months, with 30% of patients alive at 2 years. This regimen represents a useful addition to available treatment options.

Keywords: myeloma, CCNU (lomustine), idarubicin.

The optimum therapy for patients with relapsed or refractory myeloma disease is unclear. In patients progressing from first remission, treatment with the same regimen that produced the initial response will produce a second response in 50–60% cases (Belch *et al*, 1988; Buzaid & Durie, 1988). In patients with refractory disease or those progressing after second- or third-line therapy, a number of treatment regimens may be used, including dexamethasone alone (Alexanian *et al*, 1983, 1986) or combined with infused doxorubicin and vincristine (the VAD regimen) (Barlogie *et al*, 1984). VAD has been considered to be the gold standard for relapsed and refractory disease, however in the only randomized study comparing VAD with a standard alkylator-based regimen in relapsed patients, VAD was not shown to be superior to VBMCP [vincristine, BCNU (carmustine), cyclophosphamide, melphalan, prednisolone] (Mineur *et al*, 1998). A non-randomized comparison of VAD with high-dose dexamethasone alone suggested that VAD is more effective in relapsed patients but that the response rate in refractory patients is similar (Alexanian *et al*, 1986). The advantages of the VAD regimen are therefore not entirely proven. In addition, it is unsuitable for most elderly patients because of the need for central access and the high dose of dexamethasone.

Quality of life is extremely important in patients with relapsed and refractory myeloma in view of their limited life expectancy and an oral regimen would be preferable to intravenous therapy. Oral idarubicin (4-demethoxydaunorubicin), used as a single agent or in combination with prednisolone, has been shown to produce responses in 25–50% of relapsed patients (Chisesi *et al*, 1988; Alberts *et al*, 1990) and has also proved effective when combined with dexamethasone in newly diagnosed patients (Cook *et al*, 1996).

Both doxorubicin and BCNU (carmustine) have well-established activity in the treatment of myeloma. We therefore proposed to investigate the efficacy of a combination of the similar oral drugs idarubicin and CCNU (lomustine) with the addition of dexamethasone in a dose which would be suitable for older patients. In October 1993, we began a pilot study evaluating this CIDEX regimen in patients with relapsed and refractory myeloma. The study was closed in August 1997 after 60 patients had been entered and we now report the final results.

METHODS

Study design. This was a non-randomized pilot study open

Correspondence, Dr D. Samson, Department of Haematology, Imperial College School of Medicine, Hammersmith Hospital, Ducane Road, London W12 0NN, UK. E-mail: d.samson@ic.ac.uk

to patients with relapsed or refractory myeloma who had not received idarubicin or CCNU before enrolment in the study. The study was approved by the Local Ethical Committees of participating hospitals.

The chosen dose of oral idarubicin was a total of 30 mg/m^2 to be given over 3 d, i.e. approximately 10 mg/m^2/d. Idarubicin 10 mg/m^2/d for 3 d has been safely used in combination with other drugs such as cytarabine and etoposide in acute myeloid leukaemia (AML) (Jackson *et al*, 1997) and chlorambucil in lymphoma (unpublished observations). The initial aim was to use a dose of 50 mg/m^2 CCNU in combination with 30 mg/m^2 idarubicin (and dexamethasone) in a 4-weekly schedule for up to six courses. CCNU 50 mg/m^2 was used successfully in combination with melphalan, cyclophosphamide and prednisolone in a 4-weekly schedule in the third MRC Myelomatosis trial with no significant myelotoxicity (Medical Research Council's Working Party on Leukaemia in Adults, 1980). However, as idarubicin had not previously been used in combination with CCNU, an initial evaluation of myelotoxicity was made using a lower CCNU dose of 25 mg/m^2. At the time the study was commenced, CCNU capsules were available in two strengths, 10 mg and 40 mg, allowing accurate dosage on the basis of surface area, but the 10-mg capsules were subsequently withdrawn from the UK market. When it was found that the higher dose of CCNU was associated with an unacceptable incidence of severe neutropenia (see below), it was therefore not possible to evaluate an intermediate CCNU dose. The remaining patients received a standard dose of 40 mg, which equates to a dose of 25 mg/m^2 for a patient of 1·7 m^2.

Patients were required to have a neutrophil count $> 1{\cdot}0 \times 10^9$/l and a platelet count of $> 50 \times 10^9$/l at entry. An upper limit of 200 μmol/l was set for serum creatinine because idarubicinol and active metabolites of CCNU are excreted by the kidney.

Patient characteristics. No data were returned on three patients. The characteristics of the remaining 57 patients are shown in Table I. Of the 49 patients with relapsed disease, 17 were in second or subsequent relapse and eight had refractory relapse, i.e. were progressing on treatment given at relapse. Eight patients had primary refractory disease. Twenty-seven patients (45%) had previously received doxorubicin, of whom four were known to be refractory to a doxorubicin-containing regimen. Twelve patients had received prior BCNU. Although an upper limit for serum creatinine of 200 μmol/l had been set, five patients had creatinine levels between 200 and 350 μmol/l whereas three had levels over 500 μmol/l. One of these three patients was already on long-term dialysis at the time of disease progression whereas two of the three patients developed renal failure in association with progressive disease.

Treatment regimens. CIDEX was given in a 4-weekly cycle for a maximum of six courses. CCNU was given as a single dose on the first day, idarubicin 30 mg/m^2 total dose divided over 3 d and dexamethasone 10 mg twice daily for 4 d. The dose of CCNU was 25 mg/m^2 in the first eight patients, 50 mg/m^2 in the next 25 patients (group B) and 40 mg as a single dose in the final 24 patients. Patients who received CCNU 25 mg/m^2 or 40 mg were combined for analysis (group A).

Table I. Patient characteristics.

Total	57
Age (years)	Median 66 (range 39–89)
Sex	Male 38/female 19
Status	
Untested relapse 1	24
Untested relapse ≥ 2	17
Refractory relapse	8
Primary refractory	8
Prior therapy	
One regimen*	29
Two regimens*	21
Three regimens*	7
Previous ABMT/PBSCT	8
Interferon	14
Serum creatinine > 200 μmol/l	8

*Conventional chemotherapy regimen(s).
ABMT, autologous bone marrow transplant.
PBSCT, peripheral blood stem cell transplant.

Monitoring of response. Serum paraprotein concentration and/or urinary light-chain excretion were measured at the beginning of each cycle of treatment and every 4–8 weeks afterwards. Bone marrow examination was performed only if clinically indicated or required to document response in non-secretory disease or to confirm complete response (CR) and radiographs were carried out only if clinically indicated. The definitions used for response or progression were those of Blade *et al* (1998). We have considered patients meeting the criteria for CR, partial response (PR) or minor response (MR) to have had a response to treatment.

Statistical methods. Mortality from disease or treatment-related causes before the third course of CIDEX was defined as early death. Response duration and survival were analysed using GRAPHPAD PRISM software according to the product limit method of Kaplan–Meier. Progression-free survival was analysed in responders only and patients were censored if and when they withdrew because of toxicity, if they received a stem cell transplant, if they died of unrelated causes or if they were lost to follow-up. Overall survival was analysed in all patients regardless of any subsequent treatment and patients were only censored if they died of unrelated causes or were lost to follow-up.

RESULTS

Frequency of response (see Table II)

There were eight early deaths and five patients were withdrawn before completing three courses. Of the remaining 44 patients, 28 responded (17 PR, 11 MR), giving an overall response rate of 49% and a response rate in evaluable patients of 64%. Patients with untested relapse had a significantly higher response rate than patients with refractory disease. Of the four patients known to be refractory to anthracycline, one responded, one showed no

Table II. Response to treatment.

	All patients	By disease status		By CCNU dose	
		Untested relapse	Refractory disease	Group A	Group B
Total	57	41	16	32	25
Early death	8	5	3	5	3
Withdrawal	5	5	0	2	3
Evaluable	44	31	13	25	19
PR	17	14	3	10	7
MR	11	9	2	7	4
NC	6	2	4	2	4
Progression	10	6	4	6	4
Response (percentage all patients)	49	56	31	53	44
Response (percentage evaluable patients)	64	74*	38*	68	58
PR (percentage all patients)	30	34	19	31	28
PR (percentage evaluable patients)	39	45	23	40	37

*$P = 0{\cdot}025$.
PR, partial response; MR, minor response; NC, no change.

change and two progressed. There was no significant difference in response rates between groups A and B.

Toxicity

The major toxicity was neutropenia (Table III). Day 15 blood counts were returned in 42 patients who received 159 treatment courses. Grade 3 or 4 neutropenia occurred in 25% of courses and was more frequent at the higher CCNU dose (33% of courses vs. 20%). Grade 3 or 4 thrombocytopenia occurred in only 7% of courses even at the higher CCNU dosage. The frequency of grade 3 or 4 neutropenia remained high throughout treatment in group B but only one patient in group A had grade 4 neutropenia after the second course. This suggests that haematological toxicity lessened as the patient responded to treatment and marrow function improved.

Steroid-induced psychosis occurred in two patients, myopathy in another and another patient died from a bleeding duodenal ulcer. One patient developed palpitations during the first course of treatment. There was no abnormality on examination and an electrocardiograph and echocardiogram were normal. No other cardiotoxicity was reported. Nausea, vomiting and diarrhoea were reported in eight patients, WHO grade 1–2 in four of the patients and grade 3 in the other four patients. Alopecia was generally mild to moderate, with grade 3 alopecia reported in only three patients and no patient reported with grade 4 alopecia.

Toxicity in patients with renal impairment

Of the five patients with serum creatinine in the range 200–350 μmol/l, one declined further treatment after the first course, one stopped treatment after course 4 because of disease progression and the remaining three patients received six courses of treatment. No instance of neutropenia or thrombocytopenia > grade 0 was observed in these patients and no non-haematological toxicity was reported. Of the two patients who developed renal failure in association with progressive disease, one patient died at day 7 as a result of pneumonia. The second patient responded to therapy with normalization of serum creatinine after three courses of treatment and then proceeded to high-dose therapy. There was no haematological or non-haematological toxicity during the CIDEX therapy. The final patient, who was already on long-term dialysis, received three courses of treatment with no haematological or non-haematological toxicity. Four weeks later he developed a bleeding duodenal ulcer, from which he died; the platelet count was normal at this time.

Withdrawals and treatment modifications

There were five withdrawals, because of toxicity in two patients, because of poor performance status in another two patients and one patient declined further treatment. Two patients required dose reduction of dexamethasone because of psychosis and the CCNU dose was reduced from 50 mg/m^2 to 40 mg in one patient because of grade 4 neutropenia. Four patients stopped treatment before completion of six courses, two because there was no

Table III. Neutropenia and thrombocytopenia during 159 courses of treatment evaluable for haematological toxicity.

WHO grade	Neutropenia (%)	Thrombocytopenia (%)
0	43	66
1	15	19
2	17	8
3	11	6
4	14	1

Figures are percentage of total courses associated with each toxicity grading.

response (i.e. they had stable disease) and two because of neutropenia.

Remission duration and survival

Of the 28 responders, one underwent a haemopoietic cell transplant and was censored from analysis of progression-free survival (PFS) at the relevant time point. Four patients died in remission, one from fungal infection after course 5, one from bleeding duodenal ulcer after course 3 and two from unrelated causes. The remaining 23 patients have all progressed. The median PFS is 13 months, with 30% of the responding patients alive and progression free at 2 years (Fig 1). Three patients had a response lasting over 3 years. Overall survival is shown in Fig 2. The median overall survival was 15 months, with 30% of patients alive at 2 years. Median survival in responding patients was 24 months, with 30% alive at 3 years.

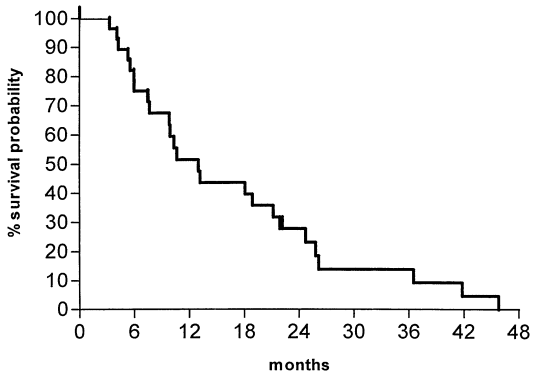

Fig 1. Progression-free survival in responding patients ($n = 28$).

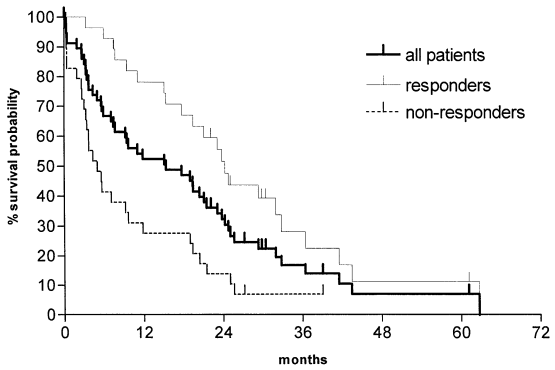

Fig 2. Overall survival in all patients ($n = 57$), in responding patients ($n = 28$) and in non-responders ($n = 29$); $P = 0{\cdot}05$ for responders vs. all patients and $P < 0{\cdot}0001$ for responder vs. non-responders.

DISCUSSION

This regimen is clearly effective in inducing response or stabilization of disease in patients with relapsed and refractory myeloma. The overall response rate of 50% including 30% PR is encouraging given that half of the patients were beyond first relapse or had refractory disease. Because the published data on the treatment of relapsed and refractory myeloma comprises predominantly small series with heterogeneous patients, as does the present study, it is not possible to determine whether this new regimen is better than other regimens for relapsed and refractory disease. However, the overall survival appears at least as good as that reported by Alexanian *et al* (1986) for the VAD regimen in relapsed patients, in which median survival was only 12 months. The regimen was well tolerated and the incidence of severe neutropenia at the lower CCNU dose was acceptable.

The lack of evidence for increased toxicity in the patients with renal impairment is of interest as idarubicin is currently not recommended for use in these patients. Urinary excretion of the drug and its metabolites appears to be more important than biliary excretion (Pannuti *et al*, 1986) and there is a significant correlation between creatinine clearance and the clearance of idarubicin and idarubicinol (Cammagi *et al*, 1992). Previous studies of oral idarubicin in myeloma and other malignancies have therefore excluded patients with serum creatinine levels above 200 μmol/l. There are no published data on the use of CCNU in patients with renal impairment. In the present series, there was no evidence of increased toxicity in the five patients with creatinine levels between 200 and 350 μmol/l at entry. However, we do not have data on serial creatinine levels to indicate whether the same degree of renal impairment persisted throughout treatment. Only three patients with more severe renal failure were included in the study; renal failure rapidly improved in one patient, one patient died early and the third died after three courses of treatment. We cannot therefore draw any firm conclusions about the possibility of increased toxicity of either idarubicin or CCNU, particularly cumulative toxicity, in patients with persistently raised creatinine levels. However, in the light of our results, it appears that patients with creatinine levels up to 350 μmol/l might be safely treated with the CIDEX regimen without dose modification. Furthermore, as VAD is widely used in patients with renal failure and the oral Z-Dex (oral idarubicin and dexamethasone) regimen may be equally effective, further studies of oral idarubicin in patients with severe renal impairment are warranted.

The metabolite of idarubicin, idarubicinol, has been shown to possess striking anti-tumour activity in doxorubicin-resistant cell lines, suggesting that it could be useful in circumventing multidrug resistance (Berman & McBride, 1992). Of the four patients in this series who were known to be refractory to doxorubicin, one entered PR on treatment with CIDEX. Although it is not possible to conclude that this response was due to the idarubicin component of the regimen, it would be consistent with the activity of idarubicin in patients refractory to anthracycline.

We conclude that CIDEX is an effective oral combination regimen for patients with relapsed or refractory myeloma and merits further evaluation in this setting. The Riverside Haematology Group, in association with the UK Myeloma Forum, is accordingly currently carrying out a randomized

controlled trial comparing CIDEX with melphalan and prednisolone in patients with myeloma at first or second relapse.

ACKNOWLEDGMENTS

We would like to acknowledge the following colleagues who also entered patients into the study: Dr C. Barton, Dr S. Basu, Dr E. Blundell, Dr S. M Fairhead, Dr P. Gravett, Dr G. Hughes, Dr E. Kanfer, Dr L. Jones, Dr J. Mercieca, Dr D. O'Shaughnessy, Dr C. Rist, Dr M. Semple, Dr C. Singer, Dr C. Tew and Dr E Watts.

REFERENCES

Alberts, A.S., Falkson, G., Rapoport, B. & Uys, A. (1990) A phase II study of idarubicin and prednisone in multiple myeloma. *Tumori*, **76**, 465–466.

Alexanian, R.A., Yap, B.S. & Bodey, G.P. (1983) Prednisone pulse therapy for refractory myeloma. *Blood*, **62**, 572–577.

Alexanian, R., Barlogie, B. & Dixon, D. (1986) High-dose glucocorticoid treatment of resistant myeloma. *Annals of Internal Medicine*, **105**, 8–11.

Barlogie, B., Smith, L. & Alexanian, R. (1984) Effective treatment of advanced multiple myeloma refractory to alkylating agents. *New England Journal of Medicine*, **310**, 1353–1356.

Belch, A., Shelley, W. & Bergsagel, D. (1988) A randomised trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients. *British Journal of Cancer*, **57**, 94–98.

Berman, E. & McBride, M. (1992) Comparative cellular pharmacology of daunorubicin and idarubicin in human multi-drug resistant leukaemia cells. *Blood*, **79**, 3267–3273.

Blade, J., Samson, D., Reece, D., Apperley, J., Bjorkstrand, B., Gahrton, G., Gertz, M., Giralt, S., Jagannath, S. & Vesole, D. (1998) Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. *British Journal of Haematology*, **102**, 1115–1123.

Buzaid, A.C. & Durie, B.G.M. (1988) Management of refractory myeloma: a review. *Journal of Clinical Oncology*, **6**, 889–905.

Cammagi, C.M., Strocchi, E., Carisi, P., Martoni, A., Tononi, A., Guaraldi, M., Strolin-Benedetti, M., Efthymiopoulos, C. & Pannuti, F. (1992) Idarubicin metabolism and pharmacokinetics after intravenous and oral administration in cancer patients: a crossover study. *Cancer Chemotherapy and Pharmacology*, **30**, 307–316.

Chisesi, T., Capnist, G., de Dominicis, E. & Dini, E. (1988) A phase I study of idarubicin (4-demethoxydaunorubicin) in advanced myeloma. *European Journal of Cancer and Clinical Oncology*, **24**, 681–684.

Cook, G., Sharp, R.A., Tansey, P. & Franklin, I.M. (1996) A phase I/II trial of Z-Dex (oral idarubicin and dexamethasone), an oral equivalent of VAD, as initial therapy at diagnosis or progression in multiple myeloma. *British Journal of Haematology*, **93**, 931–934.

Jackson, G.H., Taylor, P.R., Iqbal, A., Galloway, M.J., Turner, G., Haynes, A., Hamilton, P.J., Russell, N. & Proctor, S.J. (1997) The use of an all oral chemotherapy (idarubicin and etoposide) in the treatment of acute myeloid leukaemia in the elderly: a report of toxicity and efficacy. *Leukaemia*, **11**, 1193–1196.

Medical Research Council's Working Party on Leukaemia in Adults. (1980) Treatment comparisons in the third MRC myelomatosis trial. *British Journal of Cancer*, **42**, 823–830.

Mineur, Ph., Medarn, J.F., le Loet, X., Bernard, J.F., Grosbois, B., Pollet, J.P., Azais, I., Laporte, J.P., Doyen, C., de Gramont, A., Wetterwald, M., Euller-Ziegler, L., Peny, A.M., Monconduit, M. & Michaux, J.L. (1998) VAD or VBMCP in multiple myeloma refractory to or relapsing after cyclophosphamide–prednisone therapy (protocol MY-85). *British Journal of Haematology*, **103**, 512–517.

Pannuti, F., Cammagi, C.M., Strocchi, E., Comparsi, R., Angelelli, B. & Pacciarini, M.A. (1986) Low dose oral administration of 4-demethoxydaunorubicin (idarubicin) in advanced cancer patients. A pharmacokinetic study. *Cancer Chemotherapy and Pharmacology*, **16**, 295–299.