# Recombinant alpha-interferon as salvage therapy in multiple myeloma

## A pilot study

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## Summary

**Ten patients with end-stage multiple myeloma refractory to conventional chemotherapy and hemibody irradiation received recombinant $\alpha$-interferon as salvage therapy. The median duration of treatment was 8 weeks. One patient had an objective response and survived 8 months, whereas in the remaining 9 patients the disease progressed and median survival was 11,5 weeks. Side-effects were substantial and included confusion with extreme weakness, resulting in 5 patients refusing further therapy. The low response rate and the morbidity in this pilot study resulted in its discontinuation and the conclusion that recombinant $\alpha$-interferon as single-agent therapy used for salvage in patients with refractory myeloma is of no value.**


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Myeloma is at present considered incurable, although objective response can be achieved with single agents[1] or multiple drug combinations[2-4] leading to modest prolongation in survival. The quality of life is generally improved during this period by optimal supportive care aimed at reversal of metabolic abnormalities and relief of pain using local radiotherapy. However, loss of disease control usually occurs within 2 - 3 years and salvage therapy is then of limited benefit, although a number of alternative options exist. The latter include newer drug programmes[5] and high-dose chemotherapy followed by autologous bone marrow transplantation in which *ex vivo* purging may be used to remove contaminating malignant cells.[6] In view of the activity of recombinant $\alpha$-interferon in hairy-cell leukaemia[7] and the use of this product in myeloma,[8,9] a pilot study was undertaken to define patient acceptability, document side-effects and explore response rates in patients who had relapsed and become refractory to conventional therapy.

## Patients and methods

Ten patients between the ages of 47 years and 68 years with a confirmed diagnosis of myeloma[10] were entered into a pilot study that had received approval from the Ethics Committee of the University of Cape Town Medical School and where participation required informed consent.

All 10 patients were heavily pretreated for a median of 28 months (range 9 - 47 months); 1 received melphalan and prednisone only, 1 received melphalan, prednisone and cyclophosphamide, and the other 8, combinations of chemotherapy and sequential half-body radiotherapy. All had a response to initial treatment, but had relapsed (Table I). Recombinant $\alpha$-interferon was given on two schedules, both recommended by the supplier. Three patients received 150 x $10^6$ units intravenously once a month, and 18 x $10^6$ units subcutaneously 3 times a week (schedule A), 5 patients received daily subcutaneous $\alpha$-interferon at a dose of 3 - 9 x $10^6$ units from commencement of treatment (schedule B), and the remaining 2 patients started off on schedule A and were switched to schedule B within 3 months. Median duration of treatment was 8 weeks (range 1 - 28 weeks). Response was defined as a 50% reduction in paraprotein and improved Karnofsky performance status.[11]

## Results

One patient met the criteria for response. However, this patient had an intracerebral myelomatous deposit that increased in size during therapy and he was withdrawn from the trial after 7 months, when all disease control was lost. In the remaining 9 patients there was rapid progression of their myeloma and 3 died at 1, 2, and 3 weeks respectively after starting treatment; these patients are unsuitable for further comment. The $\alpha$-interferon was not considered to have contributed to the death of any of these individuals.

Significant side-effects were encountered during the course of $\alpha$-interferon administration on both schedules. However, the 5 patients who received higher initial doses had more prominent chills and fever spikes, but in all individuals these could be controlled with antipyretics.

Four patients complained of extreme tiredness and weakness, 4 lost their appetites and 3 experienced nausea. Two patients developed raised liver enzymes and in 1 there was persistent tachycardia on treatment. Mental confusion occurred in 4 patients. In 5 patients $\alpha$-interferon had to be discontinued at 4, 7, 8, 8 and 14 weeks respectively because of these side-effects: dose reduction was offered to these individuals, but none was willing to accept further treatment. Haematological toxicity in all these patients was insignificant.

## Discussion

Of the 10 patients treated with recombinant $\alpha$-interferon in this pilot study there was 1 responder (10%). This low figure compares with previous reports[8,9] of response rates respectively of 8% in a group of 12 treated and untreated patients and 14% in previously untreated patients with myeloma. Similarly, in 21 patients with all stages of multiple myeloma treated with $\alpha$-interferon between 1978 and 1980[12] only 3 of the 12 previously untreated individuals (25%) had a reduction in tumour mass greater than 50%, with 1 patient relapsing and 1 patient previously unresponsive to chemotherapy also having the immunoglobulin level reduced by $>$ 50%. However, in a further report from the same institution[13] 6 of 10 patients with multiple myeloma responded to $\alpha$-interferon therapy.

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**TABLE I. SUMMARY OF PREVIOUS THERAPY, α-INTERFERON SCHEDULE AND SIDE-EFFECTS**

| Sex/age (yrs) paraprotein | Previous treatment and duration | Interferon schedule and duration | Response and side-effects |
|---|---|---|---|
| M/49 IgG | M + P, DXR × 3, 40 mo. | A + B 7 mo. | 50% reduction in paraprotein; raised liver enzymes; survived 8 mo. |
| F/63 IgA | M + P, DXR × 2, 14 mo. | A + B 3,5 mo. | No response; developed pancytopenia; raised liver enzymes; tired, weak, confused; α-interferon discontinued owing to side-effects; survived 4,5 mo. |
| F/63 IgA | M,P,C, 15 mo. | B 2 mo. | No response; tired, weak, confused; anorexia, nausea; α-interferon discontinued owing to side-effects; survived 5 mo. |
| F/66 IgG | M,P,C,V, DXR × 2, 28 mo. | B 7 wks | No response; pancytopenia; became tired, weak; anorexia, tachycardia; α-interferon discontinued owing to side-effects; survived 11 wks |
| F/64 Light-chains | M + P, DXR × 2, 27 mo. | B 1 mo. | No response; fever, anorexia, nausea, confused; α-interferon discontinued owing to side-effects; survived 2 mo. |
| M/54 IgG | M + P, DXR × 2, 37 mo. | B 1 mo. | No response; tired, nausea, anorexia; survived 1 mo. |
| M/68 IgG | M + P, DXR × 2, 47 mo. | A 3 wks | No response; confused; survived 3 wks |
| M/47 IgG IgA | M + P, 30 mo. | A 2 wks | No response; fever, chills; survived 2 wks |
| F/57 IgG | M + P, DXR × 2, 9 mo. | B 1 wk | Survived 1 wk |
| F/63 IgG | M,P,C, DXR × 3, 34 mo. | A 2 mo. | No response; cold shivers, increasing temperature, headaches; α-interferon discontinued owing to side-effects; survived 4 mo. |

M = melphalan; P = prednisone; C = cyclophosphamide; V = vincristine; DXR = half-body radiotherapy.

Results of our study were inferior to alternative salvage programmes, such as the vincristine-adriamycin-dexamethasone combination,[5] although 7 of the 10 patients had IgG myeloma, which is a subgroup believed to have the lowest response rate to α-interferon.[8] Side-effects were also more severe in this series than previously reported, with extreme tiredness and mental confusion requiring interruption and eventual discontinuation of therapy in 50% of the individuals. All our patients had received previous treatment over long periods of time and their disease was rapidly progressing when α-interferon was commenced as salvage therapy.

It is concluded from this pilot study and similar published results[14] that recombinant α-interferon is without benefit when used as a single agent in patients with myeloma who have relapsed or are resistant to conventional cytotoxic and radiotherapy programmes. However, the role of this agent remains to be clarified, since a therapeutic effect has been reported in previously untreated patients[15] and those in first relapse following previous response to chemotherapy regimens.[16] Furthermore, there may be a place for alternative programmes in which interferon is combined with conventional cytotoxic chemotherapeutic agents.[17]

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