Pergamon

European Journal of Cancer, Vol. 34, No. 1, pp. 12–24, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10046-6

Current Controversies in Cancer

Should Alpha-interferon be Included as Standard Treatment in Multiple Myeloma?

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WHY USE INTERFERON FOR TREATMENT OF MULTIPLE MYELOMA?

MULTIPLE MYELOMA (MM) is a malignant B cell disorder which is still incurable. For more than 30 years newly diagnosed patients with symptomatic myeloma have been treated with induction chemotherapy involving a small number of cystostatic agents. Their median survival time has been 2–3 years. A recent meta-analysis of randomised trials performed in the late 1980s and early 1990s [1] showed that median survival after conventional chemotherapy has not improved over the last two decades (median in chemotherapy arms without interferon: 30 months, range 24–38 months). Although prolonged survival is now being achieved through the use of bone marrow and/or peripheral stem cell transplantation, the therapeutic agents applied in high-dose chemotherapy are still those which have been applied for the last 30 years. Because the biological response modifier interferon-α (IFN) is the only new substance which has recently been introduced into the treatment of multiple myeloma, its possible benefits deserve to be thoroughly evaluated.

IFN is a potent stimulator of several immune functions. It enhances the cytolytic activity of natural killer cells [2], which may be substantially reduced in advanced myeloma [3], it activates macrophages [4] and increases the expression of the major histocompatibility [5] and of tumour-associated antigens [6]. *In vitro* studies have shown a direct, dose-dependent [7] inhibitory effect on the proliferation and colony formation of myeloma cells [8, 9]. This growth inhibition has been observed both in interleukin-6 (IL-6)-dependent and IL-6-independent myeloma cell lines [10]. In addition, IFN has been reported to down-regulate the expression of the oncogenes *c-myc* and *N-ras* [11, 12] as well as of the IL-6 receptor, and to reduce the sensitivity of the receptor to its ligand [13]. Because of these characteristics, IFN seems to be a promising option in the treatment of MM.

Received 22 Sep. 1997; accepted 25 Sep. 1997.

Pilot studies on IFN in myeloma

IFN monotherapy. When IFN was first used as a single agent in the treatment of MM, the results were exciting. All four chemotherapy-resistant patients participating in that pilot study showed objective responses to IFN monotherapy [14]. In two subsequent randomised trials [15, 16], however, the response rates of 14% in the IFN arm were below the efficacy of the standard treatment. Further investigations yielded response rates of approximately 10–30% [17–22]. They confirmed IFN antitumour activity in myeloma which is comparable to that of several other cytostatic drugs when used as single agents, but still inferior to melphalan monotherapy.

Combined IFN–chemotherapy induction treatment. These observations of certain anti-tumour effects of IFN in myeloma, along with *in vitro* studies reporting synergistic activities between IN and certain cytostatic drugs [23–25] led to the combination of IFN with established chemotherapy regimens for induction treatment. Again, the first phase I–II trials of these combined IFN–chemotherapy protocols rendered very promising results, namely response rates of 75% in patients treated with IFN+melphalan/prednisone (MP) [26] and of 80%, including 30% complete responses, in patients treated with vincristine/BCNU/melphalan/cytoxan/prednisone (VBMCP) alternating at 3-week intervals with IFN-alpha-2b [27]. However, subsequent prospective randomised trials did not unequivocally confirm the initially observed superior benefits of combined IFN–chemotherapy over the standard treatment without IFN. The phenomenon of excellent results from pilot studies which cannot be reproduced in subsequent large controlled trials is not uncommon. It may

involve two biases, namely, unintentional selection of particularly responsive patients and a publication bias favouring spectacularly positive results by both authors and journal editors [28].

IFN maintenance treatment. After successful induction treatment, myeloma growth is in a plateau phase which appears to be similar to the G_0 phase of the cell cycle [29]. Since IFN has some capacity to arrest tumour cells in this resting phase of the cell cycle [30] and since non-cycling tumour cells seem to be particularly responsive to the antiproliferative activity of IFN [31], IFN treatment might be able to prolong the maintenance phase of myeloma patients. The relevance of this consideration was first investigated by Mandelli *et al.* in a randomised trial involving 101 patients who had achieved partial response (PR), complete response (CR) or stable disease after either MP or VMCP/VBAP induction therapy [32]. The first 12 patients in the treatment arm received 10×10^6 U/m^2 IFN three times a week, an uncommonly high dosage which was poorly tolerated and had to be reduced to 3×10^6 U/m^2 three times a week in all patients subsequently enrolled in the IFN arm. Patients randomised to the control arm received no maintenance treatment. The outcome of the trial was striking. Remission duration was substantially prolonged in the IFN arm (26 months versus 14 months in controls). The survival data showed a tendency towards longer survival in patients maintained with IFN (median: 52 months), as compared to unmaintained patients (median: 39 months). Subgroup analysis revealed, however, that significantly prolonged survival was only seen in patients who had responded to induction treatment with either complete or partial remissions, but not in those who had only achieved disease stabilisation.

DO MYELOMA PATIENTS BENEFIT FROM IFN TREATMENT?

Randomised trials

Combined IFN–chemotherapy induction treatment. Prospective randomised clinical trials comparing chemotherapy induction treatment with and without the addition of IFN did not unequivocally confirm the IFN benefits observed in the initial phase I–II trials. Their outcomes ranged from substantially higher response rates [33–40] and/or prolonged progression-free [34–36, 38, 40–42] and overall survival [35, 36] to little or no advantage from the addition of IFN to standard chemotherapy protocols [43–47]. Details of the various study designs and the response rates of both treatment arms are shown in Table 1.

IFN maintenance treatment. Similarly divergent results have been reported from randomised trials comparing IFN maintenance treatment with no treatment during the maintenance phase. Although relapse-free survival was consistently prolonged in the IFN arm [1, 32, 48–53], the observed gains reached statistical significance in only a few studies [1, 32, 50, 52] and were minimal in others [48, 51]. Substantial increases in overall survival were also observed in some trials [1, 32, 50, 52], but not in others.

Cumulative effect of IFN

In one multicentre trial [1], patients were randomised to receive induction chemotherapy with or without IFN. Those who subsequently entered the maintenance phase were again randomised to IFN maintenance treatment or to the untreated control group. The second randomisation was stratified according to pretreatment with or without IFN. Patients who received IFN during both the induction and the maintenance phase showed the longest remission duration (median: 21.2 months), patients who never received IFN showed the shortest (median: 6.4 months). These differences and similar ones in overall survival were statistically significant ($P<0.05$). The results obtained with that particular study design (splitting both the IFN maintenance and the control arm into subgroups of IFN-pretreated patients and those without IFN pretreatment) suggest a cumulative beneficial effect of long-term treatment with IFN.

Toxicity

Interferon-induced toxicity is dosage-dependent [54], with doses in the magnitude of 30×10^6 U daily causing

Table 1. *Characteristics of trials on combined interferon induction therapy*

[Ref.]	Number of patients		Chemotherapy	IFN dose*	Response (CR+PR)†	
	IFN	Controls			IFN (%)	Controls (%)
The Nordic Myeloma Study Group [41]	297	286	MP	9.4	44	45
Österborg and associates [33]	164	171	MP	11.7	68	42
Cooper and associates [43]	138	134	MP	3.0	38	44
Ludwig and associates [?]	125	131	VMCP	6.3	67	62
Casassus and associates [34]	102	99	VMCP/VBAP	6.0	52	36
Joshua and associates [42]	59	54	PCAB	9.4	41	48
Aviles and associates [35]	52	51	VMCP/V-MTZ-CP/BEpiVDex	9.4	81	47
Montuoro and associates [36]	51	44	MP	4.7	86	68
Corrado and associates [44]	33	29	MP	7.5	45	48
Garcia-Larana and associates [45]	26	28	MP	11.7	62	54
Galvez and associates [37]	24	23	VABP	9.4	63	39
Vela-Ojeda and associates [38]	18	18	VMCP	7.0	94	78
Vela-Ojeda and associates [38]	20	17	MP	7.0	80	71
Scheithauer and associates [39]	15	17	VMCP	6.3	67	35
Aitchison and associates [40]	15	16	Cy	3.8	53	25
Capnist and associates [46]	15	14	MP	3.8	58	64
Total	1154	1132			54.4	45.9

*10^6MU/m^2/week. MP, melphalan/prednisone; VMCP, VABP, PCAB, V-MTZ-CP, BEpi VDex, Cy.

unacceptable adverse reactions [55], while low to moderate doses (e.g. 10×10^6 U/week) generally induce only minor, tolerable side-effects. The initial treatment phase of IFN therapy is often accompanied by fever (in 30–40% of cases) and 'flu-like symptoms (40–50%), which generally subside after 2–3 weeks of treatment. Other frequent adverse effects are fatigue (30–50%) and muscle pain (10–20%). Less frequently observed side-effects are mild haemotoxicity, nausea, vomiting, dizziness, headache and local erythema. Long-term treatment may induce mild alopecia, loss of appetite or neurological or psychiatric problems (in 5–15% of cases).

IFN maintenance after autologous bone marrow transplantation

In autologous bone marrow or peripheral stem cell transplantation, most centres use a three-phase treatment design [56], namely, (1) conventional induction chemotherapy, (2) high-dose chemotherapy with or without total body irradiation supported by autologous bone marrow or stem cell transplantation and (3) IFN maintenance treatment, for which even the early results regarding freedom from symptoms and survival were encouraging [57, 58]. The beneficial effect of IFN with respect to survival was confirmed by retrospective analysis of predictive factors in a multicentre European study of 384 patients [59], but could not be found by the French study group that performed autologous stem cell transplantations in 133 myeloma patients [60]. A British randomised trial reported significant prolongations of overall survival in both complete and partial responders, while significant prolongation of remission was observed only in patients who had achieved complete remission [52]. It seems that IFN maintenance treatment is particularly beneficial in myeloma patients with low tumour burden [32, 52, 59].

Other trials

IFN combined with dexamethasone. Since corticosteroids have been reported to reduce the toxicity of IFN without ameliorating its treatment efficacy [61] and dexamethasone (Dex) is effective as a single treatment agent in myeloma, combined IFN–Dex treatment has been applied to myeloma patients. It was possible to achieve a considerable response rate of 57% in newly diagnosed patients [62]. The reported response rate of 68% in chemoresistant myeloma patients treated with IFN–Dex [63], however, could not be confirmed in a subsequent study in which IFN–Dex was compared to VAD–Dex [47]. In patients who had reached only partial remissions during conventional induction treatment, maintenance treatment with IFN–Dex made possible the achievement of complete remissions in 42% [64] and a further reduction of the M-component by >50% in 54% of patients [65]. However, the combination of IFN with high-dose Dex may cause considerable toxicity.

Meta-analysis

Rationale. The divergent results reported from the randomised trials are not surprising. Because of the initially high expectations, relatively small numbers of patients were enrolled in most trials (Table 1) and in a few studies, enrollment was even prematurely terminated. Only after several years of investigation did it become evident that differences in response rates showed a 10% improvement. Unequivocal detection of such a small difference in a single trial would, however, require the enrollment of more than 900 patients [66]. However, a sufficient number of patients can be investigated by meta-analysis of all randomised trials.

Method. In order to avoid a possible bias, all available randomised trials, concluded or still ongoing, have to be included in the meta-analysis [67]. Thus, we performed a thorough search of the medical literature, including the abstract volumes of relevant international meetings and included every trial which met the following criteria: (1) application of IFN-α; (2) randomisation into 'IFN' and control arms; (3) for induction therapy, IFN treatment had to be combined with chemotherapy, the control arm was allowed to differ only by the exception of IFN; (4) for the maintenance phase, the previous induction treatment had to be well-documented, IFN had to be given as the single agent and patients in the control arm had to be untreated during maintenance; (5) the minimum required information on induction therapy was response rates, the minimum required information on maintenance treatment was either the median duration of relapse-free survival or the median overall survival time for both treatment arms.

Meta-analysis evaluates the difference between the treatment and the control arm for each trial separately, thus cancelling out the differences in investigational conditions among the trials [68]. The results are weighted by the number of enrolled patients in each trial. Meta-analysis assumes that, even though the magnitude of treatment benefits may have been greater in some trials than in others, improved treatment efficacy in the IFN arms would be detectable in the majority of trials. According to the null hypothesis of mere random fluctuations in the treatment results, the differences observed between IFN and control arms in all evaluated trials would be normally distributed, with a mean of zero. IFN treatment can be considered to be beneficial in myeloma patients, if the mean of all observed differences is positive and deviates significantly from zero.

Results. Figure 1 presents the results of a meta-analysis of 16 randomised trials, involving 2,286 patients, on combined IFN–chemotherapy for induction treatment. Response, i.e. the achievement of CR or PR is significantly ($2P<0.0001$) superior in the IFN arms, but the average gain is only slightly less than 10%. Similarly significant (P at least <0.01), but only marginal gains between 3 and 7 months, were detected in the IFN arms in meta-analyses of relapse-free and overall survival from the randomised trials on induction and IFN maintenance treatment (eight randomised trials involving 929 patients). Figure 2 depicts the summary of relapse-free survival under IFN maintenance treatment. Although the significant benefit of IFN treatment is clearly visible, the average gain is only a few months. Our meta-analyses clearly document significant benefits from IFN treatment, but they also show that the achieved gains are only moderate.

RECOMMENDATION OF IFN TREATMENT

Medical decision-making regarding the treatment of myeloma patients with IFN involves weighing the expected gains, namely, increased quantity of life and improved quality of life from prolonged relapse-free survival, against the risks of diminished quality of life from adverse treatment effects. Since that decision is difficult, we asked myeloma patients for their opinions on this issue.

The patients' opinions

Method. We interviewed 355 U.S. myeloma patients by telephone in order to obtain their opinions regarding personal

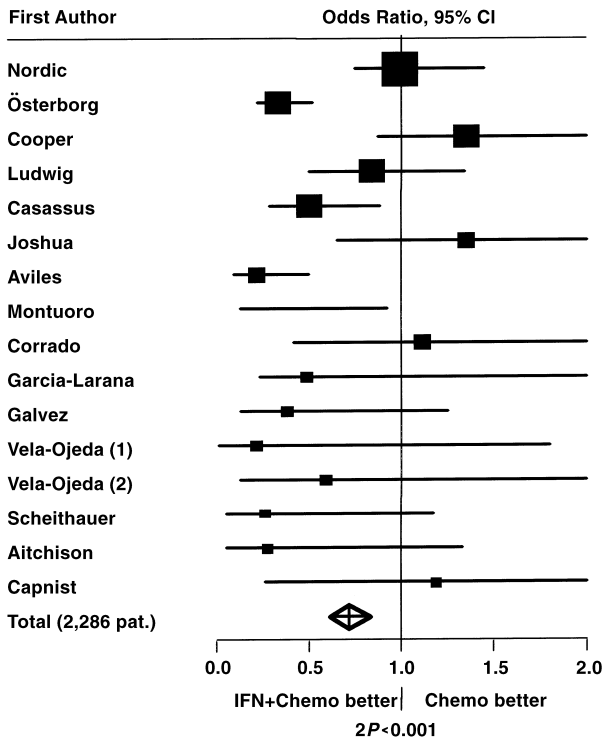

Figure 1. Meta-analysis of response rates reported from 16 randomised trials comparing combined IFN–chemotherapy with chemotherapy alone for induction treatment in myeloma patients. The squares indicate the odds ratios of each trial, their size is proportional to the number of patients enrolled. The lines cover the 95% confidence interval of each odds ratio. Superiority of IFN is located on the left-hand side of the vertical line, inferiority on the right-hand side. The total result (diamond covering the 95% confidence interval) shows clearly the significant benefit observed in the IFN arms.

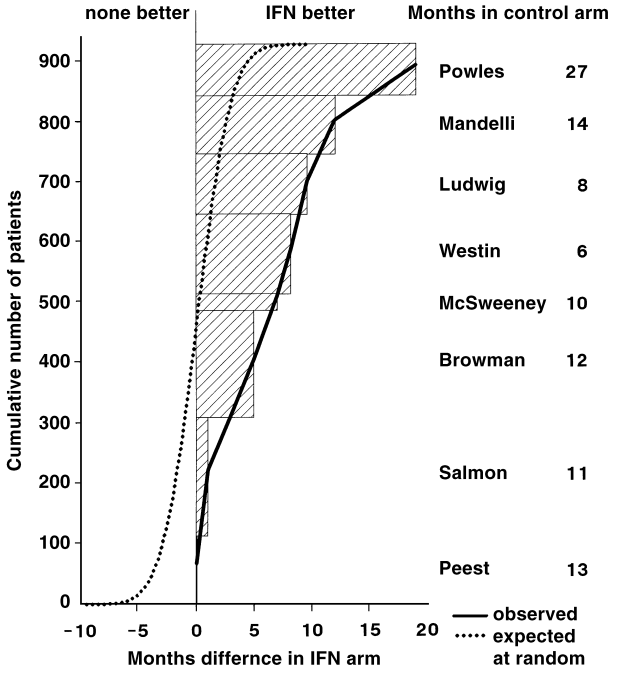

Figure 2. Summary of median maintenance duration observed in eight randomised trials in which 929 patients were enrolled, comparing IFN maintenance therapy to no maintenance treatment. The shaded bars show the differences between the IFN and the control arms and generate the curve of observed differences (solid line). The broken line indicates the cumulative normal distribution which would have occurred if the differences had been merely random fluctuations. Names refer to first authors, the associated numbers state the median durations observed in the control arm. The observed maintenance durations deviate significantly ($P < 0.005$) from the hypothetical random distribution.

acceptance or rejection of a proposed treatment which matched the conditions of IFN therapy [69]. The interviewees were informed about frequencies and characteristics of IFN toxicity, financial cost and the median gains in response rate, remission duration and survival as derived from the meta-analyses. They were then asked whether they would agree to the treatment if they could expect the following median gains: (1) 10% in response rate and 4 months in relapse-free survival and (2) 6 months in overall survival for combined IFN–chemotherapy during the induction phase, (3) 7 months in relapse-free survival and (4) 3 months in overall survival from IFN maintenance treatment.

Results. Nearly 50% of the interviewees agreed to a hypothetical induction treatment with IFN, 27 and 32% rejected treatment under conditions (1) and (2), respectively. Question (3) elicited 58% 'yes' and 23% 'no' responses, while the short overall survival time offered in question (4) was agreeable to only 32% and unsatisfactory to 55% of the interviewees. Generally, the acceptance rate of the proposed treatment increased with increasing gains in treatment outcome and rendered a break-even point between expected burdens and expected benefits at approximately 6 months' time gain (improved relapse-free or overall survival). Test/retest reliability of all the choices, determined in 36 cancer patients, was 0.896.

Patients who agreed to the proposed treatment tended to be younger (<60 years), to have had personal experience with IFN and to suffer from a more advanced stage of disease, compared with those who rejected the proposed treatment. A considerable proportion of patients (up to 25%) had difficulties in deciding. Knowledge of the 6 month risk/benefit tradeoff preferred by the majority of the interviewed myeloma patients with regard to IFN treatment may facilitate decision-making in clinical oncology.

CONCLUSIONS

Both combined IFN–chemotherapy during the induction phase and IFN maintenance treatment render significant benefits in all relevant respects, i.e. response rate, relapse-free and overall survival. However, the magnitude of these gains, which may be achieved at the cost of reduced quality of life, is only marginal. Continuous IFN treatment during both the induction and the maintenance phase seems to effect cumulative gains. In this difficult situation of medical decision-making regarding IFN treatment, the patient's personal opinion should be considered. Myeloma patients do have individual preferences with respect to IFN treatment, but the majority of the large sample of patients who stated their opinion opted for the treatment. Thus, recommendation of IFN treatment is in line with both the results of scientific research and the preference of the majority of the interviewed myeloma patients. Those facts justify the inclusion of IFN treatment into experimental study designs. Patients who, for whatever reason, are unable to contribute their personal preference to the decision-making process may be treated with

IFN in accordance with the majority decision. We conclude that IFN treatment should be offered to all eligible myeloma patients. However, their personal choice following comprehensive information about the expected benefits and risks should play a decisive role in the actual treatment decision.

We recommend IFN treatment of myeloma patients with low tumour burden, such as maintenance treatment of patients in complete remission, particularly following high-dose treatment and bone marrow or peripheral stem cell transplantation. Besides low tumour mass, other prognostic factors of IFN effectiveness have to be established by meta-analysis of the available published results. As a result, IFN treatment may in the future be given predominantly to a well-defined subgroup of myeloma patients. In these selected patients, however, a larger margin of benefits can be expected.

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Acknowledgement—Supported by the Wilhelminen–Krebsforschungsinstitut of the Austrian Forum Against Cancer.