Interferon in the Treatment of Multiple Myeloma

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Further study is required to determine which subsets of patients with myeloma will derive most benefit from interferon.

Background: The role of interferon (IFN) in the treatment of multiple myeloma has been investigated for nearly two decades. The mechanisms underlying antitumor activity of IFN may be mediated by antiproliferative and immunomodulatory effects. The benefits of treatment remain controversial, and guidelines for the use of IFN in myeloma are needed. This review evaluates available data on the impact of IFN therapy on multiple myeloma.

Methods: A MEDLINE search of published prospective, randomized trials of IFN in multiple myeloma provided the data included in this review, as well as selected abstracts presented at international meetings.

Results: IFN has complex and pleiotropic effects on human myeloma lines and ex vivo myeloma cells. An antiproliferative effect with disruption of the IL-6-mediated growth loop may be crucial, but biologic heterogeneity in myeloma may have important clinical implications for response to IFN. IFN has demonstrable antitumor activity in multiple myeloma but appears to have a modest effect on overall survival when combined with chemotherapy during induction or when used as maintenance therapy. Most studies have shown a prolongation of the plateau phase of disease with IFN of variable duration of between four and 12 months.

Conclusions: A reliable estimate of the benefit of IFN in the overall population of patients with myeloma is difficult to determine with discordant results from different trials. Possible sources of heterogeneity in randomized trials need to be identified, and recognition of subsets of patients who may benefit is important. Cost-benefit analyses with integration of quality-of-life data are essential for developing guidelines for the use of IFN in myeloma.

Introduction

Despite two decades of clinical investigation, the role of interferon (IFN) in the treatment of multiple myeloma continues to be debated. The antitumor activity and therapeutic potential of IFN in this disease was initially reported in patients treated with partially purified natural (human leukocyte-derived) IFN-γ, and small pilot studies confirmed its activity as a single agent in untreated myeloma and, to a lesser degree, in relapsed disease. The introduction of recombinant DNA technology for the production of purified IFN alleviated the problem of supply and permitted large-scale clinical trials. Preclinical studies indicating possible in vitro synergy between IFN-α and various chemotherapeutic agents in tumor clonogenic assay systems led to trials exploring the concurrent administration of IFN-α with different induction regimens to improve tumor response rates.

With accumulating evidence that continuation of chemotherapy beyond the achievement of a plateau phase in response did not improve survival, interest shifted to the investigation of IFN-α as a maintenance agent. Based on the rationale that the antiproliferative and immunomodulatory properties would be most effective in the treatment of myeloma with low tumor burden, a number of randomized trials have investigated the effect of IFN-α on response duration and survival when used alone after response to induction therapy was established. With the data available from these trials, several conclusions about the therapeutic benefits of IFN-α on different outcome measures are possible. The increasing application of high-dose therapy with stem cell rescue to augment cytoreduction and increase complete response rate has also prompted studies on the impact of IFN-α maintenance in this setting, but to date, limited data are available. Although IFN-α has been evaluated in patients with relapsed disease, IFN-α has been the most thoroughly studied of the family of IFNs in multiple myeloma and is the focus of this review.

Background

The IFNs are a family of naturally occurring, species-specific cytokines with a wide spectrum of antiviral, immunomodulatory, and antiproliferative effects. Initially identified in 1957, IFN is characterized by three principal classes -- α, β, and γ -- that are distinguishable by acid stability, cell surface receptors, chromosomal location, and primary sequence. IFN-α and IFN-β share components of the same receptor and are grouped as type I IFNs, whereas IFN-γ uses a separate receptor and is classed as a type II IFN. The demonstration of antitumor activity against different human tumors in vivo by partially purified "natural" IFN-γ was followed by the cloning of IFN-α2a and IFN-γ2b and broader clinical investigation. Preclinical studies of the IFNs in animal tumor model systems were limited by the species specificity of IFN, but the development of in vitro human tumor stem cell assays and the establishment of myeloma cell lines have facilitated study of the mechanisms mediating antitumor effects.

An inhibitory effect of IFN on in vitro colony formation and the self-renewing capacity of clonogenic myeloma cells was initially shown with further evidence of a synergistic reduction in colony formation by the combination of IFN-α and melphalan. In IFN-sensitive cells, an antiproliferative effect is shown in inhibition of cell cycle progression; among the pleiotropic effects of IFN action that might result in a block in cell-cycle traverse are suppression of Rb phosphorylation, inhibition of E2F DNA binding and c-myc expression, and down-regulation of G1 cyclins and cyclin A. The biochemical actions of IFN are attributable to activation of IFN-responsive genes and stimulation of the synthesis of different proteins. Induction by IFN-α of 2′, 5′ oligoadenylate synthetase (2, 5-A synthetase) stimulates the activity of latent ribonuclease L, an enzyme that catalyzes mRNA degradation and may explain the reduction in immunoglobulin mRNA synthesis observed following incubation of freshly isolated myeloma cells with low concentrations of IFN-α. However, a more crucial effect on disease biology may be mediated via suppression of regulatory growth factors, and studies in myeloma have focused on the potential perturbation of the important IL-6-mediated growth loop. Using an IL-6-dependent myeloma line sensitive to growth inhibition by IFN-α, Schwabe et al showed that IFN-α decreased IL-6 receptor (IL-6R) expression on the cell surface by the specific reduction of the a chain (gp80) of the IL-6R complex and a decrease in a chain mRNA expression. However, IFN-α is not uniformly growth inhibitory for myeloma lines, and
results with different myeloma lines suggest a biologic heterogeneity in IFN-α sensitivity. Jourdan et al.8 showed growth stimulation by IFN-α of five myeloma lines by induction of IL-6 mRNA synthesis and the emergence of autonomously growing sublines with autocrine IL-6 production.

IFN-α and IL-6 bind to distinct receptor complexes, but they share signal transduction pathways, activating the same members of the Stat family of transcription factors, and they also share overlapping gene regulatory pathways, i.e., transcriptional activator IFN-α-regulatory factor-1 (IRF-1) and its antagonistic repressor (IRF-2).9,10 Jelinek et al.11 showed a panel of IL-6 responsive myeloma cell lines of varying IFN-α sensitivity for the effects of IFN-α and IL-6 on IL-6R expression and transcription factor activation. IL-6R expression was down-regulated on both the IFN-α growth-stimulated line and three IFN-α growth-inhibited lines without an observed differential pattern of activation of Stat or IRF proteins to explain the opposite growth effects of IFN-α. While the precise mechanisms of IFN-α action in myeloma continue to be elucidated, the heterogeneity of IFN-α responsiveness observed in vitro has evident clinical implications; the possibility of growth stimulation of myeloma cells during treatment with IFN-α has been raised in several case reports.12,13

Clinical Studies With Interferon

Interferon in Relapsed Myeloma

In a pilot report of partially purified human leukocyte IFN in myeloma, Mellstedt et al.1 observed a reduction in paraprotein levels in four previously untreated patients with response durations of three to 19 months. Subsequent reports in small numbers of patients confirmed these initially encouraging results of the single agent activity of IFN in myeloma and were followed by larger studies of both human leukocyte IFN and recombinant IFN-α in previously treated and untreated patients. In patients with relapsed and refractory myeloma, IFN-α used as a single agent has resulted in rather limited responses of usually brief duration in the range of 10% to 20%. In a phase II study of recombinant IFN-α evaluating different dose schedules with maintenance doses of 10 x 10^6 IU/m^2 tiw, objective responses were observed in seven of 38 patients.14 Responses were seen in only two of 19 patients refractory to primary therapy compared with five of 19 relapsing patients, with improved survival in responding patients. In another small study using a different preparation of recombinant IFN-α but at comparable doses, responses were limited to two of 13 patients who had relapsed or failed prior chemotherapy.15

Interferon in Induction Therapy

In previously untreated patients, IFN-α has been investigated as a single agent for response induction, but it has been studied more extensively in combination with conventional chemotherapy regimens. The following review of the data should be prefaced by noting that the primary endpoint for statistical analysis in many of the published phase III trials has been response rate, with limited statistical power to detect survival differences between treatment arms; the significance of the degree of response as a clinically meaningful measure has been questioned.16 Besides variability in IFN dosing, schedule, and duration of therapy, different trials have used different response criteria (Southwest Oncology Group [SWOG] or Chronic Leukemia Myeloma Task Force), have often not separately analyzed patients with stable disease (ie, those not satisfying response criteria but not progressing on treatment) who may represent an intrinsically more favorable subgroup, and have varied in the duration of induction chemotherapy. These factors complicate the direct comparison of results in trials with considerable potential for heterogeneity and underscore the importance of a meta-analysis of randomized trials of IFN-α that has been undertaken by the Myeloma Trialists’ Collaborative Group.

An early randomized trial17 conducted by a Swedish group compared human leukocyte IFN alone with melphalan and prednisone (MP) as initial therapy in newly diagnosed patients with myeloma. The response rate was 44% in the MP group and 14% in the IFN group; however, overall survival of patients in the two treatment groups did not differ significantly, probably because of a crossover design allocating patients progressing on IFN to treatment with MP. Retrospective subset analysis of this study indicated a superior response to IFN in patients with IgA myeloma or light-chain disease compared to IgG myeloma. As a single agent in other smaller studies, recombinant IFN-α has yielded comparable response rates that are clearly inferior to treatment with standard chemotherapy regimens in previously untreated patients.

After the earlier trial indicating a possible differential benefit of IFN-α in IgA myeloma and light-chain disease, the Myeloma Group of Central Sweden conducted a randomized trial in which patients were stratified by M-component subtype as well as by Durie-Salmon stage and age.18 In this trial, 335 patients with untreated stage II and III disease were randomized to either MP alone or MP together with the same preparation of natural (leukocyte-derived) IFN used above. When response criteria were fulfilled, IFN-α was continued at a dose of 3 x 10^6 IU tiw along with MP at six-week intervals until disease progression. With treatment groups balanced for prognostic factors, the response rates were 42% in the MP group vs 68% in the MP/IFN group (P<.0001). However, the response rate to MP/IFN in patients with IgA myeloma and light-chain disease was 85% and 71%, respectively, compared with 48% and 27%, respectively, with MP. These differences could not be accounted for by imbalances in these subgroups with respect to age, stage, or renal function. Overall survival in the two treatment arms was not significantly different, with median survival of 29 months in the MP/IFN group and 27 months in the MP group. A survival benefit was seen in patients with IgA myeloma and light-chain disease randomized to MP/IFN vs MP (median 32 months vs 17 months, P<0.05).

A Cancer and Leukemia Group B study19 of similar design and comparable size that used the same response criteria did not corroborate a superior response rate for the combination of MP with IFN-α. In this study, 278 patients with active disease were allocated either to treatment with MP or to recombinant IFN-α 2 x 10^6 IU/m^2 tiw with MP during the first two weeks of a four-week cycle. Treatment was continued in responding patients in both arms for two years. Objective response rates were 44% for MP vs 33% for MP/IFN, with duration of response similar in the two groups and no difference in overall survival (median 3.17 years MP vs 3.0 years MP/IFN).

Several smaller trials investigating IFN in combinations with regimens other than MP in induction have yielded inconsistent results. A phase II study by the Eastern Cooperative Oncology Group20 evaluated a regimen of alternating IFN-α and VBMC (vincristine, carmustine [BCNU], melphalan, cyclophosphamide, and prednisone) in 58 previously untreated patients. VBMC and IFN-α 5 x 10^6 IU/m^2 tiw were administered in alternating three-week cycles for two years of treatment. A response rate of 80% was observed with a median response duration of 35 months and an overall survival of 42 months. In a larger phase III study conducted by the same group,21 653 patients were randomized to VBMC alone vs VBMC alternating with IFN-α or VBMC with high-dose cyclophosphamide with treatment continued for two years or until disease progression. After a median follow-up of four years, no differences were observed among the three arms in overall response rate or survival.

A French study22 allocated 201 patients to treatment with VMCP/VBAP (vincristine, melphalan, cyclophosphamide, and prednisone alternating with vincristine, carmustine [BCNU], doxorubicin, and prednisone) or the same with IFN-α 3 x 10^6 IU/m^2 tiw during the two-week interval between each cycle. In a preliminary report after a median follow-up of 36 months, no differences in response rate, overall survival, or event-free survival were detected.
Two other studies with a more complicated design investigated IFN-α in combination with other multiple drug chemotherapy in induction but reached similar conclusions. An Australian group reported a trial in which IFN-α was used together with a regimen of PCAB (prednisone, cyclophosphamide, doxorubicin, and carmustine [BCNU]) during initial treatment and then continued alone as maintenance therapy during the plateau phase. This study randomized 113 patients to receive either PCAB alone for 12 cycles or PCAB with IFN-α at $3 \times 10^6$ IU five times per week with IFN continued after 12 cycles until disease progression. The administration of IFN-α did not improve response rate, time to treatment failure, or overall survival. Similarly, a study using vincristine, doxorubicin, and dexamethasone (VAD) induction randomized 72 untreated patients to either concurrent treatment with IFN-α at $3 \times 10^6$ IU tiw during induction or as maintenance following chemotherapy. In a comparison of results with a historical control group treated with VAD alone, no significant difference was demonstrated in progression-free survival or survival between the arms.

**Interferon as Maintenance Therapy**

While the benefit of IFN appears questionable when administered concurrently with chemotherapy during induction, the potential of IFN-α as maintenance treatment in the plateau phase has been of particular interest following the initial report of an Italian multicenter study by Mandelli et al. The strategy of employing IFN-α maintenance therapy has since been tested in a number of larger studies conducted by various cooperative groups (Table).

### Randomized Trials of IFN-α as Maintenance Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients Randomized</th>
<th>Induction Regimen</th>
<th>IFN Dose</th>
<th>Median Response Duration (mo)</th>
<th>Median Survival (mo)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandelli et al²⁵</td>
<td>51</td>
<td>MP or VMCP/VBAP</td>
<td>$3 \times 10^6$ IU/m² tiw until relapse</td>
<td>26</td>
<td>52</td>
<td>0.0002</td>
</tr>
<tr>
<td>Browman et al²⁷</td>
<td>85</td>
<td>MP</td>
<td>$2 \times 10^6$ IU/m² tiw until relapse</td>
<td>17</td>
<td>45</td>
<td>0.016</td>
</tr>
<tr>
<td>Westin et al²⁸</td>
<td>61</td>
<td>MP</td>
<td>$5 \times 10^6$ IU/m² tiw until relapse</td>
<td>14</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>Salmon et al²⁹</td>
<td>97</td>
<td>VAD; VMCP/VBAP; VMCPP/VBAPP</td>
<td>$3 \times 10^6$ IU tiw until relapse</td>
<td>12</td>
<td>32</td>
<td>0.39</td>
</tr>
<tr>
<td>Ludwig et al³¹</td>
<td>46</td>
<td>VMCP; VMCP/IFN</td>
<td>$2 \times 10^6$ IU tiw x 1 year</td>
<td>18</td>
<td>51</td>
<td>0.05</td>
</tr>
<tr>
<td>Peest et al³²</td>
<td>52</td>
<td>VBAMDex; MP</td>
<td>$5 \times 10^6$ IU tiw until relapse</td>
<td>13</td>
<td>34</td>
<td>*</td>
</tr>
</tbody>
</table>

* from randomization to maintenance
** survival in months not given

IFN = interferon
MP = melphalan, prednisone
VMCP = vincristine, melphalan, cyclophosphamide, prednisone
VMCPP = VMCP plus 50 mg prednisone given on alternate days between cycles of VMCP
VBAP = vincristine, carmustine (BCNU), doxorubicin, prednisone
VBAPP = VBAP plus 50 mg prednisone given on alternate days between cycles of VBAP
In the Italian study,25 patients responding to induction chemotherapy with >50% reduction of serum M peak or with disease stabilization (defined as <50% but >25% decrease in the baseline level of M peak) were randomized to either observation or treatment with IFN. Induction therapy consisted of either MP or alternating VMCP/VBAP continued for 12 months; 101 patients satisfying the response criteria and stratified by induction regimen (45 in the MP group, 56 in the VMCP/VBAP group) were then allocated to IFN-- 3 x 10^6 IU/m^2 tiw or observation until disease progression. At the time of publication with a median follow-up of 46 months from the start of treatment, analysis showed a median duration of response from randomization of 26 months in the IFN group vs 14 months in the control group (P=0.0002) with a median survival of 52 months and 39 months, respectively. The favorable impact of IFN maintenance treatment on survival in this report was limited to patients with an objective response and was not evident in patients with only disease stabilization after induction chemotherapy. With longer follow-up, the overall survival difference between IFN maintenance and observation was not sustained.26

The National Cancer Institute of Canada (NCI-C) accrued 402 patients with symptomatic stage I and stage II and III myeloma to a trial that randomized responding patients, with >50% decrease in baseline M peak, to IFN- or observation.27 Following induction with MP, 176 responding patients were then randomized with 85 to IFN- and 91 to control. IFN- was administered at 2 x 10^6 IU/m^2 tiw until evidence of disease progression. At a median follow-up of 43 months, median survival for the IFN group was 43 months compared with 35 months for the control group (P=0.16); however, after adjustment for imbalance in performance status, a marginally significant difference was observed (44 months vs 33 months, P=0.049) favoring the IFN group. Response rates to retreatment with MP on relapse were similar in the two groups.

A multicenter Swedish and Italian study28 reported the results of a similar randomization to IFN- or observation after plateau phase had been achieved with MP. In this study, 314 patients with symptomatic stage II and III disease were treated with MP; 155 patients (49%) satisfied the criteria for achieving plateau phase, i.e., a stable M-component concentration on three consecutive measurements at intervals of four weeks. After exclusion of 30 patients for reasons of age, concomitant heart disease, or other illnesses, 64 patients were randomized to observation only and 61 patients to treatment with IFN- 5 x 10^6 IU tiw until relapse. Treatment arms were balanced for prognostic factors and number of courses of MP before randomization. Although there was a highly significant difference in plateau phase duration favoring patients treated with IFN- compared with the control arm (median duration 13.9 months vs 5.7 months, respectively, P<0.0001), median survival from the time of randomization was equivalent in the two arms at 35 vs 36 months, and 46 vs 43 months when calculated from initiation of MP treatment. After censoring of eight patients in the IFN arm who died from intercurrent illness in plateau phase, did not receive IFN, or discontinued IFN within three weeks, life-table analysis still showed no significant difference in survival. A trend towards prolongation of survival in complete responders and in patients with light-chain disease treated with IFN also failed to reach statistical significance.

The results of a negative SWOG trial of IFN-- maintenance following induction with different regimens varying in glucocorticoid dose intensity have provided interesting hypothesis-generating data.29 In this study, 509 patients who were stratified for stage and risk category (age >70 years, prior large volume radiation therapy, impaired renal function) were randomized to three induction regimens consisting of VAD, alternating VMCP/VBAP, or VMCP/VBAPP in which 50 mg of prednisone was given on alternate days between cycles of VMCP/VBAP. A total of 193 patients who achieved response by SWOG criteria (>75% cytoreduction) were allocated to maintenance with IFN- 3 x 10^6 IU tiw (97 patients) or observation (96 patients). No benefit of IFN maintenance could be shown for either relapse-free or overall survival in any subgroup. At variance with the results of the Mandelli study, in which the benefit of IFN maintenance was primarily seen in patients with the best responses to induction therapy, the SWOG study using more stringent response criteria could not demonstrate any benefit in the group of responders. In this study and in the Canadian study, observations on the outcome of patients with stable disease on induction therapy complicate the analysis of the therapeutic benefit of maintenance IFN. These patients without progressive disease but not fulfilling response criteria were ineligible for randomization to maintenance with IFN in either study. In the SWOG study, these patients were eligible for treatment with the combination of IFN-- and dexamethasone. Median survival in this latter group was 48 months from the start of IFN/dexamethasone compared with median overall survival of 32 and 38 months from randomization for IFN maintenance and observation, respectively, in the responding patients. Several studies are currently in progress to investigate the possible synergy of IFN-- and dexamethasone as maintenance therapy.

Although further cytoreduction with IFN-- and dexamethasone was achieved in approximately one third of this nonrandomized group of patients with "stable disease," an intrinsically more favorable clinical course in this group must also be considered. A secondary analysis of patients with stable disease in the NCI-C study supports the likelihood that any improvement in survival with maintenance therapy in this group will be more difficult to detect.

The Nordic Myeloma Study Group tested the strategy of integrating IFN-- during induction therapy with MP and as maintenance during the plateau phase.30 In this comprehensive, randomized, multicenter study conducted in university and county hospitals throughout Scandinavia, a relatively unselected patient set was included that represented over one half of cases reported for a defined population base. A total of 592 patients with symptomatic disease were allocated to treatment with MP with or without concurrent IFN-. MP was administered in six-week cycles and continued for at least eight courses in both groups if no disease progression was observed. Patients allocated to IFN- received 5 x 10^6 IU tiw from initiation of therapy until treatment failure of MP. Stratification was by treatment center, but the treatment groups were well balanced for stage, performance status, and -2 microglobulin. Two hundred and ninety-seven patients in the MP group and 286 in the MP/IFN-group were evaluable. Response rates were similar in the two groups (45% in the MP group vs 44% in the MP/IFN-- group), and overall median survival was nearly equivalent at 29 and 32 months, respectively. At the time of analysis, 169 patients in the MP group and 164 in the MP/IFN-- group had died, and the risk ratio for death in the MP group compared with MP/IFN-- after adjustment was 1.12 (CI 0.89-1.40; P=0.33). The only benefit observed was a prolongation of response duration in the latter group by six months. The results were based on an intention-to-treat analysis with one third of patients discontinuing IFN-- before entering plateau phase. There was no statistically significant difference in survival between patients in the IFN-- arm who stopped treatment prematurely compared with those who continued on IFN-. Retrospective analysis also failed to demonstrate a survival advantage for IFN-- in any immunoglobulin subgroup.

A smaller study reported by Ludwig et al31 used a primary and secondary randomization design to assess IFN-- during induction and maintenance. In this trial, 256 patients with myeloma in any stage were randomly assigned to treatment with VMCP alone or with concurrent IFN, with stratification by treatment center, stage, immunoglobulin class, and renal function. The duration of induction therapy was variable, depending on response, with a maximum of nine cycles for patients with stable disease. Patients with responsive or stable disease after induction therapy were then randomized to either observation or maintenance with IFN for one year. Randomization in the maintenance phase was stratified according to induction regimen (VMCP vs VMCP/IFN) and degree of response to the induction regimen (complete, partial, or stable). One hundred and four patients in the VMCP/IFN arm and 109 in the VMCP arm were evaluable for treatment efficacy, and no difference was observed in response rates between the two groups. Fewer patients showed disease progression during induction in the former group (11% vs 23%, P<0.05), but this was limited to patients with stage I and II disease. Prolongation of progression-free survival in the VMCP/IFN group compared with the VMCP group was at the limits of significance (23 months vs 16 months, respectively), but overall survival from the start of treatment was not significantly different between the
groups (39 months vs 30 months, respectively). After completion of the induction phase, 100 patients with stable or responsive disease were randomized to maintenance with IFN-α, particularly in those achieving a complete response following high-dose therapy. However, with longer follow-up, the benefit has not been sustained. In this study, 84 patients were allocated to maintenance with IFN-α at a dose of $3 \times 10^6$ IU/m² tiw until progression or to observation following high-dose therapy. At 5-1/2 years after entry of the last patient on the study, 38 patients have died (17 in the IFN arm and 21 in the control arm) with no statistically significant difference between the arms in either overall or progression-free survival. The integration of IFN with other therapy following maximal cytoreduction has not been adequately tested, and trials are ongoing to evaluate its use in this context.

**Toxicity and Cost of Interferon Therapy**

While a consensus based on the results of the randomized clinical trials cited above might be reached with respect to prolongation of plateau-phase duration by maintenance therapy with IFN-α, ascertaining its effect on overall survival remains contentious. In view of the toxicity, inconvenience, and costs associated with IFN and the modest therapeutic benefits observed, there is a critical need for cost-benefit data on which to base guidelines for its use in myeloma.

The toxicity of IFN-α is an important factor in the evaluation of randomized trials reporting results on an intention-to-treat principle, since any potential benefits may be underestimated if a significant number of patients discontinue treatment prematurely. As noted above, one third of patients in the Nordic study of MP/IFN stopped treatment with IFN before plateau phase was reached. In the NCI-C study, toxicity caused approximately 60% to reduce the dose of IFN-α, with 14% discontinuing therapy. Fever and flu-like symptoms are often experienced during the initial weeks of treatment with IFN-α but are usually self-limited. Other symptoms related to central nervous system toxicity and complaints of generalized fatigue, myalgias, or nausea may persist. Potential cardiotoxicity with exacerbation of heart failure or angina has also been noted, particularly in patients with underlying heart disease.

A cost-utility analysis was performed by Nord et al. based on the results of the Nordic trial in which the addition of IFN to MP resulted in a five- to six-month prolongation of plateau phase but with a gain in survival time that did not reach statistical significance. The analysis attempted to answer whether the addition of IFN was preferable after consideration of its impact on quality of life and whether the incremental cost is justified by the difference in outcome with this treatment. The estimated difference in mean survival between the arms in this study were compared with differences in quality of life within the framework of a threshold analysis. The calculations were based on a presumed three-month difference in survival calculated from the risk ratio of death in the two arms of the study with a 12% increase in median survival time with IFN. Calculations of the number of days in hospital, days lost from work, and cost of drug administration were factored in determining the gain in quality-adjusted life-years (QALY). This analysis suggested a gain in QALY for the addition of IFN to MP for all patients with newly diagnosed symptomatic myeloma but at a costutility ratio of $110,000 US per QALY. The limitations of the data and the analysis are recognized.

Using data derived from an overview of published studies, Ludwig et al. attempted to ascertain from the perspective of patients with myeloma the acceptability of a preferred hypothetical treatment with the toxicity of IFN and an expected gain of six months in overall or relapse-free survival. This study, based on patient interviews, reported marked contrasts in individual preferences that reflected differences in age, educational background, and previous experience with IFN. Willingness to accept treatment depended on the expected benefit; a six-month gain in overall survival or relapse-free survival with good quality of life represented a threshold for most patients. This study underscores the difficulty for both patients and physicians in decision making where a modest improvement in outcome with a therapeutic intervention may be anticipated.

**Conclusions**

With the conclusion of the larger randomized trials and with follow-up data of four to five years in most studies, a more balanced perspective on the effect of IFN-in myeloma is possible, but questions remain. Differences in trial design, eligibility criteria, the evaluable primary endpoints, and the definition of response criteria may explain some of the discrepancies in outcome among different trials. While several studies have shown an improvement in response rate when IFN-α is used during induction, other studies have failed to demonstrate any improvement. Furthermore, because of poor correlation with survival, the merit of currently used response criteria to predict clinically meaningful outcomes in the treatment of myeloma has been challenged. The initially reported benefit of IFN-α in patients with a greater degree of response to standard chemotherapy has not been well substantiated. Whether patients with complete responses following high-dose therapy will experience improvement in progression-free and overall survival with IFN-α maintenance either alone or in combination with other immunotherapy requires further study.

The identification of particular subsets of patients, characterized by immunoglobulin class or by available prognostic variables, who are more likely to benefit from IFN-α is problematic. The majority of maintenance trials have noted some prolongation of plateau phase of six to 12 months in patients treated with IFN-α, but this has not usually translated into an improvement in survival. There are concerns that this may be related to a more aggressive clinical course following relapse in patients maintained on IFN-α. The possibility of a dose-related benefit of IFN-α has been difficult to determine, since the usually tolerated dose has been established in the range of $3 \times 10^6$ IU tiw; however, trials using higher doses have not produced consistently superior results. The results of a meta-analysis undertaken by the Myeloma Trials’ Collaborative Group of randomized trials, including individual data on more than 4,000 patients, should provide a more reliable estimate of the extent of any benefits associated with IFN-α. The integration of these data with data from cost-utility analyses that assess costs of treatment and impact of treatment on quality of life will allow a more valid determination of the role of IFN-α in the management of myeloma.

**References**


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