Introduction

Twenty years have passed since interferon was clinically applied to treat multiple myeloma. Only IFN-α has been used and evaluated for its efficacy when used alone or in combination with chemotherapy and for its significance when used in the induction or maintenance therapy. Although not definitely determined, the positioning of IFN-α in the therapeutic strategy of multiple myeloma is described here with recent therapeutic results. The therapeutic
role of IFN-α for other related hematological diseases is also mentioned.

**IFN-α Therapy for Multiple Myeloma**

There have been many reports on the therapeutic results of IFN-α for multiple myeloma. Positive and negative reports have been repeatedly published. IFN-α regimens that had proven effective in pilot studies have often failed to show any significant effect in randomized comparative studies. The utility of IFN has also been discussed in terms of medical economics. IFN is now generally considered an important option for treating multiple myeloma probably because the disease remains lethal in spite of the advance of hematopoietic stem cell transplantation, i.e. it is often difficult to meet the eligibility for the transplantation since the disease frequently develops in elderly population, and because an acceptable therapeutic strategy has not been established yet. Before describing the practice of the treatment, let us consider the biological activities of IFN-α.

1. **Action mechanism of IFN-α for myeloma cells**

The use of IFN-α as a therapeutic drug for myeloma is justified from the following findings: (1) IFN-α stimulates the cytotoxic activity of NK cells; (2) it stimulates macrophages to express major histocompatibility antigens and tumor-specific antigens associated with antigen presentation; (3) it inhibits colony formation from myeloma cells in culture; (4) it inhibits the production of M protein from myeloma cells; (5) it reduces the expression of IL-6 receptor associated with myeloid cell proliferation; and (6) it down-regulates the expression of oncogenes, such as c-myc and N-ras. Based on these findings, IFN-α has been clinically applied. However, it has also been reported that IFN-α stimulated the proliferation of myeloma cells when it was used at a low concentration.

2. **Induction therapy with IFN-α**

Although randomized comparative studies initially failed to demonstrate the superiority of IFN-α, results indicating its effectiveness have recently become available.

(1) **ECOG study**

The Eastern Cooperative Oncology Group (ECOG) performed a phase III clinical study in untreated patients to compare complete response and survival rates between the VBMCP (vincristine, BCNU, melphalan, cyclophosphamide, and prednisolone) regimen and the regimen plus either IFN-α, or high-dose cyclophosphamide. IFN-α was administered at a dose of 5×10^6 units/m² thrice weekly from Day 22. The results obtained from 628 subjects showed a significantly higher CR rate in the VBMCP/IFN-α group than the VBMCP group (18% vs. 10%). Although no significant difference was noted for survival rate, the response duration was significantly longer in the VBMCP/IFN-α group. Further, the VBMCP + IFN-α group fared better than the VBMCP + high-dose cyclophosphamide group in relation to complications from serious infections. ECOG concluded that the VBMCP + IFN-α regimen was especially effective in elderly patients and for IgA-type myeloma.

(2) **Japanese multi-center joint study**

Similar results have been reported in Japan.
A study on induction/maintenance therapy with IFN-α was started in 1991 as being funded by the Foundation of Inter-disciplinary Therapies Studies. Figure 1 shows the regimen used in the study. IFN-α was administered thrice weekly from Days 22 to 42 after MCNU (ranimustine), vincristine (Oncovin®), melphalan (Alkeran®), and dexamethasone were administered. Maintenance therapy with 2 × 10⁶ units/m² (up to 3 × 10⁶ units/m²) of IFN-α was performed until the disease recurred. The study was undertaken as a single-arm pilot study including 161 patients, and resulted in a CR rate of 24%, PR rate of 51%, and median survival period of 3.6 years. The survival period was 4.3 years in patients with CR or PR.

However, the study concluded that no significance could be offered for the maintenance therapy with IFN-α. The regimen used was named the “ROAD-IN” regimen (ROAD-IN being an acronym formed from the initials of the drugs used). The protocol was based on the DMVM-IFN-α therapy which had been originally developed by Kitani, T. et al. in the Hanshin Myeloma Study Group. Although IFN-α was initially administered for 20 days from the day when the drugs were started, the duration was subsequently reduced to 12 days. A CR rate of more than 25% was obtained.

Our Kinki University group took part in these studies from the start. The results were excellent, with 46.4% (13 patients each) of CR and PR rates in 28 patients treated with the DMVM-IFN-α or ROAD-IN therapies. The overall survival rate in the CR patients (as determined by the Kaplan-Meier method) reached a plateau of about 60% at 5 years. Figure 2 shows a representative case: although the M protein was 7,000 mg/dl at hospitalization, it returned to the normal range in about 2 months.

(3) Other multi-drug combination regimens

Other multi-drug combination regimens with IFN-α include the VAD-IFN-α regimen including vincristine, adriamycin, and dexamethasone, VMCP-IFN-α regimen including vincristine, melphalan, cyclophosphamide, and prednisolone, and PACB-IFN-α regimen including prednisolone, adriamycin, cyclophosphamide, and BCNU. The regimens resulted in CR rates ranging from 1 to 30%, median remission periods from 12 to 26 months, and median sur-
4. Meta-analysis of IFN-α therapy for multiple myeloma

The efficacy of IFN-α has been analyzed according to evidence-based medicine. What is most valuable in the analysis is the meta-analysis that compares the results of several large-scale prospective randomized comparative studies. Ludwig et al., who examined 3,948 patients from 30 randomized comparative studies, showed that significantly higher CR, PR, and overall survival rates could be achieved in the IFN-α-containing chemotherapy group than the chemotherapy group, although the differences were marginal.

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An Oxford joint study group of myeloma trialists also performed a meta-analysis in 4,012 patients from 24 randomized studies. The result demonstrated that IFN-α moderately improved recurrence-free and overall survival rates. It is therefore considered that individual studies failed to show any significant difference possibly due to the small number of patients examined. Table 1 shows the results of the meta-analyses.

5. Adverse effects of IFN-α therapy

In the treatment of multiple myeloma, IFN-α causes adverse effects similar to those observed in other clinical fields. The ROAD-IN regimen caused leucopenia in 72% of the cases, thrombocytopenia in 15%, fever in 26%, and malaise in 49%. None of these adverse effects were severe enough to necessitate discontinuation of treatment.

Table 1 Meta-Analyses of the Effect of IFN on Multiple Myeloma

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<th>Significant effects in groups treated with IFN</th>
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<tbody>
<tr>
<td></td>
<td>Ludwig &amp; Fritz</td>
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<tr>
<td>Induction therapy</td>
<td></td>
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<tr>
<td>Response rate</td>
<td>Increased by 6.6%</td>
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<tr>
<td>Response period</td>
<td>Prolonged by 4.8 months</td>
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<tr>
<td>Survival period</td>
<td>Prolonged by 3.1 months</td>
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<tr>
<td>Maintenance therapy</td>
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<tr>
<td>Response period</td>
<td>Prolonged by 4.4 months</td>
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<td>Survival period</td>
<td>Prolonged by 7.0 months</td>
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effects was serious. The type and frequency of adverse effects are similar in other reports. Since IFN-α dose-dependency causes adverse effects, some patients refused to receive it at a dose of $3 \times 10^6$ units or higher: the second course of IFN-α had to be discontinued in a small number of patients.

**IFN-α Therapy for Other Hematopoietic Diseases**

IFN-α has been used to treat not only multiple myeloma, but also low-grade malignant lymphoma such as follicular lymphoma, hairy cell leukemia, and chronic lymphocytic leukemia. IFN-α has also been reported for the treatment of pre-leukemic myelodysplastic syndrome. However, IFN-α has not been so frequently used as for myeloma, and the efficacy for those diseases has not been established. The use of IFN-α for only hairy cell leukemia is covered by Japanese medical insurance. IFN-α is not considered as the first line therapy for these hematological diseases in most medical institutions. It is not highly rated even in the few institutions where it does come into consideration as the first line therapy. However, it is possible that IFN-α will play a significant role in combination with other drugs.

**Conclusions**

The efficacy of therapeutic regimens for multiple myeloma has been systematically evaluated since the MP regimen (melphalan and prednisolone) was clinically applied. Since then, many multi-drug chemotherapy regimens have been attempted, but none has become standard for the disease. Chemotherapy regimens including IFN-α have been unsatisfactory as well. At the present, IFN-α is evaluated as a therapeutic drug for multiple myeloma as follows: (1) IFN-α is not useful when used alone; (2) many investigators think that it should be used for maintenance therapy rather than induction therapy; and (3) it is effective in induction therapy only when it is combined with multi-drug chemotherapy regimens, and is more effective when its administration is delayed. Although the meta-analyses indicate that IFN-α is an important and useful drug in the treatment of multiple myeloma, evaluations of its usefulness will be modified.

Stem cell transplantation conditioned with non-myeloablative regimen has been rapidly progressing in various fields. This kind of transplantation targets patients for whom the conventional transplants have not been indicated due to the higher age and the complications affecting performance status, and the majority of patients with multiple myeloma could be included in the target for this mini-transplantation. It is expected to become a promising therapy for relatively elderly patients of 50 or older. IFN-α may play a role in the new therapeutic modality.

**REFERENCES**


5) Kitani, T.: New combination chemotherapies including IFN. *Clinical Hematology* 1993; 34:


