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EFFECT OF αIFN ON UNAGGRESSIVE IMMUNOPROLIFERATIVE DISORDERS

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ABSTRACT

Background. **α-IFN is reported to be an effective treatment for a number of lymphoproliferative diseases. Little information is available at present on its effect in unaggressive immunoproliferative disorders.**

Study design and results. **In a prospective non randomized study, 57 patients with IgG or IgA MGUS, smouldering myeloma or stage I MM treated with α-IFN (3 MU 3 times a week for at least 6 months) were compared to 129 untreated similar patients. Four patients in the IFN group showed a monoclonal component reduction >50% versus none in the control group, and 25% of patients suffered disease progression (MC increase > 50% and/or osteolytic lesions) in the IFN group as compared to 18% in the control group.**

Conclusions. **α-IFN administration at the dose used is ineffective for the majority of patients with slowly proliferating immunoproliferative disorders; only a small subgroup of them may benefit from such a treatment.**

Key words: monoclonal gammapathy, stage I multiple myeloma, indolent myeloma, interferon

Monoclonal gammapathies of undetermined significance (MGUS) are a group of slowly growing immunoproliferative disorders characterized by the presence of a serum monoclonal component (MC) that appears stable over time, bone marrow plasmacytosis <10%, and the absence of osteolytic lesions and excess urinary light chain excretion.

Closely related disorders include smouldering or indolent myeloma and non progressing first stage multiple myeloma (MM), in which the MC is higher, bone marrow plasmacytosis is >10%, some osteolysis can be detected and chemotherapy is not indicated.

The boundaries between MGUS and these disorders are often arbitrary and there is some overlap. A significant number of patients are at risk of developing a more malignant disease; in a recent review by Kyle[1] the actuarial rate of malignant transformation was 33% at 20 years. Thus, there is no doubt that we would like to get rid of a MC if we had an effective non toxic treatment. Unfortunately, at present the only possible treatment is based on toxic drugs that may cause side effects which are unwanted in unaggressive diseases; this is the main reason for not treating these patients.

α-interferon (α-IFN) at low doses is an excellent treatment for some lymphoproliferative diseases (e.g. HCL),[2] while its activity in low grade lymphomas and in multiple myeloma is still debated.[3,4] We found no information in the literature on its effect in MGUS and related disorders.

Patients and study design

A multicentric prospective, non randomized study was performed between 1988 and 1992. All patients with a marked MC (i.e. >20 g/L for IgG and >10 g/L for IgA) fulfilling the standard criteria for a diagnosis of MGUS, smouldering or

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indolent myeloma, or non evolutive first stage MM were registered in the study. Then, in some centers patients received IFN treatment while in others they were only followed up. Treatment consisted of IFNα2b 3 MU three times a week from entry into the study until disease progression. Only patients with a minimum of 6 months treatment were evaluated for response. This evaluation was essentially based on MC modifications. We defined as responders all patients showing at least a 50% decrease in MC at any time during treatment; non responders were those with either stable or progressing MC, or with any other sign of disease progression (e.g. appearance of osteolysis, increased bone marrow plasmacytosis). MC assessment was based on measurement of the monoclonal peak at serum electrophoresis. Informed consent was obtained from all patients in the treatment group. IFNα2b (Intron A, Schering Plough) was supplied by the company.

Table 1. Institutions and investigators involved in the study.

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Table 2. Evaluable patients stratified by disease and treatment.

Disease	*n*	*IFN*	*NT*
MGUS	68	7	61
Indolent myeloma	60	19	41
Stage I myeloma	36	19	17

NT: not treated.

Results

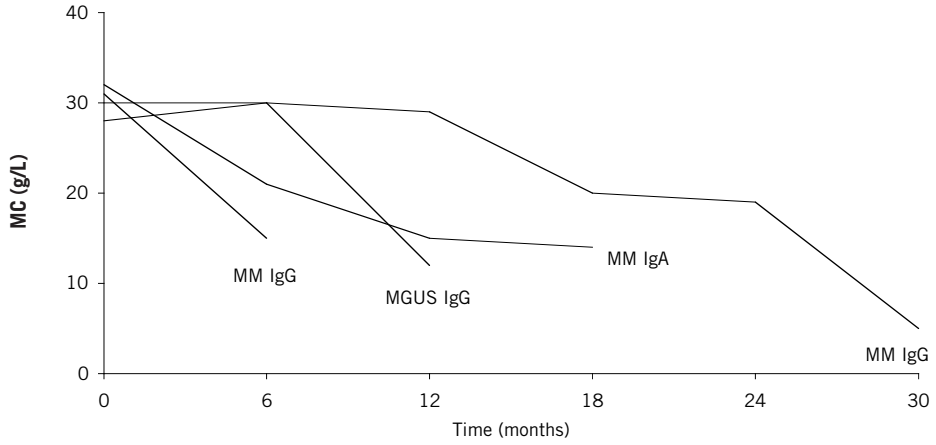
Two hundred and four patients were registered at 14 centers located in Southern and Central Italy (Table 1); 67 were treated with IFN and 137 served as controls. In all, 164 patients had a minimum follow-up of six months (45 in the treatment group and 119 in the control group) and were considered evaluable. Reasons for early drop out were loss to follow up (n=27), treatment intolerance (n=3), exitus for unrelated causes (n=6), progressive disease (n=4). Using standard criteria (5), the evaluable patients could be classified as in Table 2. Pertinent data at registration were similar in both the treatment and the observation group (Table 3).

A MC reduction ≥ 50% was observed in 4 patients in the treatment group and in none from the control group. MC variations in responders are shown in Figure 1. One hundred and forty-three patients had a stable MC, 37 in the treatment and 106 in the control group; 17 showed a MC increase >50%, 4 treated and 13 controls. Disease progression, defined as a MC increase > 50% and/or the appearance of any

Table 3. Parameters at registration, stratified by Ig type and treatment.

Parameter	*IgG*		*IgA*	
	IFN	*NT*	*IFN*	*NT*
Hb (g/dL)	13.0±1.4	13.0±2.0	12.8±1.3	13.6±1.3
WBC×10^9/L	5.7±2.4	6.4±1.7	7.3±2.5	5.5±1.4
PLT×10^9/L	235.0±82.6	230.4±73.3	245.8±152	215.2±74.2
Plasmacytosis (%)	23.6±14.7	14.1±10	13.4±6.1	15.8±9.9
MC (g/L)	27±8	22±7	18±8	18±8

Numbers are x±SD; NT=not treated.



Time 0: start of IFN treatment; MM: stage I multiple myeloma.

Figure 1. Monoclonal component modifications in the 4 patients who responded to IFN.

sign (e.g. osteolytic lesions, increase of bone marrow plasmacytosis) demonstrating disease transformation from MGUS to stage I MM or from stage I to stage II MM, was observed in 11 patients in the treatment group and 22 in the control group.

Thirteen patients died during the study; 3 in the treatment group and 5 in the control group died in disease progression, while the others died of causes not related to the immunoproliferative disease.

OS at 30 months was high in both groups, as expected for chronic unaggressive disorders. The overall probability of progression at 30 months was higher in the treatment group (Figure 2), but the difference was not statistically significant. The median follow-up time was 24 months for treated patients and 36 months for controls.

Tolerance

α-IFN side effects and toxicity were accurately monitored during treatment. Intolerable flu-like symptoms caused early treatment interruption in 3 patients. Of the 45 evaluable patients, 4 left the study after 6-18 months because of poor compliance to prolonged treatment. Liver, renal and hematological parameters, monitored throughout the study, did not show any sign of IFN toxicity. No CNS toxicity was reported. The results of the study are summarized in Table 4.

Discussion

This study shows that the majority of patients with IgG or IgA MGUS, indolent myeloma or non evolutive first stage MM do not benefit from IFN treatment at the dose used, although a few patients may show a significant MC decrease. Similar results were reported by our group in a cohort of patients with IgM-MGUS as part of a larger study on IFN in Waldenström's macroglobulinemia (WM).[6]

How do these results compare with the effect of IFN in other lymphoproliferative disorders? IFN is highly effective in HCL, with excellent responses as high as 80%,[2] while the number of good responders is much lower in low grade lymphomas and in MM (about 20%); it is in the range of 50% in WM.[6] Possible explanations for the small number of responding patients in the present study include:

a. MGUS and other related slowly proliferating clonal immunological disorders are biologically different from diseases in which IFN has been proven to be effective in a larger proportion of patients;
b. the number of patients with IgG or IgA clonal disorders (including myeloma) who respond to IFN treatment in any case is small and does not depend on tumor burden or cell kinetic characteristics. This hypothesis might also explain the variable results obtained in

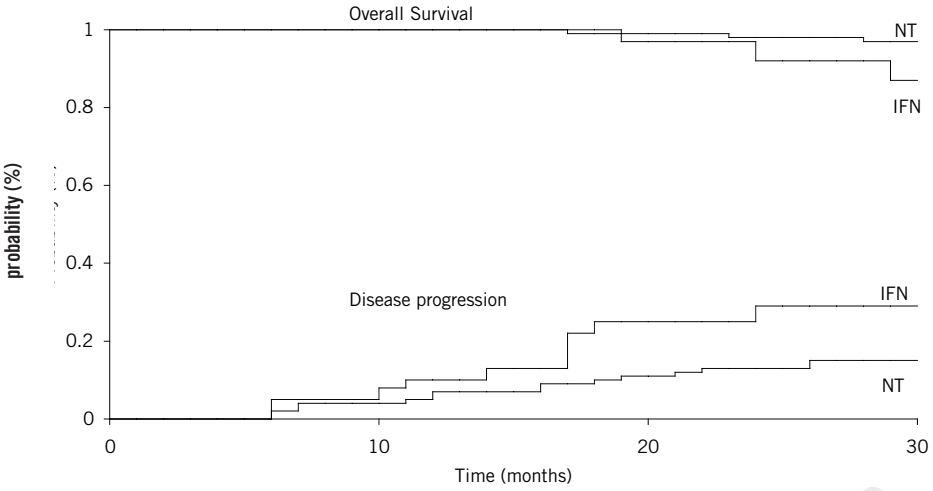


Figure 2. Overall survival and probability of disease progression for control (NT) and IFN-treated patients.

trials investigating the role of IFN in maintaining post-chemotherapy remission in multiple myeloma.[7-11]

This study was designed essentially to see if IFN treatment could produce a MC decrease in the disorders investigated; a broader and longer study would be required to document a possible effect of IFN in avoiding or delaying progression towards a more aggressive disease. However, considering that our preliminary data do not show any advantage for IFN-treated patients in avoiding disease progression, such a study does not seem worthwhile.

In any case, the possibility of obtaining a reduction in or the disappearance of a MC by IFN treatment, even in a few patients, is intriguing from a biological point of view. It is still unclear whether IFN acts directly on the proliferating clone or if its effect is mediated by other cell populations. It is also not known why only a small proportion of patient do respond; it would be clinically advantageous to be able to predict which patients will respond in order to treat only those few who would benefit from it.

Table 4. Results of the study.

		IFN		*NT*	
Enrolled		67		137	
Evaluable		45		119	
	IgG		35		103
	IgA		10		16
MC:	decrease	4	(9%)		
	stable	37	(82%)	106	(89%)
	progression	4	(9%)	13	(11%)
Disease progression		11	(24.4%)	22	(18.5%)
Exitus		5		8	
OS at 30 months		87%		97%	
PFS at 30 months		29%		15%	

NT: not treated; OS: probability of overall survival; PFS: probability of progression free survival.

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