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Adjuvant treatment of malignant melanoma with interferon after radical surgery – part II. Effect of recombinant alpha interferon

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In our randomized prospective study, patients with malignant melanoma were treated with both human leukocyte interferon alpha (HuIFN) and recombinant interferon alpha 2b (Intron) after surgical removal of primary tumor (Clark level of invasion IV, V and/or thickness exceeding 1.5 mm). They were randomized into two arms: (1) those treated with HuIFN• or with Intron; and (2) a control group with no immediate treatment. Interferon was applied through 30 weeks. Cumulative dose for HuIFN was 6×10^7 U (2×10^6 U weekly), and for Intron 9×10^7 U (3×10^6 U weekly). Both arms of the study included altogether 421 patients: 161 in the control group, 160 in the HuIFN group, and 100 patients in Intron group. The results of 5-year analysis showed significant differences in the disease-free interval as well as in survival between both arms in favour of interferon (both HuIFN and Intron) treated patients ($p < 0.005$). According to stratification by sex, the difference was significant also between female as well as male patients, of both groups ($p < 0.005$). In a majority of patients interferon application caused a flu-like syndrome, whereas adverse effects on blood count and chemistry could not be established. The treatment (given in the reported dose) was not toxic and was applied on an out-patients basis.

Key words: melanoma-drug therapy; interferon-alpha; interferon alfa, recombinant

Introduction

In the world, patients with malignant melanoma of the skin represent approximately 1 % of all cancer patients. The incidence of melanoma has been rapidly increasing, doubling its value every 6–10 years, and likewise, also melanoma-related mortality has been exhibiting a trend of constant increase.[1, 2]

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Considering the high mortality rates observed in patients with malignant melanoma (with deep level of invasion) as well as ineffective treatment of advanced disease, many studies have been investigating the potential of various treatment modalities.

Since the results of malignant melanoma treatment are still unsatisfactory, especially in advanced stages of disease, an effort should be directed to earlier treatment. Unfortunately, the results of adjuvant treatment in the early stage of the disease with chemotherapy[3] have also not confirmed the effectiveness of treatment so far.

During the last decade a number of clinical studies have been performed to investigate the therapeutic potential of interferons in the treatment of various malignant diseases.[4] Although partial and occasional complete regressions have been observed in some cancer patients,[5] the overall results of single-agent interferon treatment point out the need for further clinical and laboratory research in order to establish the role of interferon in cancer treatment, particularly in solid tumors.

In view of the previously mentioned facts, we decided to established the role of interferon as an adjunct to surgical treatment of primary malignant melanoma. A prospective randomized trial[6] was commenced in 1988 in patients with malignant melanoma stage IIA and B according to the AJCC classification.[7]

In our randomized prospective study, patients with malignant melanoma were treated with human leukocyte interferon alpha (HuIFN) after surgical removal of primary tumor (Clark level of invasion IV, V and/or thickness exceeding 1.5 mm). They were randomized into two groups: (1) those treated with HuIFN and (2) a control group with no immediate treatment. HuIFN was applied through 30 weeks in cummulative dose 6×10^7 U, and 2×10^6 U weekly. Both arms of the study included altogether 321 patients.[8]

The results of general analysis showed significant differences in the disease-free interval as well as in survival between both groups in favour of HuIFN treated patients ($p < 0.005$).

Later in the study, a group of patients treated with recombinant alpha interferon was added. In this report the analysis and comparison of various treatment modalities is presented.

Patients and methods

In the protocol only patients with histologically proven primary tumor after radical surgery were included. As mentioned previously, all the patients were in Stage IIA and IIB of the disease which means that the primary tumors were classified as Clark IV, V level of invasion and/or tumor thickness exceeding 1.5 mm. The patients were randomized into two protocol arms – those treated with HuIFN or Intron and control group with no immediate treatment after radical surgery (Controls).

All patients in both arms were on regular clinical follow-up. Complete bloods counts, blood chemistry, renal and liver functin tests were taken each check; these were performed monthly in the first 2 years, and later on in 2 month intervals. Complete evaluation of patients was done before and after therapy. Patients with relapse (in both groups) were further treated as necessary (with surgery, radiotherapy, chemotherapy) and were afterward also on regular follow-up.

Treatment – Treatment in the first group of patients consisted of i/m paplication of crude human leukocyte interferon (Imunološki zavod, Zagreb, Croatia) and started within the first month after surgical excision. Interferon was applied for 30 weeks in cumulative dose of 6×10^7 units. Each patient received 2×10^6 units of interferon weekly.

Similar regimen was applied in the second group of the treatment arm. In this group the treatment consisted of i/m application of Intron; the drug was applied for 30 weeks in cumulative dose of 9×10^7 units and each patient received 3×10^6 units of intron weekly.

HuIFN group – A total of 160 patients, 70 males and 90 females, have been entered into the HuIFN group. The mean age of patients was 48 years (48 ± 14 years, range 20–78 years). The patients were distributed according to the primary tumor site as follows: head and neck region (HN) – 15; trunk (T) – 79; limbs (L) – 66. Primary tumors were determined as superficialy spreading type (SSM) in 31 cases, nodular type (NM) in 127 cases and *lentigo maligna* type (LMM) in two cases. The level of invasion was Clark IV in 109 cases, and Clark V in 12 cases. In 39 cases the level of invasion was Clark III, but tumor thickness exceeded 1.5 mm, which was in accordance with the protocol criteria.

Intron group – A total of 100 patients were included in this group, 45 males and 55 females. Mean age of patients was 48 years (48 ± 14 years, range 20–73 years). The patients were distributed according to the primary site as follows: HN – 6; T – 54; L – 40. Primary tumors were determined as SSM type in 19 cases, NM in 79 cases and LMM in two cases. The level of invasion was Clark IV in 66 cases and Clark V in 5 cases. In 29 cases the level of invasion was Clark III, but tumor thickness exceeded 1.5 mm.

Control arm – The control arm comprised 161 randomly selected patients (71 males and 90 females) in the mean age of 52 years (52 ± 13 years, range 21–84 years). As to the primary tumor site, lesions were located in head and neck region in 16 cases, on the limbs in 70 and on the trunk in 75 cases. In 92 patients tumors were assessed as SSM type, in 3 patients as LMM and in 66 patients as NM type. The level of invasion was Clark III in 23 cases (but thickness more than 1.5 mm), Clark IV in 101 cases, and Clark V in 12 cases.

Patient distribution by various potential prognostic factors is presented in Table 1. Our analysis showed that all protocol groups, i. e. HuIFN, Intron and Controls, were similar as to their sex and age distribution. Also, there was no major difference in the site and type of primary tumor, and neither in its level of invasion.

Table 1. Comparison of HuIFN, Intron and Control groups according to the sex and age distribution, type and site of primary tumor and the level of invasion.

		HuIFN		Intron		Controls	
		No.	%	No.	%	No.	%
Sex	M	70	44	45	45	71	44
	F	90	56	55	55	90	56
Age	< 53	100	63	64	64	81	50
	> 53	60	37	36	36	80	50
Type	NM	127	79	79	79	66	41
	SSM	31	20	19	19	92	57
	LM	2	1	2	2	3	2
Local.	Trunk	79	49	54	54	75	47
	HNeck	15	9	6	6	16	10
	Limbs	68	41	40	40	70	43
Clark	III	39	24	29	29	38	23
	IV	109	68	66	66	101	62
	V	12	8	5	5	12	7
Total		160	100	100	100	161	100

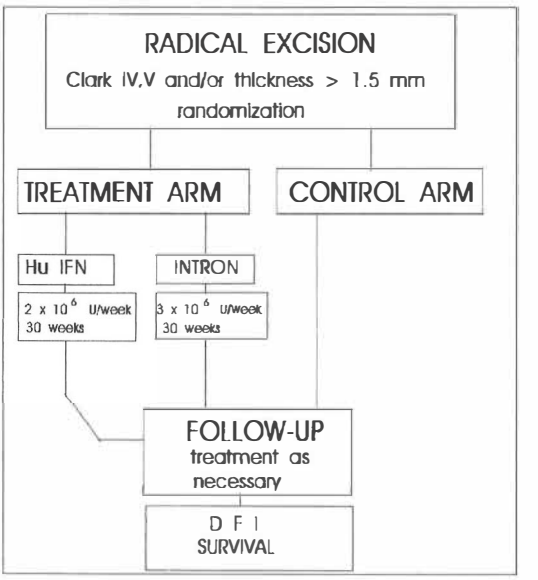

Figure 1. Protocol summary.

Statistical analysis – The statistical analysis was done using the Kaplan-Meier product-limit method[9, 10] which is a non-parametrical method to estimate the probability of an event occuring during a given time-interval. Statistical significance of graphed survival curves was tested using logrank program which performs a chi-square-like analysis.[11, 12, 13]

Results

Survival analysis

The analysis of survival in both protocol arms is presented in Fig. 2. The difference between both treated groups and the controls is significant (Intron curve vs. Controls curve and HuIFN curve vs. Controls curve, $p < 0.01$). There was no difference between both treatment groups, i. e. Intron and HuIFN.

Since the localization of primary tumor could influence the survival, the patients were analyzed by grouping according to the primary site.

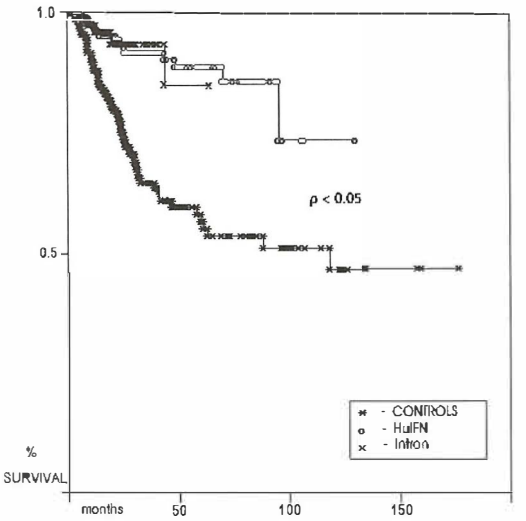

Figure 2. The comparison of survival between patients in control group, patients treated with human leukocyte interferon alpha and patients treated with recombinant interferon alpha 2b.
(Controls – control group, HuIFN – patients treated with human leukocyte interferon alpha, Intron – patients treated with recombinant interferon alpha 2b; the difference between HuIFN and controls as well as between Intron group and controls is significant, $p < 0.05$).

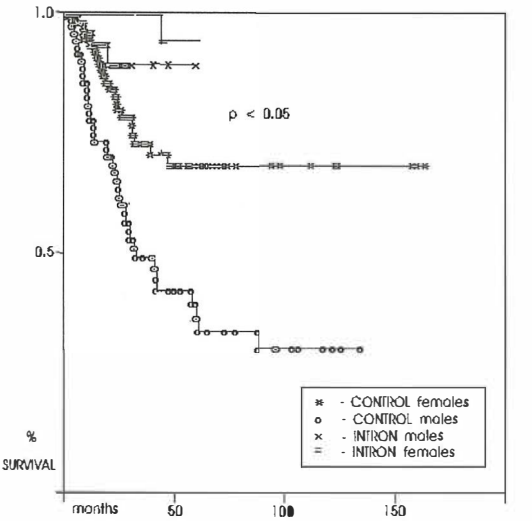

Figure 3. The comparison of survivals between Intron group and controls by sex stratification.
(Control females – female controls, CONTROL males – male controls, Intron females – female patients treated with recombinant interferon alpha 2b, Intron males – male patients treated with recombinant interferon alpha 2b).

No difference could be established between patients with primary tumor in head and neck region, limbs, or trunk.

The possible influence of age on survival was analyzed. Between the groups of patients treated with Intron age more and less then 53 years no diference could be noted.

Analysis of survival according to stratification by tumor type was performed, and there was no difference in survival between patients with nodular, lentiginous or superficial spreading type.

The difference between patients treated with intron and control patients was significant also by sex stratification (Fig. 3). Females in the treated group had better survival than female controls; likewise, male patients treated with intron survived longer than male patients in the control group (Intron females curve vs. Control females curve, and Intron males curve vs. Control males curve; $p \leqq 0.05$).

Interferon treatment was well tolerated by the majority of patients and no patient refused it because of toxic side effects. In all patients the application of interferon was followed by mild up to moderate fever (less than 39° C) which was transient. The patients also experienced flulike syndrom, which was anticipated. The application of interferon in the stated dosage exerted no effect on blood count and chemistry. In one case, as reported previously,[14] a moderate allergic reaction manifested with urticaria followed the second course of treatment in the HuIFN group. Since the fever and flu-like syndroma were transient, after pilot study it was decided that the regimen should be applied on an out-patients basis.

Discussion

The increasing incidence of melanoma and its tendency to affect younger adults, as well as relative ineffectiveness of treatment in advanced stages, point out the need for an effective adjuvant therapy.

In our study, both treatment regimens (i. e. HuIFN and Intron) resulted in prolongation of the survival of patients, since the difference between both protocol groups when compared with the controls (HuIFN vs. Controls as well as Intron vs. Controls) was significant. In addition, the difference between male as well as female patients of both groups was also significant. According to these results, it can be postulated that the interferon (both HuIFN and recombinant alpha interferon) treatment prolonged the survival of patients in treated groups.

Also, the treatment was not associated with significant toxic side effects.

Possible mechanisms of interferon action have not been fully explained yet. Theoretically, interferons could exert their antitumor effects in three ways: (1) via the host immune system; (2) by altering some non-immune host/tumor cell interactions; or (3) by direct effects on the tumor cells. Data from laboratory animal experiments suggest that interferon act best when tumor load is low, such as was the situation in our study.[6, 8] Interferons are also an important part of lymphokine cascade. It is reasonable to conclude, that interferon could act as a biological response modifier through many yet uknown mechanisms including lymphokine cascade.

According to our results, the adjuvant interferon (both HuIFN and Intron) treatment can be advised in cases with prognostically unfavourable melanoma, i. e. primary melanoma tumors with Clark IV, V level of invasion and/or a thickness more than 1.5 mm.

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