Rad Hrvatske akad znan umj med [469] XXVIII (1996), 7–20

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MELANOMAS. INTERFERON THERAPY

Immunotherapy has been used for the treatment of human cancers since Coley's report in 1893[1]. A number of immuno-stimulants have been applied in cancer treatment[2,3]. Interferon (IFN) is the first human cytokine to be widely studied

Our first results with peritumoral and intratumoral application of human natural leukocytic interferon (HNLI) in melanoma patients were published in 1981[4], and the last in 1989[5].

Markovic et al [6] evaluated the effect of HNLI after surgical procedure in 11 patients with skin melanoma and malignant neoplasm of the breast for the values of C_{19} - steroids and particularly of dehydroepiandrosterone The application of HNLI in a dose of $2x10^5$ IU resulted in normalization of C_{19} - steroid metabolism

The experience of Knežević et al.[7] suggests that HNLI increases the invasiveness and lytic activity of macrophages. The activated macrophages are significantly larger. Another characteristic of HNLI application is the proliferation of lymphoid tissue. HNLI stimulates the infiltration of tumor stroma with the masses of lymphocytes and macrophages, they pass into the streaks of tumor cells and destroy them A comparison of the changes in parenchyma and tumor stroma before and after HNLI therapy has shown that it takes 2-4 weeks to make the defence stronger A significant role of HNLI is the activation of regional lymph nodes even if it has not been applied directly to them It seems that HNLI strongly increases the active defence of lymph nodes against the metastasis. In many nodes, a hyaline mass surrounding damaged cell debris, and necrotic tumor cells were found They observed it in head and neck tumors, gynecologic carcinoma and breast cancer. In all these cases, HNLI was applied locally, peritumorally and intratumorally, and not to regional lymph nodes.

A literature survey demonstrated a low but significant response rate in patients with disseminated menalomas after systematic use of r IFN alpha. In a clinical trial Robinson et al.[16] achieved complete remission in four out of 40 patients (10%) with cutaneous primaries, whereas six (15%) melanoma patients had partial remissions, with an overall response rate of 25%. In two patients, complete remission persisted 15 and 32

months from the onset of treatment, respectively. Interferon was given in a dose of 10 million IU/M2 subcutaneously three times *per* week for one year Response rates of 10 and 20 % have been reported by most investigators using different interferons and different dosing schedules[17-25]. A small proportion of patients with disseminated malignant melanomas may achieve a complete response and some of these may have a prolonged remission (5 out of 50 patients)[26-27]. Von Wussow et al. [28] studied the effect of intralesional injection of HNLI and r.IFN alpha 2b in 51 patients. There was complete or partial regression of injected nodules and 21% of objective systematic responses (i e regression of noninjected metastasis outside the lymphatic drainage region of the injected tumor).

The aformentioned studies and results have justified further research of IFN in the treatment of melanoma

PATIENTS AND METHODS

PATIENTS

Twenty-seven patients (14 before and 13 after surgery) were treated with r.IFN alpha 2c Four patients were treated with HNLI. Six patients were male and 21 female, aged 28-78 years The size of the melanomas at the longer diameter were from 5 to 56 mm, and at the shorter diameter from 5 to 50 mm The sites of the tumor were leg 14, back 7, arm 3, sub-and retromandibular 2, face 2, axilla 1, anocutaneous border 1 and hard palate 1 Clinical stage I (melanoma confined to the skin) was recorded in 22 patients, clinical stage II (regional lymph node involvement) in two patients and clinical stage III (disseminated disease) in three patients Clinical stage I group consisted of T_1 (melanoma confined to the epidermis, radial, superficial growth phase) in one patient, T_2 (vertical growth phase, nodular melanoma) in 17 patients and T_3 (satellite appearance) in four patients

INTERFERON

Recombinant HuIFN alpha 2c was applied locally peri- and intratumorally. The duration of treatment was from one day through four weeks In two patients, r.IFN alpha 2c was administered intralymphatically The number of injections was 1-40 Interferon was not administered on Saturdays and Sundays A single dose was 6 mcg (corresponding to 1.36×10^6 IU standard Gxa01-901-535), and the total dose was 120 mcg in two cases after and in five cases before surgery A single dose was 150 mcg (corresponding to 3.4×10^6 IU standard Gxa 01-901-535), and the total dose was 300 mcg in nine cases before surgery and in seven cases after surgery. After surgery, one patient (No 15, Table 3) received 60 mcg in 10 injections, and one (No 17, Table 3) 45 mcg in seven injections One patient (No 16, Table 3) received 75 mcg and 30 mcg additionally in two intralymphatic applications, and one (No 25, Table 3) received 15 mcg intralymphatically

HNLI was applied locally. One patient received 25 injections and a total dose of $1.2x10^6$, one patient 18 injections and a total dose of $0.5x10^6$. One patient received a daily dose of $2x10^6$ for 60 days, and one - the same daily dose for 60 days in addition to the same dose intramuscularly every other day

CLINICAL EVALUATION OF THE RESULTS

Clinical results were evaluated on the basis of the tumor size before and after interferon therapy.

PATHOHISTOLOGIC EVALUATION

The pathohistologic confirmation of the clinical diagnosis was done on the bioptic material Excised tumor represented the biotoptic material

IMMUNOHISTOLOGIC EVALUATION

The immunohistologic evalution of the results primarily took into consideration lymphoid cells and macrophages in stroma

0 = no response, nonreactive stroma

+ = poor response, scattered lymphoid cells

++ = moderate response, numerous lymphoid cells, narrow infiltration areas, few macrophages

+++ = good response, massive infiltration of lymphoid cells, numerous macrophages

++++ = very good response, massive infiltration and formation of lymphoid nodules in stroma, numerous macrophages

RESULTS

Generally speaking, according to the clinical evaluation, the tumor size was reduced by more than 50% in four patients, by more than 25% in eight patients and by less than 25% in two patients after interferon treatment Before surgery, the appearance of the tumor was changed, the surface peeled off and the edges were becoming clearly bordered in all patients.

Data on seven living out of the fourteen patients treated with interferon before surgery, are presented in Table 1 Three patients (Nos 3,4), Clark level II-III, Breslow

level 1 0 to >2 0 mm, clinical stage I, T_1 - $2N_0M_0$ classification, are still alive five or more years after the treatment Patient No. 1, with a melanoma sized 50-55 mm and satellites on the planta of the right foot, Clark level V, Breslow level >2.5 mm, clinical stage II, $T_3N_1M_0$ classification, refused amputation of the right leg above the knee and accepted the interferon treatment. After the treatmant, the tumor was so strongly delineated from the healthy tissue that the surgeon pecled the tumor off from the planta of the right foot The amputation of the right leg above knee was thus avoided due to the interferon treatment. Three out of seven patients (Nos 5,6,7) Clark level III-IV, Breslow level >2 5mm, clinical stage I, $T_2N_0M_0$ classification, are still alive four years after the treatment

Table 1

Before surgery

Living melanoma patients

PATIENT No	AGE	SEX	TUMOR SITE	CLARK	BRESLOW (mm)	CLINICAL STAGE	SURVIVAL (years)	IMMUNOLOGIC GRADE	DURATION OF TREATMENT (WEEKS)	r IFN alpha 2c TOTAL AMOUNT IN MGC	REMARKS
1	1907	M	Planta right leg	V	>2 5 IV	II T3N1M0	6	III	4	120	After 6 years of follow-up no contact with the patient due to the war
2	1942	I	Right lower arm	II	2 0 III	I T2N0M0	6	III	4	300	
3	1941	I	Left lower leg	III	2 0 III	I T2N0M0	6	I	4	300	
4	1931	I	Right lower leg	II	1 0 II	I T1N0M0	6	III	4	300	
5	1946	M	Left Upper arm	III	>2 5 IV	I T2N0M0	4	III	4	300	
6	1922	M	Back	III	>2 5 IV	I T3N1M0	4	I	4	300	
7	1928	M	Back	IV	>2 5 IV	I T2N1M0	4	III	4	300	

Data on seven deaths in fourteen patients, Clark level III-V, Breslow level 2.0 to > 2.5 mm, who were treated with interferon before surgery, are given in Table 2 Three clinical stage III, classification $T_3N_1M_1$ patients (Nos. 8,11,14), two clinical stage I, classification $T_3N_0M_0$ patients (Nos. 9,13) and two $T_2N_0M_0$ classification patients (Nos. 10, 12) lived for 1 - 3 years after the treatment.

Table 2

Before surgery

Deaths in melanoma patients

PATIENT No	AGE	SEX	TUMOR SITE	CLARK	BRESLOW (mm)	CLINICAL STAGE	SURVIVAL (years)	IMMUNOLOGIC GRADE	DURATION OF TREATMENT (WEEKS)	r IFN alpha 2c TOTAL AMOUNT IN MGC	REMARKS
8	1912	I	Right submandibular	IV	>2 5 IV	III T3N1M1	2	I	4	120	
9	1948	F	Right lower leg	III	>2 5 III	I T3N0M0	3	I	4	120	
10	1944	I	Left lower leg	IV	>2 5 II	I T2N0M0	3	III	4	300	
11	1927	I	Right retromandibular	III	>2 5 IV	III T3N1M1	2	I	4	120	
12	1939	I	Back	IV	>2 5 III	I T2N0M0	2	II	4	300	Bleeding
13	1922	I	Right lower leg	III-IV	2 0 II	I T3N0M0	2	III	4	300	
14	1944	I	Right upper leg	V	>2 5 IV	III T3N1M1	1	I	4	120	

Data on seven living out of the thirteen patients treated with interferon after surgery are given in Table 3 Thirteen melanoma cases were treated with interferon after surgery. Seven of them are still alive. six patients Clark level III-IV, Breslow level 2.0 mm to >2 5 mm, clinical stage classification T_2-$3N_0M_0$, and one patient clinical stage II classification $T_3N_1M_0$. Three patients (Nos 15,16,17) have survived for 6-7 years, and four cases (Nos. 18,19,20,21) for 3-4 years up to the present Patient No 16, Clark level IV, Breslow level >2 5 mm, clinical stage II, $T_3N_1M_0$ classification is still alive six years after the surgery. In addition to $24x10^6$ units locally, the patient also received $10x10^6$ units intralymphatically into the leg.

Data on six deaths in thirteen patients treated with interferon after surgery are given in Table 4 Those patients, Clark level III-V, Breslow level >2 5 mm, clinical stage I, clinical grade T_2-$3N_0M_0$, lived for 2-5 years after the treatment. In two cases, Nos. 22 and 25, the tumor was not completely removed Case No. 25 with a melanoma not completely removed on anocutaneous border received only one intralymphatic injection of $5x10^6$ units and lived for three years after the surgery.

Table 3

After surgery

Living melanoma patients

PATIENT No	AGE	SEX	TUMOR SITE	CLARK	BRESLOW (mm)	CLINICAL STAGE	SURVIVAL (years)	IMMUNOLOGIC GRADE	DURATION OF TREATMENT (WEEKS)	rIFN alpha 2c TOTAL AMOUNT IN MIOC	REMARKS
15	1951	F	Left axilla	III	>2.5 III	I T2N0M0	7	++++	2	60	
16	1956	M	Left upper leg	IV	>2.5 IV	II T3N1M0	6	+++	2	105	Intralymphatic
17	1938	F	Back	III	>2.5 III	I T2N0M0	6	++++	2	45	
18	1922	F	Right lower leg	V	>2.5 IV	I T2N0M0	4	+++	4	300	
19	1916	F	Right lower leg	IV	>2.5 III	I T3N0M0	4	+	4	300	
20	1930	F	Face	IV	>2.5 IV	I T2N0M0	3	+++	4	300	
21	1938	F	Back	III	2.0 III	I T2N0M0	3	++	4	300	

Four patients were treated with human natural leukocytic interferon (HNLI). In one melanoma patient, a fifteen-year-old girl with a lesion on the nose, whose diagnosis was confirmed by incision biopsy, complete remission was achieved after four weeks of treatment, including eighteen injections and a total of $500x10^5$ units. The girl is still alive 10 years after the treatment. In a patient aged 75 with a lesion on the hard palate and a poor prognosis, complete remission was achieved locally after four weeks of treatment with 25 injections and a total of $1.2x10^6$ units, but there were no effects on the lung and neck metastases. The patient died one year after the HNLI treatment. In two patients (aged 63 and 70) with recurrent melanomas within the surgical scar, in one in the form of satellites and in the other a tumor within the scar, both with a poor prognosis, the tumors were treated with a daily dose of $2x10^6$ HNLI for sixty days. Recurrent melanoma regressed completely. In the patient with satellite metastases, 75% of the nodules disappeared completely and the remaining were reduced in size. In both patients, both the original surgical specimens and recurrences were confirmed by microscopic examination. Both patients died within 2 years after the treatment.

Table 4

After surgery

Deaths in melanoma patients

PATIENT No	AGE	SEX	TUMOR SITE	CLARK	BRESLOW (mm)	CLINICAL STAGE	SURVIVAL (years)	IMMUNOLOGIC GRADE	DURATION OF TREATMENT (WEEKS)	r IFN alpha 2c TOTAL AMOUNT IN MGC	REMARKS
22	1951	F	Right upper leg	V	>2.5 IV	I T2N0M0	2	III	4	120	Tumor was not completly removed
23	1931	M	Neck	IV	>2.5 IV	I T2N0M0	2	III	4	120	
24	1953	F	Back	V	>2.5 IV	I T2N0M0	2	II	4	300	
25	1938	F	Anocutaneous border	IV	>2.5 IV	I T2N0M0	3	IIII	1 day	15	Intralymphatic Tumor was not completely removed
26	1928	F	Right upper leg	IV	>2.5 IV	I T2N0M0	3	II	4	300	
27	1959	F	Left lower leg	III	>2.5 III	I T2N0M0	5	III	4	300	

DISCUSSION

A variety of clinical staging classifications have been recommended for a melanoma. Perhaps the most simple and commonly used is clinical stage I melanoma confined to the skin (T_1 superficially spreading melanoma, radial melanoma, T_2 nodular melanoma, T_3 nodular melanoma with satellites), clinical stage II when there is regional lymph node involvement (N1), and clinical stage III when there is dissemination of the disease (M1).

The likely outcome in an individual is determined by the depth to which the tumor has spread into the skin, the site of the tumor, the sex and age of the person, and many of other variables.

In general, patients with lesions on the head and neck, trunk, hands and feet have a poorer prognosis than those with lesions on the arms and legs The clinical presence of ulceration and bleeding in melanoma is a sign of poor prognosis The presence of microscopic satellites also means a poor prognosis, as well as metastases to regional lymph nodes, but such patients still live longer than those with metastases beyond the regional lymph nodes Older age has been shown to be an unfavorable prognostic factor. Overall, women tend to have a better long-term prognosis than men, as well as patients under 50 years of age as compared to older age groups

While melanoma is confined to the epidermis, it is known as *in situ*, level I or intraepidermal melanoma which is noninvasive, has no ability to metastasize and if removed at this stage, a cure will result in almost 100% of the cases[15] If the growth pattern changes from the superficial spreading growth phase to the vertical growth phase (melanoma which has invaded from the epidermis into the dermis), the tumor has a potential to enter the blood and lymphatic vessels, and spread elsewhere in the body from the primary site

The prognosis of melanoma is inversely related to the depth of tumor invasion This concept, suggested by Mehnert and Heard[8] has been refined by Clark et al [9] who have defined five levels of microinvasion, and by Breslow[10] who has introduced the quantitative measurment of the vertical thickness of melanoma with the use of ocular micrometer Clark et al.[11] claim that primary melanomas evolve through two clearly defined phases the radial growth phase and the vertical growth phase Only the cells in the vertical growth phase exhibit all the properties of fully transformed cells A variety of new cell-surface molecules are present on vertical growth melanomas, including the gangliosides GD2 and GD3 All these factors are relevant to invasive and metastatic behavior and selective growth advantage

Breslow[12] has suggested that lesions with a thickness of less than 0 76 mm carry an excellent prognosis Slingluff et al [13] found that 4 8% developed recurrences, but those with a 3-mm thickness and patients with Clark IV or V lesions had a poor prognosis.

To evaluate the interaction of many prognostic factors, Mackie et al.[14] have developed a prognostic scoring system Eleven prognostic factors are assigned a point value. The higher the patients score, the worse the prognosis. Tumor ulceration and satellite presence are poor prognostic signs.

Is there any evidence that the use of interferon can raise the survival rate of patients or at least improve the quality of life of melanoma patients? The effects of IFN on clinical prognosis are not yet completely known Is it possible to delay recurrence in patients?

Partial regression, a decrease in the size and change of melanoma are seen in almost 100% of patients. Does this mean a better quality of life and a prolonged survival for melanoma patients?

Two patients belonged to clinical stage I, classification T_1 (radial melanoma with good prognosis), one of them received r IFN alpha 2c before surgery and is still alive six years after the surgery, and the other patient, who received HNLI, is still alive nine years after the surgery

Clinical stage I, classification T_2 (vertical growth phase, nodular melanoma), was diagnosed in seventeen patients, and seven of them received r IFN alpha 2c before surgery. Five out of these seven patients are still alive, two for six years and three for four years after the treatment, while two patients died, one of them two years and the other three years after the treatment It seems that in this group the survival rate is better

than could have been expected if only surgery had been performed. Ten patients received r.IFN alpha 2c after the surgery, and five patients are still alive, one of them for six and one for seven years, one for four years and two patients for three years after the treatment Five patients died, three of them lived for three years and two lived for two years after the treatment.

In this group in which r IFN alpha 2c was applied after surgery, the survival rate is lower in comparison with the group in which r IFN alpha 2c was applied before surgery.

Clinical stage I, classification T_3 (satellite melanoma) consisted of four cases with poor prognosis. Two patients who received therapy before the surgery, died two and three years after the treatmant, respectively One patient (Table 3, No 16) is still alive six years after the treatment and one died two years after the treatmant (Table 4, No 23).

Clinical stage II, classification T_3N_1 (with nodular involvement and poor prognosis), was found in two patients, who are still alive six years after the treatmant.

Clinical stage III, classification $T_3N_1M_1$ (melanoma with distant metastases and a very poor prognosis) consisted of three patients who received HNLI and two who received r IFN alpha 2c Three patients with metastatic melanoma received HNLI, two of them showed complete regression locally, one patient showed partial regression, but they all died from distant metastases within two years after the treatmant Two patients who received r IFN alpha 2c before surgery died within two years after the treatment.

What can be said about the efficacy of interferon in the treatment of melanoma based on our experience and our method and schedule of application?

1 Local application of interferon is efficient in melanoma clinical stage I classification $T_1N_0M_0$ with or without subsequent surgery, and is especially recommended on cosmetically difficult localizations

2. Interferon is useful as an adjuvant treatment in clinical stage I, classification T_2 and $T_3N_0M_0$ and clinical stage II, classification $T_3N_1M_0$ The recommended route of administration is local interferon treatment for four weeks (3-5 times per week) before and for twelve weeks (1-2 times per week) after surgery A significant role of local tumor application of interferon is the activation and hyperplasia of regional nodes. The local application of interferon hinders the growth of tumor cells and preventing dispersion of the neocytes, inhibits micrometastasis thereby reducing the number of tumor recurrences, increasing the chance of survival and improving the quality of life. According to our results, interferon application before surgery is more efficient than that after surgery.

3 Interferon therapy of metastatic melanoma is of a limited efficacy, as shown by our results. A response rate similar to that achieved by conventional chemotherapy has been accomplished in studies using higher interferon doses and much longer interferon treatment[26-28].

In patients with metastatic disease, it is important to find effective adjuvant and minimally toxic therapy to stimulate the resistance of the body. The identification of human melanoma cell surface antigens has led to the development of an array of mouse monoclonal antibodies against glycolipid surface antigens. Such antibodies, if specially prepared to overcome the immunogenicity of mouse monoclonal antibodies[29-31], might provide a useful and efficient combination with r.IFN alpha which could enhance the immune activity against distant metastatic melanoma cells.

Acknowledgements: The authors would like to thank Boehringer Ingelheim for the donation of r IFN alpha 2c for our research.

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SUMMARY

Twenty-seven patients were treated with r IFN alpha 2c (fourteen before and thirteen after surgery) Four patients received human natural leukocytic interferon (HNLI) Interferon was administered locally.

Out of two patients belonging to clinical stage I, classification T_1 (radial melanoma with good prognosis), one received r.IFN alpha 2c before surgery and is still alive six years after the surgery, and the other received HNLI, and is still alive nine years after the surgery.

Clinical stage I, classification T_2 (vertical growth phase, nodular melanoma) included seventeen patients, seven of them received r IFN alpha 2c before surgery Out of these seven patients, five are still alive, two for six years and three for four years after the treatment, while two patients died, one of them two years and the other one three years after the treatmant It seems that in this group, the survival rate is better than could have been expected if only surgery had been performed Ten patients received r IFN alpha 2c after surgery, and five patients are still alive, one for six and one for seven years, one for four years and two patients for three years after the treatment Five patients died, three of them lived for three years and two lived for two years after the treatment

In this group, in which r IFN alpha 2c was applied after surgery, the survival rate is lower in comparison with the group in which r IFN alpha 2c was applied before surgery

Clinical stage I, classification T_3 (satellite melanoma) consisted for four cases with poor prognosis Two patients who received therapy before surgery, died two and three years after treatment, respectively One patient (Table 3, No 16) is still alive six years after the treatment and one died two years after the treatment (Table 4. No 23)

Clinical stage II, classification T_3N_1 (with nodular involvement and poor prognosis), included two cases still alive six years after the treatment.

Clinical stage III, classification $T_3N_1M_1$ (melanoma with distant metastases and very poor prognosis) consisted of three patients who received HNLI and two who received r IFN alpha 2c Three patients with metastatic melanoma received HNLI, two

of them showed complete regression locally, one patient showed partial regression, but they all died from distant metastases within two years after the treatment Two patients who received r IFN alpha 2c before surgery died within two years after the treatment

What can be said about the efficacy of interferon in the treatment of melanoma based on our experience and method and schedule of application?

1 Local application of interferon is efficient in melanoma clinical stage I classification $T_1N_0M_0$ with or without subsequent surgery, and is especially recommended on cosmetically difficult localizations

2. Interferon is useful as an adjuvant treatment in clinical stage I, classification T_2 and $T_3N_0M_0$ and clinical stage II. classification $T_3N_1M_0$ The recommended route of administration is local interferon treatment for four weeks (3-5 times per week) before and for twelve weeks (1-2 times per week) after surgery A significant role of local tumor application of interferon is the activation and hyperplasia of regional nodes. The local application of interferon hinders the growth of tumor cells and preventing dispersion of the neocytes. inhibits micrometastasis thereby reducing the number of tumor recurrences, increasing the chance of survival and contributing to a better quality of life. According to our results, interferon application before surgery is more efficient than that after surgery.

3 Interferon therapy of metastatic melanoma is of a limited efficacy, as shown by our results A response rate similar to that achieved by conventional chemotherapy has been achieved in studies using higher interferon doses and much longer interferon treatment

In patients with metastatic disease, it is important to find effective adjuvant and minimally toxic therapy to stimulate the resistance of the body. The identification of human melanoma cell surface antigens has led to the development of an array of mouse monoclonal antibodies directed against glycolipid surface antigens Such antibodies, if specially prepared to overcome the immunogenicity of mouse monoclonal antibodies, might provide a useful and efficient combination with r.IFN alpha 2c which could enhance the immune activity against distant metastatic melanoma cells.

MELANOMI TERAPIJA INTERFERONOM

S A Ž E T A K

Dvadesetsedmoro bolesnika liječeno je lokalno s rekombinantnim interferonom, a četvoro bolesnika s prirodnim humanim leukocitnim interferonom. Od dvadesetsedmoro bolesnika liječenih s rekombinantnim interferonom, četrnaestoro je primalo rekombinantni interferon prije, a trinaestoro nakon kirurškoga zahvata

O učinkovitosti primjene interferona u liječenju melanoma na osnovi našega nacrta, načina primjene i iskustva možemo reći kako je lokalna primjena interferona

učinkovita kod melanoma kliničkoga stupnja I klasifikacije $T_1N_0M_0$, što je zanimljivo kod tumora lokalizacija kojih nije pogodna s kozmetskog stajališta Interferon kao pomoćna terapija melanoma koristan je u kliničkom stupnju I klasifikacije T_2 i $T_3N_0M_0$, zatim u kliničkom stupnju II klasifikacije $T_3N_0M_0$ i u kliničkom stupnju II klasifikacije $T_3N_1M_0$ Preporuča se lokalna primjena interferona tijekom 4 tjedna, 3-5 puta u tjednu prije kirurškoga zahvata Značajna uloga lokalne primjene interferona je aktiviranje i hiperplazija regionalnih limfnih čvorova Lokalna primjena interferona u i u blizini tumora pomaže, uz ostale aktivnosti, blokiranje tumorskih stanica, sprječava disperziju malignih stanica, inhibira mikrometastaze, smanjuje mogućnost ponovne pojave tumora, poboljšava izglede bolesnika za preživljavanje Primjena interferona prije kirurške intervencije je učinkovitija, prema našim rezultatima, od primjene interferona nakon kirurške intervencije, ali najbolji put je primjena i prije i nakon kirurške intervencije

Liječenje interferonom metastatskog melanoma, tj. kliničkoga stupnja III klasifikacije $T_3N_1M_1$, bilo je ograničene učinkovitosti u našim ispitivanjima. Učinkovitije rezultate liječenja metastatskog melanoma, slične rezultatima postignutima s uobičajenom kemoterapijom, opisali su drugi autori koji su rabili mnogo veće doze rekombinantnog interferona i puno dužu primjenu interferona Za bolesnike oboljele od metastatskog melanoma potrebno je naći učinkovitu pomoćnu terapiju u svrhu pojačanja otpornosti organizma, koja je minimalno toksična Identifikacija površinskih antigena dovela je do razvitka niza mišjih monoklonskih protutijela protiv glikolipidnih površinskih antigena stanice humanoga melanoma Takva monoklonska protutijela, priređena tako da premoste imunogenost mišjih monoklonskih protutijela, bilo bi svrhovito vezati s rekombinantnim interferonom u svrhu pojačanja imunološke aktivnosti protiv metastatskih melanomskih stanica

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Primljeno na 10 sjednici IV Razreda 16 VII 1992