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Impact of high dose chemoimmunotherapy after surgery on the overall and disease-free survival in advanced stage malignant melanoma

BACKGROUND: *To investigate the impact of high dose chemoimmunotherapy in addition to surgery on the cumulative survival and disease-free survey of malignant melanoma patients.*
METHODS: *A total of 86 malignant melanoma patients [35 females (40.7%), 51 males (59.3%), mean age: 55.5] were treated according to their stages between Februrary 1997 and June 2007. After surgery, adjuvant immunotherapy was applied to patients in Stage 2, while adjuvant chemotherapy and adjuvan immunotherapy were administered to those at Stages 3 and 4.*
RESULTS: *Overall rate of mortality was 31.4% (27/86). The most frequent postoperative complications were wound infection (n=8, 9.3%) in the early period and lymphedema in lower extremities (n=4, 4.6%) in the late period. Temporary and tolerable complications ensourcing from chemoimmunotherapy were encountered in 9 (10.4%) patients. The survival rates and disease-free periods of combined treatment protocol were found to be similar to those in ECOG 1684 and ECOG 1690 studies.*
CONCLUSION: *Adjuvant immunotherapy and chemoimmunotherapy seem to improve overall survival and disease-free survey in malignant melanoma. Further clinical studies are necessary to demonstrate the actual effectivity of this promising protocol in the management of malignant melanoma.*

KEY WORDS: Adjuvant, Chemotherapy, Immunotherapy, Malignant melanoma, Surgery, Survival.

Introduction

Malignant Melanoma (MM), is a tumor of melanocytes that originate from neural crest. Any cell capable of producing melanin in the body can lead to MM. It exhibits rapid proliferation and not only skin but also subcutaneous tissue and retina may be involved. It constitutes only 2% of all cancers, but it is responsible for 65-70% of mortalities due to skin cancer [1-3].

Rapid progression and poor response to treatment bring about high mortality rates even in the early stages of MM [1-3]. Therefore, MM still remains as a therapeutic challenge and attempts are directed for earlier diagnosis and more adequate surgical management supported by adjuvant chemotherapy and immunotherapy to achieve more acceptable rates of survival and disease-free period. For this purpose, we have exclusively ana-

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lyzed the patient-related, disease-related and treatment-related factors in a group of melanoma patients to assess their impact on rates of survival and disease-free survey.

Materials and methods

Study Design
This prospective study was performed in the surgery department of a tertiary care center between February 1997 and June 2007 after the approval of the Institutional Review Board. A total of 86 malignant melanoma patients [35 females (40.7%), 51 males (59.3%); mean age: 55.5] were enrolled. Patients were allocated to different treatment groups after staging. In addition to surgery, adjuvant immunotherapy was applied to patients in Stage 2; while adjuvant chemotherapy and adjuvan immunotherapy were administered to those at Stages 3 and 4.

Surgical treatment

Surgical intervention was selected with respect to the stage of the tumor and prognostic factors. Type of surgery consisted of total excision with wide margins (TE), TE and locoregional lymph node dissection (LRLND) and abdominoperineal resection. Only 25 patients at stage 2 underwent TE, while TE & LRLND were performed on 25 patients at Stage 2, 37 patients at Stage 3 and 14 patients at Stage 4. Four patients with rectal MM underwent abdominoperineal resection (Miles operation).

Medical Treatment

Adjuvant Immunotherapy: Induction dose of interfero was administered intravenously at 20X10 MU/ m^2 5 days a week for a month. Maintenance dose was administered subcutaneously at 10X10 MU / m^2 / 3 days a week for 11 months.
Adjuvant Chemotherapy: Dacarbazine (DTIC) was administered at a dose of 200 mg / m^2 / 5 days a month for 3 months.
Other treatment modalities: In patients with a history of adjuvan immunotherapy / chemoimmunotherapy, or local recurrent disease or local / distant metastases, the following therapeutic options were utilized:
I) Hyperthermic isolated organ perfusion (in cases with extensive satellite lesions);
II) Fotemustine at a dose of 100 mg / m^2 / once a week for 3 weeks initially. After a resting period of 4 weeks, administered at 100 mg / m^2 / once in 3 weeks for 1 year;
III) Temozolamide 150-200 mg/ m^2 /for 5 days followed by a resting period of 28 days.
The average duration of follow-up was 37.6 months. Patients were followed-up every month in the first year, every 3 months in the second year and every 6 months in the following years.
Statistical Analysis: Statistical analysis of the data is performed using Statistical Package for Social Sciences (SPSS) 11.5 for Windows (SPSS Inc., Chicago, IL). Descriptive data is expressed as mean ± standard deviation for continuous variables and as % for categorical variables. Overall and disease-free survival rates are assessed by Kaplan-Meier estimates using Log-Rank test. For each risk factor, overall as well as 1st and 3rd year survival rates are calculated. Clinical data for our MM series are presented on Table 1. The results were assessed within a 95% reliance and at a level of $p<0.05$ significance.

Results

Twenty-seven of 86 patients (31.4%) died in the follow-up period. In 8 patients (9.3%), lymphocele and wound infection, that responded well to antibiotics and drainage, were observed at the site of lymph node dissection. In 4 patients (4.6%), lymphedema resistant to medical treatment was diagnosed. Metastases in liver and pelvis were determined in 17 and 4 patients respectively. Correlation of risk factors to overall and disease-free survival rates at 1-year and 3-year are shown in Table II. Eye colour (p=0.866), type of surgery (p=0.192) and history of trauma or intense exposure to sunlight (p=0.275) are found not be significantly related to the overall survival rate or disease-free survival rates at 1-year and 3-years.

TABLE I - *Distribution of MM patients with respect to primary localization, histological type and Clark, Breslow and TNM Staging Systems.*

Primary localization	no (%)	Histology	no (%)	Clark Stage	no (%)	Breslow Stage	no (%)	TNM Stage	no (%)
Head-Neck	12 (14.11)	Superficial	23 (26.7)	I	1 (1.26)	I	3 (3.72)	IB	3 (3.5)
Upper extremity	15 (17.4)	Nodular	42 (48.8)	II	14 (17.2)	II	16 (19.75)	IIA	19 (22.1)
Lower extremity	39 (45.3)	Acral	13 (15.1)	III	22 (27.16)	III	36 (44.44)	IIB	13 (15.1)
Trunk	8 (9.3)	Lentiginous	2 (2.35)	IV	35 (43.2)	IV	26 (32.09)	III	37 (43.02)
Back (Low)	1 (1.2)	Metastatic	6 (7.0)	V	9 (11.18)			IV	14 (16.2)
Back (Up)	7 (8.1)								
Anal canal	4 (4.7)								

TABLE II - *Correlation of risk factors to the overall survival rate and disease free survival rates at 1-year and 3-years.*

		Frequency (n/N)	Overall survival (%)	1-year disease free survival	3-year disease free survival	P
Tumor location	Head-Neck	4/12	66.7	91.7	62.5	<0.001
	Upper extremity	2/15	86.7	100.0	83.3	
	Lower extremity	14/39	75.0	92.3	68.1	
	Trunk	2/8	80.2	100.0	85.7	
	Back (Low)	1/1	0	0.0	0.0	
	Back (Up)	2/7	71.4	100.0	71.4	
	Anal canal	1/4	75.0	100.0	66.7	
Tumor histology	Superficial	5/23	78.3*	95.7	79.8	0.023
	Nodular	13/42	69.0*	90.5	72.6	
	Acral	3/13	76.9*	100.0	71.4	
	Lentiginous	0/2	100.0	100.0	100.0	
	Metastatic	5/6	16.7	100.0	16.7	
TNM Stage	IB	0/3	100.0 †,‡	100.0	100.0	<0.001
	IIA	0/19	100.0 †,‡	100.0	100.0	
	IIB	0/13	100.0	100.0	100.0	
	III	14/37	62.2	100.0	68.3	
	IV	12/14	14.3	64.3	10.7	
Clark Stage	I	0/1	100.0	100.0	100.0	0.007
	II	0/14	100.0 †,¶	100.0	100.0	
	III	4/22	84.6 ¶	100.0	87.0	
	IV	17/35	57.6	94.7	57.9	
	V	5/9	44.4	66.7	44.4	
Breslow Stage	I	0/3	100.0	100.0	100.0	<0.001
	II	0/16	100.0 †	100.0	100.0	
	III	7/36	84.3 †	97.4	82.5	
	IV	19/26	26.9	84.6	33.7	
Treatment Modality	Surgery	0/7	100.0	100.0	100.0	
	Surgery + immunotherapy	0/9	100.0§	100.0	100.0	
	Surgery + immunotherapy + chemotherapy	26/69	62.3	92.8	64.8	0.033

*Statistically significant difference with metastatic group; † Statistically significant difference with Stage 4; ‡ Statistically significant difference with Stage 3; ¶ Statistically significant difference with Stage 5; § Statistically significant difference with surgery+immunotherapy+chemotherapy

Discussion

In surgically treated MM patients at Stages 2 and 3, rate of recurrences are as high as 60% and 75% respectively [4]. Our aim was to investigate if we could achieve lower rates of recurrence owing to chemotherapy and immunotherapy performed after surgery. However, interpretation of the impacts of chemotherapy and immunotherapy on survival rates is difficult due to the dominance of patients at stages 3 and 4.

In ECOG 1684 study, a total of 280 MM patients at stages 2B and 3 were enrolled. Interferon α-2b was administered in high dose for induction in first month, and at maintenance dose for the following 11 months to 143 patients. Remaining 137 patients served as controls and the average duration of follow-up was 7 years. Duration of survival in the treatment and control groups were 46 and 33.6 months; and disease-free survival rates were 20.4 and 11.5 months respectively. The difference between treatment and control groups was statistically

TABLE III - *Overall and disease-free survival rates in ECOG 1684, ECOG 1690 studies and our series.*

	Median disease-free survival (months)	Median overall survival (months)
ECOG 1684 High dose INF-α 2b (5)	20.4	45.6
ECOG 1684 Control (5)	12	34.6
ECOG 1690 High dose INF-α 2b (6)	30	61.2
ECOG 1690 Control (6)	19.2	72
Our series	18.6	42.4

significant [5]. In ECOG 1690 study, a total of 642 MM patients were allocated into three groups and followed-up for 52 months: Group I received high dose interferon-α 2b, Group II received low dose interferon-α 2b and Group III was control. Five-year survival rates in groups I and III were 44% and 35%; while cumulative survival rates were 53% and 54% respectively [6]. High dose interferon treatment was beneficial for disease-free survival, while no significant difference could be observed between groups in terms of overall survival. The increased rates of overall survival may be due to the administration of additional high-dose interferon to patients with recurrence after surgery in Group III (6). Comparison of our results to ECOG 1684 and 1690 studies are demonstrated on Table III. The median duration of follow-up is just 37.6 months and only 9 patients had interferon treatment after surgery. These are limitations for the extrapolation of our results and restrict the comparability of our outcomes to other studies.

Adjuvant immunotherapy consisting of low dose interferon-α 2a was found to improve disease-free survival; however no beneficial impact on the overall survival could be detected [7]. Therefore, we administered only high dose interferon-α 2b in our series. Comparison of MM patients receiving high dose interferon-α 2a for 12 weeks to surgical treatment group revealed no difference in terms of disease-free survival and overall survival. This result was attributed to the short duration of interferon treatment. Low-dose interferon-α 2b treatment was found to provide no improvement in overall and disease-free survival rates of MM [8]. In Thompson's study, combination of DTIC and interferon was not superior to DTIC alone. This could possibly be due to the low dose of DTIC in the combination protocol, hence we applied DTIC in conventional doses. Bajetta reported that comparison of three groups receiving DTIC and high dose interferon-α 2b, DTIC and low dose interferon-α 2b and DTIC alone did not reveal any difference in terms of survival [9]. These results were for the early period only, and longer duration of follow-up may yield more accurate data. In contrast, Falkson demonstrated that dose interferon-α 2b in addition to DTIC prolonged the survival of MM patients than DTIC alone [10,11]. Taking all the data into account, we gave high dose interferon-α 2b to patients at stage 2B and higher stages. Rather than chemotherapy or immunotherapy alone, combined chemoimmunotherapy was advocated for advanced stage MM patients 12. However, there exists no standard postoperative treatment protocol for these cases. We hope that our study contributes to the constitution of such a regimen.

Small number of patients in our series and involvement of cases with recurrent disease that had not initially participated in the study may influence our relatively low rates of survival. Due to these 2 factors, it may be more appropriate to evaluate this study as an intermediary analysis. Chemoimmunotherapy was predominantly utilized since patients were at advanced stage of disease.

Conclusion

Adjuvant chemotherapy and adjuvant immunotherapy seems to contribute to achieve better overall and disease-free survival rates in surgically treated advanced stage MM patients. Studies on larger series are necessary to support the actual effectivity of chemoimmunotherapy and to establish a standard therapeutic protocol.

Riassunto

Lo studio rappresenta un'indagine sull'impatto di alte dosi di chemio-immunoterapia in aggiunta alla chirurgia sulla sopravvivenza globale e sull'intervallo esente da malattia di pazienti affetti da melanoma maligno.

Sono stati studiati un totale di 86 pazienti affetti da melanoma maligno (35 donne pari al 40,7%, e 51 uomini pari al 59,3%, tutti dell'età media di 55,5 anni, trattati a seconda dello stadio della malattia tra febbraio 1997 e giugni 2007. Dopo l'atto chirurgico nei pazienti in stadio 2 era stata adottata una terapia adiuvante immunoterapica, mentre nei pazienti in stadio 3 e 4 era stata adottata una terapia adiuvante sia chemioterapica che immunoterapica.

Risultati: la mortalità generale è stata del 31,4% (27/86). Le più frequenti complicazioni postoperatorie sono state l'infezione della ferita (n=8, 9,3%) nel periodo precoce ad il linfedema delle estremità inferiori (n=4, 4,6%) nel periodo tardivo. Complicanze temporanee e tollerabili insorte dopo chemio-immunoterapia si somno registrate in 9 pazienti (10,4%). L'incidenza della sopravvi-

venza e dei periodi esenti da malattia nei protocolli di trattamento combinato sono risultati simili a quelli degli studi ECOG 1684 ed ECOG 1690.
In conclusione i trattamenti adiuvanti immunoterapici e chemioimmunoterapici sembrano migliorare la sopravvivenza globale e la sopravvivenza libera da malattia nel melanoma maligno. Sono necessari ulteriori studi clinici per confermare l'efficacia di questi promettenti ptotocolli per il trattamento del melanoma maligno.

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