European Review for Medical and Pharmacological Sciences 2015; 19: 1640-1644

Improvement of survival in patients with melanoma and non-melanoma skin cancers compared to patients without double cutaneous malignancies

U. BOTTONI[1], G. PAOLINO, D. DIDONA, P. CORSETTI, R. CLERICO, C. CANTISANI, A.G. RICHETTA, V. ARCIDIACONO[1], E. SCALI[1], G. PRANTEDA[2], S. CALVIERI

Unit of Dermatology, School of Medicine, "Sapienza" University of Rome, Rome, Italy
[1]Unit of Dermatology, School of Medicine, University Magna Graecia, Catanzaro, Italy
[2]Unit of Dermatology, II School of Medicine, "Sapienza" University of Rome, S. Andrea Hospital, Rome, Italy

Abstract. – OBJECTIVE: The worldwide incidence of cutaneous malignant melanoma (MM) has been rising steadily over the past 30 years. At the same time non-melanoma skin cancers (NMSC) are the most prevalent type of cancer in United States and Europe. Up to date, no paper has explored the influence on the general survival in patients with MM and NMSC. We decided to perform a study with the aim to evaluate the different survival in patients with MM-NMSC compared to control patients (MM-CTRL).

PATIENTS AND METHODS: To evaluate prognosis in both groups, we analyzed disease-free survival (DFS) and overall survival (OS).Kaplan-Meier product was performed for the survival analysis. Median DFS was 73 months in group and 72 months in MM-CTRL patients ($p = 0.4$); while, median OS was 74.2 months in MM-NMSC patients and 63.1 in MM-CTRL ($p < 0.001$). Also at Odds-Ratio (OR), the statistical significance was maintained ($p < 0.007$) with a better prognostic value for MM-NMSC.

RESULTS: Among group patients, the ones with a basal cell carcinoma showed a batter behavior, than the ones with squamous cell carcinoma ($p = 0.01$).

CONCLUSIONS: Patients with MM-NMSC showed a better survival than MM-CTRL patients ($p < 0.001$). The causes of this improved survival are still unknown; probably the endogenous immune response can play a pivotal role in this class of patients. However, further studies are necessary to better understand this phenomenon, not yet explored in literature.

Key Words:
Basal cell carcinoma, Squamous cell carcinoma, Melanoma, Skin neoplasm.

Introduction

The worldwide incidence of cutaneous malignant melanoma (MM) has been rising steadily over the past 30 years and despite intense efforts of prevention, advanced melanoma is still a fatal disease with stable mortality rates[1-5]. At the same time, non-melanoma skin cancers (NMSC) are the most prevalent type of cancer in United States and Europe[6].

The association with MM and other internal malignancies (above all non-Hodgkin lymphomas, breast cancers, pancreas cancers and renal cancers) is well documented, with discordant results in term of disease free survival (DFS) and overall survival (OS)[7,8]. In the worldwide literature, several papers had always focused their attention on the etiopathogenesis (as well on the treatments) of patients with MM and NMSC, but, up to date, no paper has explored the influence on the general survival in patients with MM and NMSC compared to patients with only MM, with effort to consult works about.

In this regard, during our clinical practice in our Departments, we observed survival differences for patients with MM-NMSC than patients with only MM. For this reason and starting from a recent published paper[9], we decided to study if there was any bio-statistical correlation to support this theory.

Patients and Methods

Clinical and pathological data were all obtained from MM electronic database formed by

Corresponding Author: Dario Didona, MD; e-mail: onlypaper@libero.it

the data from Institute of Dermatology Sapienza University of Rome and Dermatology of University of Magna Graecia. We computer-searched the clinical records of all our melanoma patients to find the ones that presented one or more skin carcinomas: basal cell carcinomas or squamous cell carcinomas that is NMSC. This group of patients was selected regardless the time of onset (whether before or after the diagnosis of MM). The control group was composed by MM patients without a history of NMSC and/or other malignancies (MM-CTRL). The patients were selected from the general group of MM patients, according to a simple randomization 1:3. In order to prevent selection bias, the simple randomization was performed using a computational random number generator.

For both MM-NMSC and MM-CTRL patients, the following parameters were registered: sex (female or male), age (≤ 60 or ≥61 years), anatomic site of the primary tumor (axial/peripheral), Breslow thickness (≤ 1.00 mm; ≥ 1.01 mm) and metastases to loco-regional lymph nodes. These parameters are the same used by Balch et al. for AJCC classification[10].

To evaluate prognosis in both groups, we analyzed DFS and overall OS. DFS was calculated as the time interval between the diagnosis of the primary tumor and the first metastatic event and/or last follow-up. OS was calculated as the time interval between the first visit and the date of death and/or last follow-up. Patients that were lost to follow-up or that were alive at the time of last follow-up were censored at the date of their last follow-up. Regarding MM-NMSC, at first, we evaluated the survival analysis including all MM-NMSC patients; while in a second time we performed the same analyses differentiating subjects in two sub-groups: the ones that removed basal cell carcinoma (BCC) from the ones that removed squamous cell carcinoma (SCC).

Statistical Analysis

Kaplan-Meier product was used to estimate survival curves and the log-rank test was used to evaluate differences between MM-NMSC patients and MM-CTRL subjects. Finally, an Odds ratio (OR) was performed in order to evaluate the relative risk of recurrences in the samples analyzed.

In all statistical methods used, a p value < 0.05 was considered significant.

Results

A total of 139 patients with MM-NMSC, were included in our analysis (110 basal cell carcinomas + 29 squamous cell carcinomas); they were 7.5% out of 1.850 patients present in our melanoma database. In MM-NMSC patients, the diagnosis of a non-melanoma skin cancer was done in 85 patients after a MM diagnosis, in 28 patients before, while in 26 was synchronous. As control (MM-CTRL), 430 MM patients without an epithelial cutaneous malignancy were chosen. They were selected according to a simple randomization 1:3, using a computational random number generator.

Regarding the baseline characteristics of MM-NMSC patients, 80 patients were male and 59 were female. Median age of the patients was 65 years, ranging between 25-90. Patients with age ≤ 60 years were 47, while those with age ≥ 61 years were 92. Regarding Breslow thickness, 104 patients showed thickness ≤ 1.00 mm and 35 patients ≥ 1.01 mm and (median Breslow 0.4 mm). Analyzing AJCC stage at diagnosis , 38 patients showed AJCC stage 0, 66 patients were in stage IA, while 18 patients were in stage IB, 5 patients in stages IIA, 5 patients in stage IIB, 2 patients in stage IIC and 5 in stage IIIA (Table I).

Table I. Baseline characteristic of group patients (MM-NMSC) and control (MM-CTRL).

	MM-NMSC	MM-CTRL
Gender		
Male	80	196
Female	59	234
Age		
≤ 60	47	291
≥ 61	92	139
Stage		
0	38	115
IA	66	217
IB	18	54
IIA	5	13
IIB	5	13
IIC	2	6
IIIA	5	12
Breslow		
≤ 1.00	104	343
≥ 1.01	35	87
Onset NMSC		
Before MM	28	–
After MM	85	–
Synchronous	26	–

Characteristics of MM-CTRL patients are shown in Table I. Their clinical-pathological features presented a prevalence of female patients with an age ≤ 60 years, while Breslow thickness and AJCC 2009 staging were comparable with the ones registered for MM-NMSC.

Concerning the DFS, progressions were found in 7.7% of MM-NMSC patients and in 11.6 % of CTRL ones, with a median DFS of 73 months in group and 71 months in MM-CTRL patients (p = 0.4). Regarding OS, median OS was 74.2 months in MM-NMSC patients and 63.1 in MM-CTRL ($p < 0.001$) (Figure 1). Evaluating OR between the two samples, the statistical significance was maintained ($p < 0.007$) with a better prognostic value for MM-NMSC patients (Table II).

Finally, analyzing MM-NMSC according to the epithelial type of malignancy, we found that a significant better prognosis in the long term was observed in the sample of patients with basal cell carcinoma (median OS of 74.2 months with p = 0.01 and an OR value of 3.5 with p = 0.01) and not in the group of patients with MM and squamous cell carcinoma (p = 0.5).

Discussion

NMSC are the most common type of tumor in United States and Europe with a worldwide continuous increase in the incidence. At the same time, the incidence rate for cutaneous MM has trebled in the last two decades[11]. Sometimes, the two types of tumors coexist in the same patient and this may be a result of shared genetic susceptibility (for instance fair skinned people), environmental exposure (sunburn), iatrogenic factors (people under treatment with BRAF inhibitors) and/or increased skin cancer surveillance in individuals diagnosed with MM or NMSC[9,12,13].

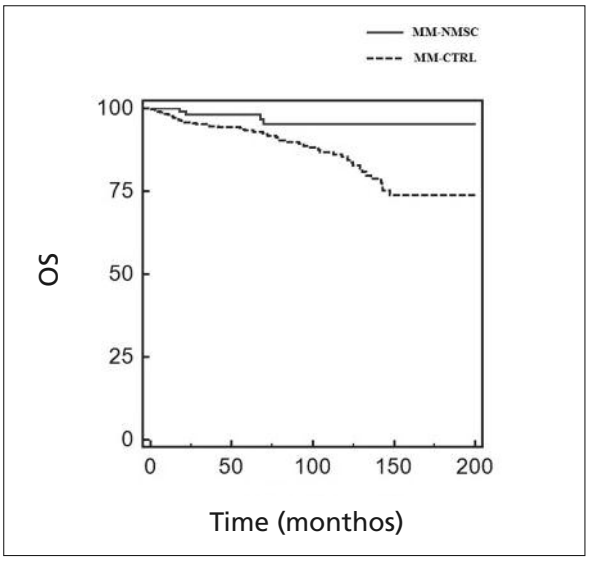

Figure 1. Overall survival (OS) of group patients (MM-NMSC) compared to control (CTRL).

Table II. Odds-Ratio (OR) analysis.

	OR	95% CI	p
MM-NMSC Vs. MM-CTRL	4.1	1.4-11.6	0.007
BCC Vs. MM-CTRL	3.5	1.2-9.9	0.01
SCC Vs. MM-CTRL	1.14	0.3-3.9	0.8

Clinical prognosis and risk of recurrences in group patients (MM-NMSC) and relative sub-groups (MM-BCC and MM-SCC), compared with control patients (MM-CTRL). BCC indicates basal cell carcinoma; SCC indicates squamous cell carcinoma; 95% CI indicates 95% confidence interval. In Italic significant values.

According to our data, MM-NMSC patients are 7.5% of all our MM patients and they are more frequent in older male patients. These data are similar to the ones presented recently in 2014 by Asgari et al[9]. They found NMSC in approximately 12% of patients with MM and both tumors were more common among males and older subjects. However, the authors did not focused on the survival of these subjects.

Despite the higher presence of male patients in MM-NMSC group than in MM-CTRL, we found a better OS in MM-NMSC patients. This observation was strongly confirmed by statistical analyses: $p < 0.001$. Obviously increased skin cancer surveillance in individuals given the diagnosis of MM or NMSC could improve the prognosis, but we must take into account that both our groups of patients (MM-NMSC and MM-CTRL) underwent the same type of follow up tailored on their AJCC 2009 staging that was comparable in both groups as showed in Table I[10].

We know from the literature that MM is strongly associated with sun-UV exposure above all intermittent high sun-UV exposure, dealing to sunburns[14]. Only lentigo maligna melanoma (LMM) is considered different from the general group of melanoma namely superficial spreading melanoma, because it is related to a chronic exposure to sun-UV. Regarding skin carcinomas, BCC is considered by several authors[7] more related to

intermittent high sun-UV exposure with sunburns, even if some authors do not agree with this model[15]. While, SCC is considered as more related to chronic exposure to sun-UV[7,16,17]. According to these data most MM and BCC may present the same important risk factor of intermittent high sun-UV exposure with sunburns. This could explain the fact that MM and BCC may appear in the same patients more frequently than MM and SCC, even if this cannot justify the better prognosis (Table II). Regarding other MM models, the better survival observed in our sample of MM-NMSC patients is very similar to the prognosis seen in melanoma patients with unknown primary (MUP) [17]. It has been suggested that the immunologic response in the primary tumor regression, may contribute to the more favorable outcomes seen in MUP patients[18]. Similarly, an endogenous immune response can determine the better outcome in MM-NMSC patients[19-21].

Conclusions

Patients with MM-NMSC showed a better survival than MM-CTRL group patients. The causes of this improved survival are still unknown; probably the endogenous immune response can play a pivotal role in this class of patients. However, further studies are necessary to better understand this phenomenon, not yet explored in literature.

Statement of Interests

The preparation of this paper was funded by Associazione Romana Ricerca Dermatologica.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Garbe C, Leiter U. Melanoma epidemiology and trends. Clin Dermatol 2009; 27: 3-9.
2) De Vries E, Coebergh JW. Cutaneous malignant melanoma in Europe. Eur J Cancer 2004; 40: 2355-2366.
3) Karim-Kos HE, de Vries E, Soerjomataram I , Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer 2008; 44: 1345-1389.
4) Bosetti C, La Vecchia C, Naldi L, Lucchini F, Negri E, Levi F. Mortality from cutaneous malignant melanoma in Europe. Has the epidemic levelled off? Melanoma Res 2004; 14: 301-309.
5) Van der Leest RJ, de Vries E, Bulliard JL, Paoli J, Peris K, Stratigos AJ. The Euromelanoma skin cancer prevention campaign in Europe: characteristics and results of 2009 and 2010. J Eur Acad Dermatol Venereol 2011; 25: 1455-1465.
6) Wysong A, Ally MS, Gamba CS, Desai M, Swetter SM, Seiffert-Sinha K. Non-melanoma skin cancer and NSAID use in women with a history of skin cancer in the Women's Health Initiative. Prev Med 2014; 69: 8-12.
7) Matin RN, Szlosarek P, McGregor JM. Synchronous melanoma and renal carcinoma: a clinicopathological study of five cases. Clin Exp Dermatol 2013; 38: 47-49.
8) Bhatia S, Estrada-Batres L, Maryon T, Boque M, Chu D. Second primary tumors in patients with cutaneous malignant melanoma. Cancer 1999; 86: 2014-2020.
9) Asgari MM, Warton EM, Quesenberry CP, Koralek DO, Taylor M. Risk of subsequent cutaneous squamous cell carcinoma in patients with melanoma. J Am Acad Dermatol 2014; 71: 521-528.
10) Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, Buzaid AC, Cochran AJ, Coit DG, Ding S, Eggermont AM, Flaherty KT, Gimotty PA, Kirkwood JM, McMasters KM, Mihm MC Jr, Morton DL, Ross MI, Sober AJ, Sondak VK. Final version of 2009 AJCC melanoma staging and classification. J Clin Onc 2009; 27: 6199-6206.
11) Lens MB, Newton-Bishop JA. An association between cutaneous melanoma and non-Hodgkin's lymphoma: pooled analysis of published data with a review. Ann Oncol 2005; 16: 460-465.
12) Crocetti E, Carli P. Risk of second primary cancers, other than melanoma, in an Italian population-based cohort of cutaneous malignant melanoma patients. Eur J Cancer Prev 2004; 13: 33-37.
13) Chu EY, Wanat KA, Miller CJ, Amaravadi RK, Fecher LA, Brose MS, McGettigan S, Giles LR, Schuchter LM, Seykora JT, Rosenbach M. Diverse cutaneous side effects associated with BRAF inhibitor therapy: a clinicopathologic study. J Am Acad Dermatol 2012; 67: 1265-1272.
14) Bataille V. Sun exposure, sunbeds and sunscreens and melanoma. What are the controversies? Curr Oncol Rep 2013; 15: 526-532.
15) Kaskel P, Lange U, Sander S, Huber MA, Utikal J, Leiter U. Ultraviolet exposure and risk of melanoma and basal cell carcinoma in Ulm and Dresden, Germany J. Eur Acad Dermatol Venereol 2014; 29: 134-142.
16) Skotarczak K, Osmola-Ma kowska A, Lodyga M, Po-la ska A, Mazur M, Adamski Z. Photoprotection: facts and controversies. Eur Rev Med Pharmacol Sci 2015; 19: 98-112.

17) Cigna E, Tarallo M, Sorvillo V, Piperno A, Scuderi N. Metatypical carcinoma of the head: a review of 312 cases. Eur Rev Med Pharmacol Sci 2012; 16: 1915-1918.

18) Clerico R, Bottoni U, Paolino G, Ambrifi M, Corsetti P, Devirgiliis V, Calvieri S. Melanoma with unknown primary: report and analysis of 24 patients. Med Oncol 2012; 29: 2978-2984.

19) Kamposioras K, Pentheroudakis G, Pectasides D, Pavlidis N. Malignant melanoma of unknown primary site. To make the long story short. A systematic review of the literature. Crit Rev Oncol Hematol 2011; 78: 112-126.

20) Giuliano AE, Moseley HS, Irie RF, Golub SH, Morton DL. Immunologic aspects of unknown primary melanoma. Surgery 1980; 87: 101-105.

21) Litvak DA, Gupta RK, Yee R, Wanek LA, Ye W, Morton DL. Endogenous immune response to early- and intermediate stage melanoma is correlated with outcomes and is independent of locoregional relapse and standard prognostic factors. J Am Coll Surg 2004; 198: 27-35.