ORIGINAL ARTICLE

UDC: 616-006.81-033.2-07/-08
DOI: 10.2298/VSP131014052K

Clinicopathological characteristics, diagnosis and treatment of melanoma in Serbia – the Melanoma Focus Study

Kliničkopatološke karakteristike, dijagnoza i lečenje melanoma u Srbiji – The *Melanoma Focus* studija

Lidija Kandolf-Sekulović*†, Nada Babović‡, Neven Jokić‡, Mirjana Balić§, Borislava Nikolin‖, Dejan Nikolić¶, Zlata Janjić, Željko Mijušković*†, Milica Rajović† ††, Marijan Novaković † ††, Svetislav Vrbić§, Ivica Pejčić§, Predrag Kovačević‡‡, Dragan Mihajlović§§, Tatjana Roganović‖, Vicko Ferenc‖, Jelena Nikolić**, Marija Marinković‖ ‖, Zorana Bizetić‡**

***Clinic for Dermatovenerology, ††Clinic for Plastic and Reconstructive Surgery, Military Medical Academy, Belgrade Serbia; †Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia; ‡Institute of Oncology and Radiology of Serbia, Belgrade, Serbia; §Clinic for Oncology, ‡‡Clinic for Plastic and Reconstructive Surgery, Clinical Center, Niš, Faculty of Medicine, Niš, Serbia; ‖Institute of Oncology of Vojvodina, Sremska Kamenica, Serbia; ¶University Hospital Medical Center "Bežanijska Kosa", Medical Faculty, University of Belgrade, Belgrade, Serbia; **Clinic for Plastic and Reconstructive Surgery, Clinical Center of Vojvodina, Novi Sad, Serbia; §§Clinical Center Niš, Niš, Serbia; ‖ ‖Clinical Center of Vojvodina, Novi Sad, Serbia**

Abstract

Background/Aim. Treatment options for metastatic melanoma in Serbia are limited due to the lack of newly approved biologic agents and the lack of clinical studies. Also, there is a paucity of data regarding the treatment approaches in different tertiary centers and efficacy of available chemotherapy protocols. The aim of this study was to obtain more detailed data about treatment protocols in Serbia based on structured survey in tertiary oncology centers. **Methods.** Data about the melanoma patients treated in 2011 were analyzed from hospital databases in 6 referent oncology centers in Serbia, based on the structured survey, with the focus on metastatic melanoma patients (unresectable stage IIIC and IV). **Results.** A total of 986 (79–315 in different centers) patients were treated, with 320 (32.45%) newly diagnosed patients. There were 317 patients in stage IIIC/IV, 77/317 aged < 50 years. At the time of diagnosis 47.3% of patients were < 60 years of age (24.2% < 40 years, 23% 50–59 years, 52.6% > 60 years). At initial diagnosis 12.5% of patients were in stage III and 4.5% in stage IV. The most common type was superficial spreading melanoma (50–66%), followed by nodular melanoma (23.5–50%). Apart from the regional and distant lymph node metastases, the most frequent organs involved in stage IV disease were distant skin and soft tissues (12–55%), lungs (19–55.5%), liver (10–60%), and bones (3–10%). The first line therapy in stage IV metastatic melanoma was dacarbazine (DTIC) dimethyl-triazeno-imidozole-carboxamide in 61–93% of the patients, while the second line varied between the centers. Disease control (complete response + partial response + stable disease) was achieved in 25.7% of the patients treated with the first line chemotherapy and 23.1% of the patients treated with the second line therapy, but the duration of response was short, in first-line therapy 6.66 ± 3.36 months (median 6.75 months). More than 90% of patients were treated outside the clinical trials. **Conclusion.** Based on this survey, there is a large unmet need for the new treatment options for metastatic melanoma in Serbia. The development of national guidelines, and greater involvement in international clinical studies could lead to widening of treatment options for this chemotherapy resistant disease.

Key words:
melanoma; diagnosis; neoplasm staging; neoplasm metastasis; therapeutics; clinical protocols.

Apstrakt

Uvod/Cilj. Terapijske mogućnosti za metastatski melanom u Srbiji su ograničene zbog nedostupnosti novoodobrenih bioloških lekova i veoma malog broja multicentričnih internacionalnih kliničkih studija. Takođe, postoji mali broj podataka o terapijskom pristupu metastatskom melanomu u različitim tercijarnim centrima i efikasnosti raspoloživih protokola hemioterapije. Cilj ove studije bio je da se dobiju detaljniji podaci o protokolima lečenja u Srbiji, na osnovu strukturisane ankete u tercijarnim onkološkim centrima. **Metode.** Podaci o obolelima od melanoma, lečenih u 2011. godini u Srbiji, dobi-

Correspondence to: Lidija Kandolf Sekulović, Clinic for Dermatology, Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia. Phone: +381 11 360 85 83. E-mail: lkandolfsekulovic@gmail.com

jeni su i analizirani iz bolničkih baza šest referentnih onkoloških centara u Srbiji, na osnovu strukturisane ankete, sa fokusom na metastatski melanom (inoperabilni stadijum IIIC i IV). **Rezultati.** Ukupno je lečeno 986 (79–315 u različitim centrima) bolesnika, od čega je 320 (32,45%) bilo novodijagnostikovanih. Bilo je 317 bolesnika u stadijumu inoperabilnog melanoma IIIC/IV, 77/317 (24,29%) starosti < 50 godina. U vreme postavljanja dijagnoze 47,3% bolesnika bili su < 60 godina starosti (24,2% < 40 godina, 38% 40–60 godina, 46% > 60 godina). Kod 12,5% bolesnika dijagnoza je postavljena u stadijumu III, a kod 4,5% u stadijumu IV bolesti. Najčešći kliničkopatološki tip bio je površnošireći (50–66%) i nodularni melanom (23,5–50%). Osim regionalnih i udaljenih metastaza limfnih čvorova, najčešće zahvaćeni organi u IV stadijumu bolesti bili su; udaljene metastaze kože i mekih tkiva (12–55%), pluća (19–55,5%), jetra (10–60%) i kosti (3–10%). Prva linija terapije u inoperabilnom stadijumu III i stadijumu IV metastatskog melanoma bio je dakarbazin (dimetril-triazeno-imidazol-karboksamid – DTIC) kod 61–93% bolesnika, dok je druga linija varirala između centara. Kontrola bolesti (kompletan odgovor + parcijalan odgovor + stabilna bolest) ostvarena je kod 25,7% bolesnika lečenih prvom linijom hemioterapije i 23,1% bolesnika sa drugom linijom terapije. Trajanje odgovora bilo je kratko: u prvoj liniji terapije 6,66 ± 3,36 meseci (medijana 6,75 meseci). Više od 90% bolesnika lečeni su van kliničkih studija. **Zaključak.** Ovo istraživanje ukazuje da postoji velika potreba za novim terapijskim opcijama za lečenje metastatskog melanoma u Srbiji. Razvoj nacionalnih smernica i veće učešće u međunarodnim kliničkim studijama može dovesti do proširenja opcije za lečenje ove bolesti otporne na hemioterapiju.

Ključne reči:
melanom; dijagnoza; neoplazme, određivanje stadijuma; neoplazme, metastaze; lečenje; protokoli, klinički.

Introduction

The data about the epidemiology and clinicopathological characteristics of melanoma in South East Europe are scarce, with majority of information obtained from the cancer registries. Based on the Cancer Registry of Central Serbia, crude incidence of melanoma in 2009 was 9.3 in males and 7.7 in females, while age-standardized rate was 5.5 in males and 4.5 *per* 100,000 population [1]. In total, around 500 new cases of melanoma are diagnosed in Serbia annually and the incidence is rising reflecting the same trends noted in the rest of the Europe and the world [1]. However, due to underreporting, the epidemiological registries often contain a lot of missing data, especially on clinicopathological characteristics. Also, there are no data about the standard procedures in melanoma diagnosis and treatment in Serbia so far.

The aim of this study was to obtain more detailed data about demographics, clinicopathological features, diagnostic and treatment protocols in Serbia based on structured survey in tertiary oncology centers.

Methods

Data about the patients with melanoma treated in 2011 were analyzed from hospital databases in 6 referent oncology centers in Serbia, based on the structured survey, with the focus on metastatic melanoma patients (unresectable stage IIIC and IV). The structured survey was approved by Ethics Committees in all the participating centers. The participants answered the survey based on the data from the hospital registries. Survey retrieved data about the number of treated patients, newly diagnosed melanoma cases, age and sex distribution, localization, clinicopathological type, clinical stage at diagnosis. For inoperable stage III and stage IV metastatic disease, treatment protocols, disease control rates [complete response (CR) + partial response (PR) + stable disease (SD)] for 1st or 2nd line therapy and duration of response were analyzed. The standard surgical treatment consisted of excision of melanoma with the margins recommended by European guidelines [2, 3]. Collected data were presented using descriptive statistical analysis.

Results

Based on the data from the structured survey, a total of 986 (79–315 in participating centers) patients were treated, with 320 (32.45%) newly diagnosed patients. There were 877 (92.41%) cutaneous melanoma, 13 (1.37%) mucosal, 24 (2.53%) ocular, 24 (2.53%) unknown primary melanoma, and other and unspecified location, 11 (1.11%) and 37 (3.75%), respectively, because of the unavailability of data in some centers.

The distribution of the patients between the centers is presented in Table 1.

Out of 965 patients treated in 2011 with available data on age, 319 (33%) were < 50 years of age. There were 317 patients in stage IIIC/IV and in this group 77/317 (24.29%) patients were < 50 years of age. At the time of diagnosis 47.3% of the patients were < 60 years of age (24.2% < 40

Table 1

The distribution of the patients diagnosed with melanoma in Serbian tertiary oncology centers

Oncology center	Number of patients (%)
Institute of Oncology and Radiology of Serbia	315 (32)
Military Medical Academy	273 (28)
Clinical Center Nis	129 (13)
Institute of Oncology of Vojvodina	96 (10)
Clinical Center „Bezanijska Kosa“	94 (9.5)
Clinical Center of Vojvodina	79 (8)
Total	986 (100)

years, 23% 50–59 years, 52.6% > 60 years). The age distribution of all the patients and in patients with unresectable stage III and stage IV disease is presented in Figure 1.

The most common type was superficial spreading melanoma (50–66%), followed by nodular melanoma (23.5–50%). The wide range of distribution between clinicopathological types is due to the restrospective nature of the study and lack of predefined criteria for primary and secondary nodular melanoma.

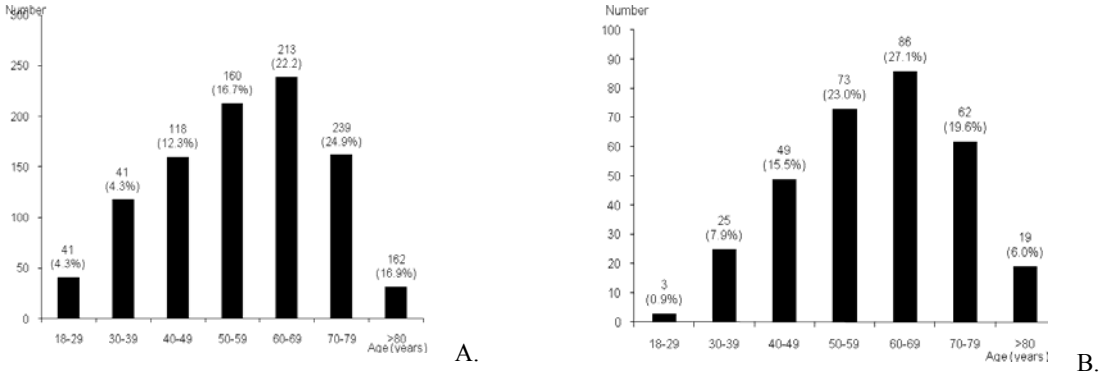

Fig. 1 – Age distribution in: A) All the treated patients; B) The patients with unresectable stage III and stage IV melanoma (Serbia, 2011).

Clinical stage at diagnosis is presented in Figure 2. At initial diagnosis, 12.5% of the patients were in stage III and 4.9% in stage IV. In the patients with localized disease and complete histopathological reports, 232/548 (42.3%) presented with high-risk melanoma, of which 131 (50%) were thicker than 4 mm. Only 17 (3.1%) patients were diagnosed with *in situ* melanoma, and in 217/548 (39.59%) melanoma with Breslow thickness of < 1 mm were noted.

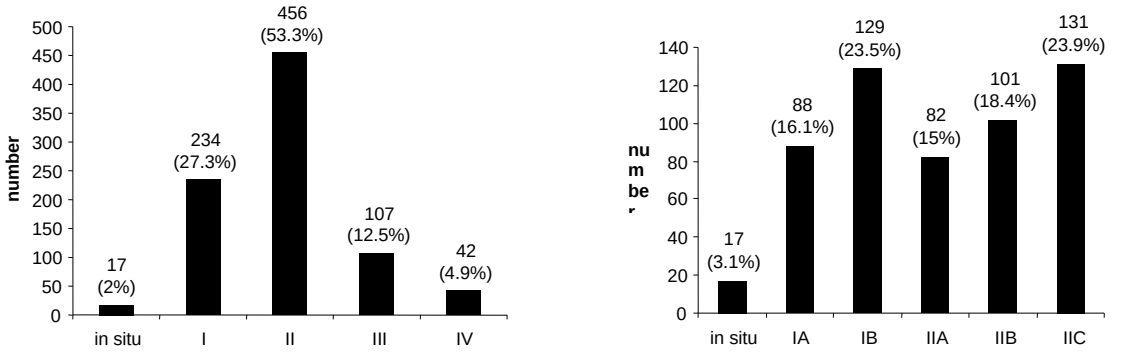

Fig. 2 – Clinical stage at the time of the diagnosis in Serbian melanoma patients treated in 2011.

Apart from the regional and distant lymph node metastases, the most frequent organ involved in stage IV disease were distant skin and soft tissues (12–55%), lungs (19–55.5%), liver (10–60%), and bones (3–10%). Brain metastases were detected in an average of 15.48% of the patients (3.5% at the Military Medical Academy, Belgrade, Serbia, to 25% in the Clinical Center Niš, Niš, Serbia).

The median time to diagnose melanoma from patient referral to the hospital to histopathological analysis was 22 days (21–35 days), and the median time for histopathological analysis from the time of surgery was 8.5 days (7–15 days).

Regarding to surgical treatment, in 4 of 6 centers sentinel lymph node biopsy was available, but is still not the standard surgical treatment for all the patients with indication for this procedure. After complete surgical resection in stage II and stage III melanoma the standard of care was regular follow-up of the patients at 3 month interval. Adjuvant treatment with interferon-α is not reimbursed by the national healthcare provider. The systemic treatment of melanoma in Serbia is based on chemotherapy regimens outside the clinical trials in more than 95% of patients. In 37/317 (11.67%) patients with stage IV disease surgery was performed – in cases with solitary metastases or for palliation.

The first line therapy in unresectable stage III or stage IV metastatic melanoma was administered in 271/312 (86.8%) patients, and complete data about the treatment were available for 171 patients. Dacarbazine (dimethyl-triazeno-imidazole-carboxamide – DTIC) monochemotherapy was most frequently used, in 60.97–93% of the patients in different centers. The second most common first-line chemotherapy regimen was cisplatin-vinblastin-dacarbazine (CVD) in 5–39.1%. In ≤ 5% of the patients cisplatin-dacarbazine was administered as the first line option, and in 2% carboplatin-paclitaxel in only one center. Disease control (CR + PR +

SD) was achieved in 25.7% of the patients treated with the first line chemotherapy; complete response was noted in 3.5%, partial response in 5.3%, stable disease in 17%, and disease progression in 74.3% of patients. Also, the duration of response to chemotherapy was short: in first-line therapy 6.66 ± 3.36 months (median 6.75 months) (Table 2).

Table 2

Systemic treatment of melanoma patients in Serbia, 2011

Parameters	First-line therapy	Second-line therapy
Treated patients, n (%)	271/312 (89.7%)	50/132 (37.8%)
Regimens (%)	DTIC 60.97–93% CVD 5–39.1%. DTIC-CDDP 5% in 2 centers Carboplatin-paclitaxel 2% in 1 center	CVD (5–39.1%) DTIC-CDDP 5% in 2 centers Carboplatin-paclitaxel 30%
Response rates (CR + PR + SD)	ORR 25.7% CR 3.5% PR 5.3% SD 17% PD 74.3%	ORR (CR + PR + SD) 23.1% PD 76.9%
Duration of response (months), $\bar{x} \pm SD$	6.66 ± 3.36	6.75 ± 0.75

DTIC – dimethyl-triazeno-imidazole-carboxamide; CVD – cisplatin, vinblastin, dacarbazine; CDDP – cis-diaminedichloroplatinum; CR – complete response; PR – partial response; SD – stable disease; PD – progresion of disease; ORR – overall response rate.

The second-line therapy was employed in 50 of 132 (37.8%) patients with available data with variable regimens among the centers: dacarbazine based regimens (CVD) 20%, DTIC-cis-diaminedichloroplatinum (CDDP) 80%, vinblastin-bleomycin-cisplatin in 100% of patients in one center and carboplatin-paclitaxel in 30% of patients in another center. Second-line therapy achieved disease control (CR + PR + SD) in 23.1% of patients and this response was also short-lived (6.75 ± 0.75 months) (Table 2).

Discussion

Data about the clinicopathological characteristics and treatment patterns of metastatic melanoma in Serbia are scarce. As far as we know, this survey was the first attempt to form national melanoma data register and to colect data about therapeutical approach to these patients. In this study the basic clinicopathological characteristics and treatment patterns were analyzed based on the data from the structured survey from six tertiary oncology centers in Serbia. In 2011, 986 patients with melanoma were treated, 317 with unresectable stage III and stage IV metastatic disease. The most common type of melanoma was superficial spreading type and nodular melanoma, which is in line with other studies from Europe and US [4–7]. In newly diagnosed patients with localized disease, 234/548 (42.7%) of the patients were presented with high-risk melanoma, of which 131 (50%) were of ≥ 4 mm Breslow thickness (stage IIC). Only 17 (3.1%) patients were diagnosed with *in situ* melanoma, and in 217/548 (39.59%) melanoma with Breslow thickness of < 1 mm was noted. It is in line with previously published data from the single tertiary institution in Serbia, and also the main difference compared with data from Western Europe, USA and Australia, where up to 70% of patients are diagnosed as in situ or thin melanoma [4–7]. This points out to the late diagnosis, and an urgent need for efficient primary and secondary prevention measures. Also, there is a possibility that in this survey a substantial proportion of thin and *in situ* melanomas were not recorded since they were treated in regional centers and private practice. Thus, the central melanoma registry is needed to cover all (or at least the majority) of diagnosed melanoma cases.

The standard surgical treatment of melanoma in all centers consists of excision with the margins up to 2 cm, based on the European guidelines [2, 3]. In 4 of 6 centers sentinel lymph node biopsy is available, but in some institutions it is still not the standard surgical treatment for all patients with indication for this procedure.

In stage IV of the disease, the patients most frequent had distant skin and soft tissues metastases (12–55%), followed by metastatic disease in lungs (19–55.5%), liver (10–60%), brain (3.5–25%) and bones (3–10%). The large differences between centers are attributed to the different structure of the patients in different centers. More relevant data will be available with the establisment of the Central registry of melanoma of Serbia.

In 2011 and until the submission of this article, the only reimbursed treatment for metastatic melanoma by National Insurance Fond in Serbia was dacarbazine (DTIC). It was used as the first-line treatment in 60.97–93% of the patients in the participating centers. In 5 centers monochemotherapy was employed in up to 93% of patients while in one CVD polychemotherapy was used in 39.3% of patients as the first-line option. This points out to the need for the national guidelines and establishment of standard-of-care treatment for metastatic melanoma in Serbia. Concerning the overall systemic treatment patterns in unresectable stage III and stage IV disease, > 95% of patients are treated outside the clinical trials. Having in mind that even now in the era of approved and registered biologic drugs for metastatic melanoma like vemurafenib and ipilimumab, clinical trials remain as one of the first treatment options, large inaccessibility of patients to clinical trials with the new more promising treatments is evident.

Based on the previous studies [8, 9], dacarbazine has an overall response rate of ≤ 20% and complete response rate of 2–3% and this is in line with our data. Even in patients with complete responses, these are rarely durable, 6.6 months in our survey. Similar figures were found in previous studies [8, 9]. Based on the European and US treatment guidelines vindesine, fotemustine, paclitaxel are also indicated as monochemotherapy in first or second-line treatment with similar efficacy [2, 3, 10]. However, vindesine and fotemustine are not registered and paclitaxel is registered but not reimbursed in Serbia. The only second line options is polychemotherapy with dacarbazine and platinum compounds ± vinblastine (CVD), although CVD regimen was found in the previous study not to be effective in second-line setting in patients previosly treated with dacarbazine [11]. This is the reason why in the modern treatment of metastatic melanoma, cytotoxic chemotherapy is largely abandoned as the first-line option, except in much selected cases (BRAF wild-type tumors, ipilimumab-resistant disease and unavailability of clinical studies). In Serbia, it is still the standard of care.

Conclusion

This study revealed a large unmet need for the new diagnostic and treatment options for melanoma, especially for metastatic melanoma in Serbia. The development of the national guidelines, access to novel treatment options and greater participation in international clinical studies could lead to widening of treatment options for this agressive malignant disease.

Acknowledgement

The study was supported by an unrestricted educational grant from Roche Srbija.

R E F E R E N C E S

1. *Miljuš D, Vukičević A, Živković S*. Cancer incidence and mortality in central Serbia (1999–2007) Belgrade: Cancer Registry of Serbia, Institute of Public Health of Serbia "Dr Milan Jovanović-Batut"; 2010.
2. *Dummer R, Hauschild A, Guggenheim M, Keilholz U, Pentheroudakis G*. ESMO Guidelines Working Group. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23(Suppl 7): 86−91.
3. *Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Spatz A,* et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. Eur J Cancer 2012; 48(15): 2375−90.
4. *Lasithiotakis K, Leiter U, Krüger-Krasagakis S, Tosca A, Garbe C*. Comparative analysis of incidence and clinical features of cutaneous malignant melanoma in Crete (Greece) and southern Germany (central Baden-Württemberg). Br J Dermatol 2006; 154(6): 1123−7.
5. *Nagore E, Oliver V, Botella-Estrada R, Moreno-Picot S, Guillén C, Fortea JM*. Clinicopathological analysis of 1571 cutaneous malignant melanomas in Valencia, Spain: factors related to tumour thickness. Acta Derm Venereol 2006; 86(1): 50−6.
6. *de Vries E, Boniol M, Doré JF, Coebergh JW*. Lower incidence rates but thicker melanomas in Eastern Europe before 1992: a comparison with Western Europe. Eur J Cancer 2004; 40(7): 1045−52.
7. *Holterhues C, Hollestein LM, Nijsten T, Koomen ER, Nusselder W, de Vries E*. Burden of disease due to cutaneous melanoma has increased in the Netherlands since 1991. Br J Dermatol 2013; 169(2): 389−97.
8. *Lebbe C, Lorigan P, Ascierto P, Testori A, Bédane C, Middleton M,* et al. Treatment patterns and outcomes among patients diagnosed with unresectable stage III or IV melanoma in Europe: a retrospective, longitudinal survey (MELODY study). Eur J Cancer 2012; 48(17): 3205−14.
9. *Eigentler TK, Caroli UM, Radny P, Garbe C*. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol 2003; 4(12): 748−59.
10. National Comprehensive Cancer Network. NCCN Guidelines. Melanoma v2. 2014. Available from: http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf
11. *Propper DJ, Braybrooke JP, Levitt NC, O'Byrne K, Christodoulos K, Han C*, et al. Phase II study of second-line therapy with DTIC, BCNU, cisplatin and tamoxifen (Dartmouth regimen) chemotherapy in patients with malignant melanoma previously treated with dacarbazine. Br J Cancer 2000; 82(11): 1759−63.

Received on October 14, 2013.
Accepted on March 13, 2014.
On Line-First July, 2014.