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Stage III/IV Melanoma in Poland: epidemiology, standard of care and treatment related costs

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Abstract

Objectives: Melanoma is the most serious type of skin cancer. New methods offering significant benefits for advanced melanoma treatment are needed and in order to assess their cost-effectiveness reliable data on epidemiology, standard of care, adverse events and costs are required. The aim of this project was to collect such information using surveys in Poland.

Methods: A questionnaire focused on the disease characteristics, treatment patterns, health care resources utilization and costs among melanoma patients (stage III/IV) was designed.

Direct medical costs from Polish Public Payer perspective (National Health Found) were computed using data from the survey.

Results: Increase in incidence and mortality rates due to melanoma in subsequent years is observed.

Regardless of the disease stage about ¾ of the patients had a surgical procedure in the past. Among melanoma patients receiving best supportive care, 77.5% received one and 15% received two chemotherapy schemes.

Total yearly cost (including drugs costs, resources used) for 1st, 2nd and 3rd line therapy is respectively 6 522.99 PLN, 12 627.25 PLN and 9 267.39 PLN.

Conclusions: An increase in incidence and mortality rates of melanoma in subsequent years is expected. Costs related to advanced melanoma treatment compared to other oncological indications seem to be moderate. This reflects lack of major advances in melanoma treatment for many years with a steady, high mortality and short survival of patients with advanced disease.

Key words: epidemiology, standard of care, costs of stage III/IV melanoma treatment in Poland

Background and objectives

Melanoma is the most serious type of skin cancer. It is derived from melanocytes localized mainly (90% of cases) in the skin. Rarely it may occur as primary unknown, or localized in mucous membrane of the mouth and genitals or in the eyeball [1]. Being diagnosed at an early stage is curable in many cases (by simple surgical excision). However, at later stages of the disease it is considered fatal and long-term survival relate to few patients [2].

Over the past few decades, a constant, dynamic increase in the incidence of melanoma is observed and the continuation of this trend will cause an increase of morbidity [3]. Therefore, new methods of treatment that may offer significant benefits in treating patients with advanced melanoma are compiled and analysed. In order to assess their cost-effectiveness via pharmacoeconomic modelling data on epidemiology, current standard of care, adverse events and costs are needed. The aim of this study was to collect such information using surveys in major centres in Poland.

Methodology

The results are presented in substantially separate areas (epidemiology, patient care, medical expenses, adverse events) based on the available data. When performing a survey it is always a problem how to standardise the available data and how to handle the missing information, if present. In this study, the following general rules have been applied.

In case when the data were given in several questionnaires, the arithmetic mean was calculated. If the values given by the respondents differed significantly from each other, the range of values was presented in brackets.

The survey included the most important centres in Poland, and the results should be treated as opinions of respondents, not as a result of quantitative estimates of each centre. Due to that reason statistical analysis was not performed. In case the respondents were asked for a structure of patients, and the categories did not sum to 100%, it was assumed a mistake and corrected for – i.e. the percentages were scaled up or down. This scaling was not performed however, if the highlighted categories did not have to be separate or deplete the population, e.g. in determining the percentage of patients who performed various diagnostic procedures.

All the cases in which no answer was given were not included into the analysis. The final analysis was based on a smaller number of surveys then.

In some cases the information could be deduced from answers to several questions in the survey (e.g. in the area relating to standards of care and cost). In this case, the aggregation of data was performed, in effort to select the most reliable and accurate information.

Data sources

This paper presents the results of the analysis of data provided in a survey regarding the standard practice of melanoma treatment in Poland. The survey was conducted in four centres in Poland with slightly different clinical approach to melanoma patients:

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A questionnaire was designed and implemented in MS Excel. The survey questions encompassed: the disease characteristics, current treatment patterns, health care resources utilization and costs among patients diagnosed with melanoma (stage III/IV).

The survey consisted of four sections:

- Epidemiology - included, among others, information on the prevalence of melanoma, severity degree, the presence of BRAF mutation and incidence rates, morbidity and mortality.

• Standards of treatment - included information about the 1st, 2nd and 3rd line of treatment used in each centre, including dosage, frequency of administration and the percentage of patients treated. This section also contained information about the frequency of surgery or palliative radiotherapy.

• Resources costs –in this section costs of melanoma treatment in different lines were included, with special attention paid to costs of performed procedures / diagnostic tests, drugs and the resources used for drugs administration. All information related to the resources used in melanoma treatment was the basis for the final costs calculations which were based on public payer available cost data (NHF).

• Adverse events - a summary of the standards and the cost of adverse events (taking into account the degree of toxicity) occurring during treatment of melanoma.

Cost evaluation

Resources costs and standard of care data for melanoma patients were divided into three therapy lines, and information such as treatment scheme, drug cost and performed diagnostic procedures were collected. The costs of adverse events associated with therapy were also obtained.

Direct medical costs were computed using the data from the presented survey and the unit costs from the Public Payer in Poland (the National Health Found, NHF) [9,10,11,12].

Results

The survey was distributed in four hospitals in Poland covering the majority of advanced melanoma patients being treated; therefore the results can be regarded as a reliable estimate of the current situation in Poland.

Epidemiology

Incidence and mortality rate:

Year	1998	2002	2003	2004	2005	2006	2007	2008	2009	2010
Incidence rate (per 100,000)	4.00	5.21	5.61	5.73	6.26	6.35	6.69	7.06	7.94	8.80
Mortality rate (per 100,000)	2.70	2.30	2.88	2.82	2.80	3.04	3.14	3.27	3.27	3.67

This data indicate a noticeable increase in the incidence and mortality rates in subsequent years. The incidence rate doubles its value about every 10 years. Using a linear trend extrapolation, it is expected that the incidence and mortality rate for year 2012 will amount to about 8.85 and 3.57 respectively (per 100,000).

The prevalence rate for year 2008 is equal to 17.3 per 100,000 inhabitants.

Patients with melanoma stage I and II represent a total of 70% of all patients (respectively 30% and 40%). Roughly 25% of patients are those with stage III, and 5% with stage IV at the time of diagnosis. The proportion of patients with resectable melanoma amounts to 80%. 15% patients have an unresectable stage III melanoma and the remaining 5% are patients – unresectable stage IV.

Standard care for unresectable / metastatic patients:

Since the time of introduction to the clinical practice BRAF-inhibitors, in patients with unresectable disease, the test for the presence of BRAF mutation has been a routinely performed and a positive result of this study has been obtained in 45% of cases.

Among all melanoma patients (regardless the stage), more than ¾ had a surgical procedure in the past. At a certain stage of treatment, palliative surgery is performed in about 14% of patients with non-resectable melanoma. In approximately 21.5% cases, palliative radiotherapy is used along or as a combination with the surgery. All patients with brain and painful bone metastasis received palliative radiotherapy as a standard of care.

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Poland in selected cases with melanoma in transit – the electrochemotherapy was performed.

In cases qualified to the systemic palliative therapy, 77.5% patients received one and 15% - two chemotherapy lines together with best supportive care (BSC). Approximately 49.75% of patients who underwent 1st line and 89% of patients after 2nd line therapy received BSC instead of next line treatment.

1st line therapy:

Approximately 7.5% of these patients did not receive chemotherapy due to poor clinical condition or lack of informed consent.

Treatment scheme

According to clinical experts, about 88.5% (39.5%, 13%) receive 1st line (2nd line, 3rd line) of chemotherapy at one point of their treatment.

	Treatment scheme (drug name)	% of patients treated	Dosage (mg/m^2 per 3 weeks)	Treatment duration (weeks)
1.	DTIC (dacarbazine)	70 (5 - 100)	1 265.63 (937,5 – 2 000)	18.5 (8 – 24)
2.	DDP (cisplatin)	30 (25 - 95)	70 (60 – 80)	21 (18 – 24)
	DTIC		850 (800 – 900)	
	VBL (vinblastine)		6.9 (4,8 – 9)	

2nd line therapy:

	Treatment scheme (drug name)	% of patients treated	Dosage (mg/m2 per 3 weeks)	Treatment duration (weeks)
1.	BLEO (bleomycin)	33.33	33.75	24
	DTIC		900	
	VCR (vincristine)		9	
2.	Carboplatin	24.56	300	21
	Paclitaxel		150	
3.	DTIC	16.67	1000	15
4.	DDP	16.67	56.25	20
	Paclitaxel		202.5	
5.	DDP	8.77	80	18
	DTIC		800	
	VBL		4.8	

3rd line therapy:

	Treatment scheme (drug name)	% of patients treated	Dosage (mg/m2 per 3 weeks)	Treatment duration (weeks)
1.	Carboplatin	50	300	17.5
	Paclitaxel		150	
2.	Paclitaxel	50	300	5

Treatment schemes used in melanoma treatment in Poland (including the percentage of patients applying a particular treatment, average dose and duration of treatment) are presented below.

Melanoma treatment costs

The drug costs were based on data from treatment schemes for each therapy line (see standard care for patients) and on the drug pricing data from the Public Payer in Poland (NHF). When calculating the cost, it was assumed that no patient receives a dose greater than the maximum refunded value.

The costs of resources used for drug administration were calculated by setting the average number (per year) of performances of various resources (one-day hospitalization, overnight hospitalization or ambulatory visit) and their unit cost.

The costs of medical procedures were calculated by estimating the percentage of patients in whom a procedure is used, the frequency of performances (per year) and their unit cost, according to NHF. The following diagnostic procedures were included in estimating: CT scan (computed tomography), X-ray, USG (ultrasonography), laboratory test, MRI, Bone Scintigraphy.

Treatment costs:

	Drug costs (PLN)	Cost of resources used for drug administration (PLN)	Costs of medical procedures (PLN)	Total yearly cost (PLN)
1st line	1 488.14	3 060.72	1 974.13	6 522.99
2nd line	4 361.12	6 292.00	1 974.13	12 627.25
3rd line	2 821.26	4 472.00	1 974.13	9 267.39
TOTAL COST	8 670.52	13 824.72	5 922.39	28 417.63

All costs associated with melanoma treatment in Poland are presented below.

The patient's body surface area was taken as 1.7 m2.

Adverse events costs

The following costs are presented for adverse events that occur most frequently concomitantly/after therapy with DTIC (according to BRIM-3 study [4]). It is expected that in the case of politherapy with DTIC and different drugs, adverse events are similar (although the frequency of particular actions may differ).

Discussion

Data collected from four experts practicing at the leading Polish oncological centres in Poland reviled that in Poland, the treatment of melanoma patients is based on the recommendation of the European Society of Medical Oncology and the Polish Oncological Union.

Adverse event (grade*)	Cost of pharmacotherapy (PLN)	Cost of medical procedures (PLN)	Total cost (PLN)
Arthralgia (grade 3)	113.27	356.65	469.92
Fatigue (grade 3)	n.a.	n.a.	n.a.
Nausea (grade 3)	n.a.	2 860.00	2 860.00
Diarrhea (grade 3)	n.a.	2 860.00	2 860.00
Headache (grade 3)	56.95	142.66	199.61
Vomiting (grade 3)	n.a.	2 860.00	2 860.00
Neutropenia (grade 3)	n.a.	n.a.	n.a.
Neutropenia (grade 4)	1 767.29	4 004.00	5 771.29

* Grade according to Common Terminology Criteria for Adverse Events, CTCAE, version 4.0 [5]
** Cost of medical resources includes: hospitalization, ambulatory visit or skin lesion removal (with histological observation)

Based on data from the Polish Cancer Registry the incidence of melanoma is increasing each year. This is in line with the observed in other European countries trend of incidence of melanoma skin cancer. This phenomenon is linked to specific behaviour: e.g. winter holidays, sun seeking as well, as to improved rates of diagnosis resulting from better detection of melanoma. The risk factors are also acute, irregular and excessive exposure to the sun, mainly during childhood, and the increasing usage of sun beds. Melanoma is more frequent among people in the higher socioeconomic groups and among northern European populations. This is probably due to their higher excessive intermittent exposure to UV radiation combined with a light skin type [6].

The total yearly cost (including cost of drugs, resources used for drugs administration and medical procedures) for the 1st, 2nd and 3rdline therapy is respectively 6 522.99 PLN, 12 627.25 PLN and 9 267.39 PLN.

The highest costs of adverse events are observed for neutropenia grade 4 (5 771.29 PLN).

Recently the new groups of medication have been approved by the FDA to treat patients with late-stage melanoma stage IV or unresectable stage III: ipilimumab in March 2011 and vemurafenib in August 17, 2011. The mechanism of action of ipilimumab is blockade of the CTLA-4 inhibitory signal, and allowing the CTL cells to destroy the cancer cells [7]. BRAF inhibitors such as vemurafenib and dabrafenib produce tumor shrinkage, progression-free and survival time benefits in large proportion of patients. The side effects related to the new drugs are different than those of classical chemotherapy. Ipilimumab treatment has been associated with severe immunological adverse effects due to T cell activation. The most common side effects of BRAF pathway inhibitors are: hyperkeratosis, pyrexia, arthralgia and palmar-plantar erythrodysaesthesia syndrome. Other skin-related toxicities of interest included photosensitivity and squamous cell carcinoma/keratoacanthoma.

Due to high unmet medical need for effective treatment of melanoma Health Technology Assessment (HTA) agencies in some countries already started the assessment of cost – effectiveness for new drugs. Recently in UK NICE have issued a Final Appraisal Determination document with a positive approach to targeted melanoma therapy with vemurafenib, a BRAF inhibitor [8]. Such decisions by HTA agencies will make innovative treatment available for patients.

Conclusions

Increase in the incidence and mortality rates of melanoma in subsequent years is expected;

The drug most commonly used in 1st and 2nd line melanoma treatment is dacarbazine (alone or as a component of a multidrug therapy);

Paclitaxel is the most commonly used medication in case of progression on therapy with dacarbazine.

The overall costs related to advanced melanoma treatment seem to be moderate, compared to other oncological indications. On the other hand, this situation reflects lack of major advances in this treatment for many years with a steady, high mortality and short survival of patients with advanced disease.

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