Cutaneous Melanoma Medicamental Therapy Possibilities in Latvia

ABSTRACT
The incidence of cutaneous melanoma in Latvia has been rapidly increasing, especially during the last decade. The process of melanoma is difficult to predict, also the treatment is hard, because the choice of medicines is not big, and there are no convincing prognosis markers that would allow to successfully choose the most appropriate therapy for every patient. The medicine which is most often mentioned in different countries’ melanoma treatment guidelines is α interferon, but its use is restricted due to the great toxicity and low efficiency of the medicine. In Latvia the patients have one more therapy possibility – virus medicine Rigvir. In the case of metastatic melanoma, the aim of the therapy is to prolong the non-progression period and strive for survival extension, maintaining at the same time proper quality of life. Last year two new medicines were announced in the world for the treatment of metastatic melanoma, one of which at the present time is available in Latvia only for patients who are included in the clinical trial.

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The incidence of melanoma in Latvia has been rapidly increasing during the last decade: from 5,5 per 100 000 people in 2000 to 9,7/ 100 000 people in 2010 (Figure 1).

Women have higher incidence; in 2010 it was 11,25/ 100 000 women. The incidence among men is lower; however, from 2000 to 2010 it has increased more than twice (Figure 2).

During the last decade in Latvia, 160-220 new melanoma cases have been diagnosed annually. In approximately 65% of the cases cutaneous melanoma is diagnosed in Stages I and II. It is not much, considering that cutaneous melanoma is a tumour of visual localisation. Unfortunately, the number of patients with no determined stage of the disease is growing.

The prognosis of melanoma is closely related to the stage of the disease, which depends on tumour thickness, the existence or absence of ulceration, involvement of lymph nodes in the pathological process, and the presence of remote metastases. For Stage I and II patients whose melanoma thickness is less than 1 mm, the 5 year survival is 94-97%.

On average, in thick melanoma cases (thickness according to Breslow 1,01–4,0 mm) the 5-year survival is 68-91%. The survival rates drop if lymph nodes are involved in the pathological process, but in the cases of remote metastases the survival on average is 6-9 months; less than 15% live for three years [1, 2].

Surgery is the main melanoma treatment method which is to be supplemented by medicamental therapy, especially in the cases when the disease has spread to lymph nodes – in Stage III – or if there is high risk of recurrence or metastases according to other prognosis markers. At present, there is no common standard for medicamental treatment of melanoma, the guidelines of various countries recommend different medicines and different doses. There is no common opinion regarding which patients definitely need adjuvant therapy; also there is no golden standard in the cases when medicamental therapy is used. The
situation concerning medium-risk melanoma cases is especially unclear; and it is very difficult in the cases of metastatic melanoma.

The first years after the surgery are important from the prognostic point of view, because it is exactly during those first 3 years after the tumour excision when 80% of metastases or recurrence develop. If melanoma thickness is >1,5 mm and the disease is progressing, it occurs on average 12-16 months after the surgery [3].

According to Cancer-registry data in Latvia, from 2000 to 2008 71,9% of Stage III melanoma patients were treated only surgically, and only 18,9% received interferon (IFN) therapy after the surgery. In Stage IV of the disease almost half of the patients received only symptomatic therapy. Chemotherapy or therapy with IFN (after the surgery or without it) has been used in 13,5% of the cases.

Figure 1

Alpha Interferon

One of the longest and most widely used agents for melanoma adjuvant therapy is α interferon (IFN α). It has antiviral, antiproliferative, and immunomodulatory effect [4].

According to ECOG (The Eastern Cooperative Oncology Group) 1684 research data which included 287 patients with high-risk melanoma, dividing into treatment and control groups and treating with high doses of IFN α 2b (initially four weeks administering 20 million units/ m² in the vein and continuing the therapy with the maintaining dose of 10 million units/ m² subcutaneously 48 weeks more), credible extension of progression-free period (1,7 years compared to 1 year in the control group), and the extension of total survival to 3,8 years compared to 2,8 years in the control group were stated. Nevertheless, the therapy was difficult to tolerate, with many significant side-effects [5]. Even low doses of IFN significantly decrease the quality of life of the patients [6].

IFN α is a recognized therapeutic agent in both Europe and America, but until now its mechanisms of action have not been fully explored [7, 8]. After the meta-analysis of 13 trials, Wheatley (Wheatley et al.) concluded that IFN therapy has a 3% relation to the 5-year survival increase [9].

In Latvia high IFN doses are not used in melanoma therapy.

In many places in Europe the low- and medium-dose IFN therapy is being practiced, although it does not significantly affect the total survival of the patients. Also in Latvia melanoma patients are treated with low and relatively medium doses, but the selection criteria for starting the therapy are not always precisely defined.

The French doctor Grob with 30 years of experience in treating melanoma patients, in the European Association of Dermato-Oncology (EADO) conference which was devoted to melanoma treatment problems and its adjuvant therapy, concluded that the best strategy is early adjuvant therapy – therapy before the detection of macrometastases (J.J. Grob, EADO conference 2011).
Patients with medium-risk melanoma often do not receive medicamental treatment after the surgery. Although ultrasonography may show the lymph nodes as intact, it does not always guarantee good prognosis, because there is lack of information on the presence of micrometastases which are possible to detect in histological tests, although discussions have lately emerged on their relation to the outcome of the disease. However, often the prognosis of the disease is influenced by other, unrecognised factors, therefore the question is topical of starting medicamental therapy for the patients without metastases in the regional lymph nodes.

**Rigvir**

In Latvia patients have the possibility apart from IFN therapy to receive treatment with *ECHO* 7 virus medicine Rigvir which is registered for the prophylaxis of melanoma metastases and recurrence as well as for the local therapy of cutaneous and subcutaneous metastases. In Latvia the medicine *Rigvir* was registered in 2004, and starting from 2005 it was introduced in the clinical practice. Then there was a break in the manufacturing, and since July, 2008 it is available in the practice constantly. Since July, 2011 *Rigvir* is included in the list of compensated medicines.

*Rigvir* selectively affects the cells of a sensitive tumour and, inducing specific immunity to itself, activates the cells of the immune system. The cytolytic function is selective - it refers only to malignant cells, excluding the damage of healthy tissue cells. *Rigvir* incites the emergence (expression) of tumor-associated differentiation antigens on the surface of non-lysed malignant cells and suppresses MAGE – the expression of melanoma-associated antigens which are associated with the progressive growth of melanoma. The altered surface structures of malignant cells turn into the target structures for cytotoxic mechanisms of the immune system. [14].

The idea of using viruses in antitumour therapy is old around the world – one of the first reports on the response reaction of a tumour to an oncolytic virus is dated with 1896, and Dock has described it in *Am J Med Sci* in 1904 [10]. Presently in the sphere of oncolytic viruses active work is being done by the Australian company *Viralytics*, carrying out clinical trials with the agent *CAVITAK (Coxsackievirus A21)* also on melanoma patients [11].

Further on we would like to demonstrate some results obtained in retrospective in the data analysis of those patients who had received virotherapy with *Rigvir* from 2008 to 2011.

**Retrospective Data Analysis on the Use of Rigvir**

It has to be emphasised that the data analysed were not obtained in a clinical trial or observation. The data analysed was retrospective and obtained from records that were made in the ambulatory patient cards during daily work. The data and patients have not been especially selected; the information recorded was the one found in the ambulatory patient cards. For that reason it is impossible to trace the survival of the patients, also the duration of the observation cannot be standardized.

The division into stages corresponds to the records in the ambulatory patient cards, but those do not always correspond to 2002 or 2010 American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) melanoma classification. Some data is missing on the presence or absence of ulceration, the test of sentinel nodes is made rarely. Due to those reasons the determined stage may not correspond to the actual stage (cases are possible when the actual stage is higher). Such inaccuracies may influence the interpretation of the summarized data.

The analysed data was on the use of *Rigvir* in cutaneous melanoma therapy in RAKUS LOC, Piejūras hospital Oncology Clinic in the city of Liepāja, and in Latvian Virotherapy center.

298 ambulatory patient cards were available of patients who had been operated due to cutaneous melanoma. After the surgery, the therapy with *Rigvir* was received by 116 patients (38,9%), 97 patients (32,6%) were observed dynamically, and 85 patients (28,5%) received other type of therapy.

Further on, 174 ambulatory patient cards were analysed; they were Stage I-III patients who had received virotherapy (99 patients) or were observed dynamically (75 patients). The division of the patients in stages: Stage I: in *Rigvir* group – 46 patients, in the control group –
Stage II: in Rigvir group – 44 patients, in the control group – 36; and Stage III: in Rigvir group – 9 patients, in the control group – 8. The period of data analysis: from 1 January, 2008 to 1 February, 2012.

Methods of Statistical Analysis

In the data analysis the survival analysis methods were used. The observation period for all patients started on the date when the surgery was made. The dependent variable was the time until the progression of the disease (the disease-free time interval), by that understanding the date of diagnosing metastases or recurrence of the disease. For the patients who did not develop metastases and did not have recurrence during the time period of the observation, the participation in the research was finished (the observation was censured) on the date of the last visit recorded in the medical documents. The analysis was performed in the sub-groups depending on the stage of the disease.

The disease-free time among the patients who received Rigvir in therapy and among the patients who did not receive medicamental therapy after the surgery, was calculated with the Kaplan-Meier method, and the difference in the survival was tested with the logrank test. The Cox regression analysis was used to calculate the relationship of the disease progression threats (relationship of risk (HR) with 95% credibility interval).

Results

For Stage II melanoma patients the disease-free time interval statistically credibly differed between the two analysed groups in favour of those who received therapy with Rigvir (Figure 3).

Analysing the predicted disease-free interval according to melanoma Breslow depth if it was ≤ 4,0 mm, the patients who received virotherapy with Rigvir (n=77) had better chances to live without metastases or recurrence than the patients who were only observed (n=58). In the high-risk melanoma group (melanoma thickness ≥ 4,01 mm) HR=37 and p < 0,056. The number of patients in the Rigvir group was 20, and in the dynamically observed group – 25.

The actual disease-free period was also summarised during the individual observation course for every specific patient included in the retrospective analysis. The patients were divided in groups by the stage of the disease and type of the therapy. Figures 4 and 5 illustrate the course of the disease described in the retrospective analysis for Stage II cutaneous melanoma patients: in the group of patients treated with Rigvir the progression of the disease was determined in 6 out of 44 patients during the observation time. In the dynamically observed group of Stage II patients, which was available for the retrospective analysis, 21 out of 36 patients developed recurrence of the disease or metastases.

The good tolerance of the medicine Rigvir definitely has to be emphasised, because none of the studied ambulatory patient cards had any records of caused significant side-effects, intolerance of the medicine, or the termination of the therapy due to toxicity.

Metastatic Melanoma Therapy

The treatment of melanoma patients in the situations when remote metastases have developed is very problematic. If any standard agent can be discussed at all, it is the long known dacarbazine. NCCN (National Comprehensive Cancer Network) guidelines in the USA advise also temazolomide, high doses of interleikin-2, paclitaxel with or without carboplatin [12]. The response reaction, treating with dacarbazine is 8-20%, full response reaction is observed in approximately 5% of the cases, and it is short-term (4-6 months) [13]. In Latvia dacarbazine has been used comparatively rarely in the last years, but sometimes other combinations of chemotherapy drugs are used; nevertheless, the majority of the patients receive symptomatic or life quality improving therapy.
HR=0.15, 95% CI, p < 0.001

Figure 3. Kaplan-Meier Estimates of Progression-free Survival (stage II).

Figure 4. The time of follow-up and time to disease progression in Stage II melanoma patients treated with Rigvir

In 2011 it was widely reported of two new, effective medicines for metastatic melanoma therapy – vemurafenib and ipilimumab, which by now have already been introduced in the clinical practice and NCCN guidelines. Latvian oncologists and dermatologists are now participating in a clinical trial with vemurafenib which is effective for patients whose melanoma cells contain a mutation in codon 600 of BRAF gene.

Melanoma treatment is difficult in any of its stages, because the course of the disease is hard to predict, and there are no clear selection criteria and prognostic markers regarding the choice of the therapy.

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