Digest of scientific - practical seminar with international participation

"Melanoma of Skin: achievements and prospects" 12 of April 2013, Kyiv

Summary:

On April 12, 2013 it was scientific - practical seminar with international participation "Melanoma Skin: Achievements and Prospects", which was considered the most important issues related to melanoma and skin cancer. Worldwide it's observed the incidence' increasing of skin cancer, unfortunately, this trend is observed in Ukraine too. Therefore, the relevance of this seminar is long overdue. The speakers presented data of the problem's condition and made an overview of modern diagnostic and therapeutic methods. The seminar attracted the attention of oncologists, dermatologists and chemotherapeutists, which directly faced with this problem every day.

Keywords: melanoma , skin cancer, diagnosis, treatment, seminar.

Since the 70s of last century the problem of malignant tumors of the skin pigment has increasingly become a subject of research. International symposia and conferences devoted exclusively to this disease are initiated, STI Profile - cancer clinics are created.

The conference devoted to the problems of skin tumors are produced in Ukraine for the first time, and I must say that the necessity of such forum is long overdue.

The conference was opened by **MD S.I. Korovin** (the Head of Science - Research Branch of the skin and soft tissues tumors of the National Cancer Institute (Kyiv, Ukraine)) with the report "Melanoma Skin: state of the problem in Ukraine", in which is described the general situation of the morbidity of skin cancer in the Ukraine. Over last 10 years it was marked the increasing of the morbidity of non-melanoma skin cancers by 16.1%, and skin melanoma by 36%.The morbidity of non-melanoma and melanoma skin cancers in 2010 was respectively 42,3 and 6,7 per 100 thousand population.The speaker also noted a similar situation in the global medical practice, due to factors such

as increased ultraviolet loading and the migration of population, what allowed to settle entire continents by races are not evolutionarily adapted to high solar activity.

According to the statistical analysis of the 1998-2008 years among non-melanoma skin cancers basal cell carcinoma predominants (71%); second place squamous cell carcinoma followes (19,9%). In most patients with skin's bazalioma (91,6%) it is determined I-II stages of disease, and only in 0,55% cases is observed distant metastases; survival median in the generalized form of the disease is 8-14 months. 2011 was celebrated by breakthrough in targeted therapy in dermatoonkology. In particular for the treatment of metastatic and locally-widespread basal cell carcinoma was reported drug Erivedge (Vismodegib), which showed 58% objective answers.

The most dermatoonkologist's attention melanoma skin is attracted, which by incidence occupies the 16th place among all malignancies in our country, and in rate of increase in incidence is the leader (+5,4% per year). Average cumulative 5-years survival of melanoma patients in our country is 48,5%.

According to the meta-analysis (Hui S.K., Wong T.W.) all countries of the world are divided into four categories based on mortality rates of patients with melanoma (case fatality ratio, CFR = percentage of deaths's number per year from melanoma to number of newly diagnosed cases of melanoma by year). 1st - (CFR <20%): North America, Australia, New Zealand; 2nd - (CFR 20-30%): Western Europe; 3rd - (CFR 30-50%): South and Central America , Eastern Europe, Western Asia; 4th - (CFR> 50%): Asia and Africa. In 2008, in Ukraine there were found 2731 new cases of melanoma and 1075 our citizens died, so CFR was in 39,3%. At the same time, according to statistics from 2000 to 2011 it was marked the decrease of this index by 8,7%.

B.V.Litvinenko (the chief doctor of the universal dermatological clinics Euroderm, (Kyiv, Ukraine)) with report "Dermatoscopy in the diagnosis of melanoma: the role and significance", continued seminar, highlighted dermatoscopy as a new step in the early detection of skin cancers. The speaker gave statistics, according which the

diagnosis of melanoma with the use a conventional visual examination and clinical ABCD rule are unreliable in every 3rd case.

Dermatoscopy is relatively young method of diagnosis, which over last 10 years rapidly developing, as evidenced by the number of publications have increased almost 10 times during this period. It was briefly reviewed the history of development of this method, particularly it was noticed the latest achievement of this direction - Digital dermatoskopic systems with a central server. This technology was approved by the FDA in September 2011, based on peer review over 100,000 verified cases and has the ability to direct comparison with the global dermatoskopic database.

The most interesting from a practical point of view is using of digital dermatoskopic systems, what allows to make a photo documents, creates mole's maps and conducts basic analysis of geometry images. Method of using is based on 2 step method: digital photography entire body, followed by digital dermatoscopy individual tumors. These systems improved the level of diagnostic accuracy in the evaluation of pigmented lesions on the skin on more than 40%, and the sensitivity and specificity on 6% and 19% respectively. In addition, digital dynamic monitoring of pigment formation "fuzzy behavior" greatly improves control over them.

M.M. Kukushkina (the scientific - research department of skin's tumors and soft tissues of the National Cancer Institute (Kyiv, Ukraine)) presented a report about the biopsy of patrol lymphatic node in skin's melanoma. Lymphotropic color, radionuclide techniques and their combination are used for their identification. In cases of primary tumor localization near the regional lymphatic collector (for example, melanoma of scalp and neck) it's invaluable the intraoperative using of 3D visualization and navigation in the searching of the guard lymph nodes.

The prognostic significance for the occurrence of micrometastases in regional lymph nodes have thickness of tumor by Breslow more than 1.0 mm, tumor ulceration, level of invasion according to Clark IV-V, the young age of the patient, mitotic index>

0, absence of tumor - infiltrating lymphocytes, male sex of the patient and regression of the primary tumor.

The prognostic significance of guard lymph node's biopsy in melanoma skin is proved in result of research Multicenter Selective Lymphadenectomy Trial-I (MSLT-I): overall 5-year survival of patients with micrometastases in guard lymph nodes amounted 72,3 ± 4,6%, and without micrometastases - 90,2 ± 1,3%. The research found a significant increase in 5-year disease-free survival among patients who were underwent biopsy of guard lymph nodes, compared with patients who were underwent only wide excision of the tumor: it was 78,3% and 73,1% respectively. At the same time, the overall 5-year survival rate was the same: 87,1% and 86,6% respectively.

The further analysis of the survey results MSLT-I became interesting, according to which among patients are subjected to observation with delayed regional lymph dissection, clinical metastases were observed in 25% less than among patients with micrometastases, which were defined by guard lymph node's biopsy. That is, in some patients with micrometastases in guard lymph nodes is no further progression of the disease with the macro metastases's development.These guard lymph nodes are called false-positive.

The question of the necessity for regional lymph dissection after detecting micrometastases in guard lymph nodes is opened.Therefore, in 2004, the second multicenter study MSLT-II started, during which patients with micrometastases of melanoma skin are randomized into 2 groups: in first group to patients are performed an urgent regional lymph dissection, and in the second the patients are observed with using ultrasound regional lymphatic collector.

To resolve this issues the staff at the National Cancer Institute are working, who proposed the original study design in which the patients with local melanoma skin are randomized into 2 groups: in first are carried out a wide excision of skin tumor with a

“guard” lymph node’s biopsy, and in second - only wide excision of the primary tumor. It is planned to investigate indicators of disease-free and overall survival in both groups.

K.M. Khobzey (the dermatologist of universal dermatological clinic Euroderm, (Kyiv, Ukraine)) made a report "Sunscreens: Myths and Reality", dedicated to the primary prevention of melanoma, which is to limit the sunbathing’s reception and tanning salons, to avoid insolation from 10:00 to 16:00; protect the skin from UV radiation; the using of closed wear and sunscreen; periodic visiting to the dermatologist for follow-up.The speaker noted that in 2009 the International Agency for Research on Cancer of the World Health Organization concluded about the carcinogenic effect to humans of sunbeds and translated it into a higher risk category for cancer, as in most countries there were imposed restrictions on using of tanning beds in childish and young age.

Particular attention the repoter devoted to the sunscreens’s application as one of the stages of prevention of melanoma and skin cancer. The basic principles of their using include: using sunscreen with SPF 30-50; compliance the correct dose per unit area (2mg/sm) for 15 to 30 minutes exposition; proper frequency of application (every 2 hours during sun exposure, and immediately after swimming or excessive sweating), using additional protective equipment (long pants, skirts, shirts / blouses with long sleeves, a hat with a wide brim and sunglasses).

Professor E.N. Imyanitov (the head of tumor growth’s biology from Scientific Research Institute of Oncology M.M.Petrova (St. Petersburg, Russia)) spoke about "Laboratory studies of the skin’s tumors," in which he recalled the following features immunogenicity of melanoma as lymphocytic infiltration, the antibodies excavation, cases of spontaneous regression, the occurrence of melanoma in the donor site to the recipient and efficacy of immunomodulators in the treatment of melanoma, indicating a violation of the structure at the molecular - genetic level and requires the development of diagnostics in this direction.

Speaker carefully outlined the mechanism of gene specific signals of tumor cells, including BRAF signal. There were presented data on the genes mutations depending on the location of melanoma: it is proved that with the melanoma skin of areas without chronic sun damage in 50% of cases are observed BRAF-mutation, and 20% - NRAS-mutations, whereas in melanoma skin of areas with chronic sun damage are observed BRAF-and NRAS-mutations in 10% of cases. These data allow the development of targeted therapy.

To determine the BRAF-mutation is using allele-specific polymerase chain reaction in real time and DNA sequencing, ie determining its nucleotide sequence.

In 2011, the FDA reported inhibitor of BRAF-mutation – vemurofenib, that caused an objective response in 53% of patients, who received treatment for unresectable or metastatic melanoma before, with the median duration of response was 6,7 months.

Professor I.Y. Halaichuk (the head of oncology, radiation diagnosis and therapy department and radiation medicine of Ternopil State Medical University I. Gorbachevskogo) considered the topic "The problems of interferon and radiation therapy in patients with melanoma skin". The speaker recalled that interferons belong to a class of cytokines, they activate immune cells (natural killer cells and macrophages) and promote recognition of tumor cells by regulating antigen presentation of T-lymphocytes.

The author said that by meta-analysis the results of treatment 6067 patients with high-risk melanoma skin, conducted in 2008, it was found that adjuvant interferon therapy reduces the risk of the recurrence, improves overall survival, but the absolute benefit is small and accounts for only 3-5%.

In 2010 there were published the results of a comparative study on the using of low-dose interferon for 18 and 60 months, in which has not been proven advantage in prolonged regimens.

In 2012 the research results ECOG 18991were reported, in which patients with III stage of disease were divided into 2 groups: in the study group patients received long-acting interferon, and control subjected to monitoring. As the result of analysis there were found that adjuvant therapy with interferon of prolonged action slightly reduces the relative risk of death. Moreover, the effect of interferon therapy is higher in the presence of ulceration of the primary tumor and micrometastases in regional lymph nodes.

One of the most interesting questions of interferon therapy is using it in high doses. Back in 1996, J.Kirkwood presented the results of a study that showed a significant excess in disease-free and overall survival among patients that were treated with high interferon therapy. Unfortunately the results of these studies have not been confirmed by others.

PhD Y. Shparyk (the head of the chemotherapy department of Lviv national oncology regional treatment-diagnosis center (Lviv, Ukraine)) highlighted the theme "Chemotherapy of melanoma". Despite the fact that the history of melanoma chemotherapy began with the 1970s, convincing positive results in cytostatic treatment until recently has not been achieved.The standard chemotherapeutic treatment of generalized skin melanoma is dacarbazine monochemotherapy, despite the fact that no study did not prove the efficiency of dacarbazine compared with placebo. Moreover, the efficiency of treatment doesn't depend on the input mode (850 - 1000 mg / m^2 / day on 1 day or 250 mg / m^2 / day on 1-5 days) and amounts 10-20%. The using of different chemotherapy schemes (such as the so-called Dartmudskiy mode) or chemo-immunotherapy with using interferon and interleukin did not show advantages over monochemotherapy of dacarbazine. Most sensitive to dacarbazine treatment is

metastasis to the skin, the subcutaneous tissue, the lymph nodes and the lungs. With metastases to the brain the drug of choice remains temozolamid, that penetrates the blood-brain barrier.

2011 was named the year of melanoma by president of ASCO George Sledge in connection with FDA approval ipilimumab and vemurafenib, and perhaps the combination of these drugs is the most promising today.

Prof. L.V. Demidov continued the theme treatment of melanoma with the report "Metastatic melanoma: the main direction of therapy in recent years" (the head biotherapy department RCRC RAMS (Moscow, Russia)), who presented data on the using of vaccine therapy. In particular, it was stressed about the importance of HLA-typing when using vaccines Melacine (allogeneic melanoma cell lysate): in the study SWOG-9035 among patients are expressing two or more antigens with "five" Mitchell (HLA-A2, HLA-A28, HLA-B44, HLA-B45, HLA-C3), it is marked the increasing in 5-year disease-free survival by 24% compared with patients are subjected the observation; but if there was 0-1 antigen expression, the results of treatment in both groups were similar.

Randomized research of III phase to equalize performance dacarbazine with autologous dendritic vaccine as a first-line therapy for metastatic skin melanoma didn’t show advantage in the using of vaccine. In a randomized reaserch of III phase with the using of autologous vaccine based on heat shock proteins HSPPC-96 there was shown the efficiency of vaccine therapy only with metastases in the skin and the soft tissues.

The biggest breakthrough in vaccinotherapy is observed, when using antigen specific antitumor immunotherapy, directed exclusively to cells that carry specific antigen. During the treatment all the known levels of antitumor immunity are involved and immune system are "learnt" to fight with tumor cells.

An absolute breakthrough in immunotherapy of melanoma is the using of ipilimumab - monoclonal antibody blocking antigen cytotoxic T-lymphocytes-4 (CTLA-4).The drug stimulates intensive proliferation of T-cells and is a kind of non-specific immunotherapy. Ipilimumab was approved by the FDA for the treatment of unresectable or metastatic melanoma in 2011 based on research MDX010-20. In this study, patients with generalized skin melanoma were randomized into 3 groups: one received ipilimumab, the second - gp100 peptide vaccine, the third - both drugs. An objective response was observed in 10,9% of patients are treated with ipilimumab, 1,5% - in the group receiving the vaccine and 5.7% - in the group receiving both drugs. Thus in some patients there was a progression of the disease on a background of therapy with ipilimumab followed by regression. More impressive there were the survival rates of patients are treated with ipilimumab: 1-year survival was 46% and 2-year was 24%. In the treatment it was noted a clear correlation between the occurrence of autoimmune side effects (vitiligo, autoimmune colitis, hepatitis, hipofizyt) and tumor response to treatment.

The report "Vemurafenib: the data of clinical research and personal experience" was made by professor Axel Hauschild ((Kiel, Germany)). The reporter brought to the attention of the audience that in Germany until 2011 the main treatment of generalized melanoma was monotherapy with dacarbazine, temodal and fotemustyn or polychemotherapy with carboplatin and paclitaxel. One of the most promising areas of generalized skin melanoma’s treatment is using the targeted agents, due to a variety of gene mutations. In 40-60% cases the skin melanoma is associated with BRAF mutations, which cause constitutive activation of downstream signals by the MAPK way. About 90% of these mutations lead to the replacement of glutamate for valine at codon 600 (BRAF V600E); it is known and other activating mutations (eg, BRAF V600K, BRAF V600R).

In August 2011 after multicenter randomized phase III FDA has approved a new targeted agents – the inhibitor BRAF gene, for the treatment of unresectable or

metastatic melanoma with a mutation of the BRAF V600E gene. In the research of the phase I the objective response was achieved in 81% patients (2 full regressions, 24 partial regressions). In the research of the phase II involving patients who had received prior treatment for melanoma with a mutation of BRAF V600E, the objective response was obtained in 53% of cases, the median duration of response was 6,7 months. In the research of Phase III in patients with previously untreated unresectable melanoma of stage IIIC or stage IV with BRAF V600E mutation vemurafenib was associated with a relative reduction in the risk of death by 63% and the risk of tumor progression by 74% compared with dacarbazine. In this case, the median of progression-free survival with vemurafenib was 6,9 months, in the introduction of dacarbazine – 1,6 months; and median overall survival respectively was 13,6 and 9,7 months.

The most frequent complications of vemurafenib therapy were skin manifestations (rash, photosensitivity, hyperkeratosis, changes in the structure of hair and alopecia), arthralgia, weakness. Note that in 20-30% of patients during treatment keratoakantoma and squamous cell skin cancer was appeared, in addition among 468 patients, who participated in the research phase II-III there were found 8 cases of the new melanoma.

Unfortunately, shortly after tumor regression during treatment with vemurafenib in most cases there is further progression of the disease. One of the possible ways to overcome vemurafenib resistance is its combined using with MEK inhibitor.

Professor Litus O.I. (the main freelance dermatologist of MoHP Ukraine (Kyiv, Ukraine)) reported about the prospects of dermatoonkology's development in Ukraine. The speaker stressed that skin tumors today account for 39,5% of tumors's total number. "Sticking points" of dermatoonkology development in Ukraine are the lack of funding, the lack of health care and education reform in Ukraine, the presence of interdisciplinary competition instead of cooperation, the lack of a systematic approach in solving the patients's problems, the lack of clear protocols for diagnosis and treatment in dermatoonkology, the poorly organized supply of statistics for diagnosed cases of skin cancer at the regional and national levels, the lack of awareness and culture of the

population. It was suggested the introduction of 3 level interdisciplinary approach and "route of patient". The speaker announced the next steps, which include carrying out the action "The week of diagnosis the skin cancer" (May 13-19, 2013), within the framework of it will be "The day of diagnosis the skin melanoma " on May 17, 2013 under the auspices of the international organization Euromelanoma.