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**A SUMMARY OF PRESENTATIONS**

**NOVEL MOLECULAR TARGETS IN MELANOCYTIC NEOPLASIA**

Dr. Boris Bastian, Professor of Dermatology and Pathology at the University of California in San Francisco, provided the opening keynote at the conference. He and his team were instrumental in developing the genetic map of the different melanoma types. As he published in *NEJM* in 2005, different melanomas have different mutations, according to their clinical phenotypes and presentation. The four main types of melanoma are:

- **Superficial spreading melanoma**, which usually appears on the trunk and limbs in patients with many nevi; the most common mutation found in these melanomas is BRAF (v-raf murine sarcoma viral oncogene homolog B1).
- **Lentigo maligna melanoma** appears on the face and usually does not harbour the BRAF mutation. Some of them have KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) or NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) mutations.
- **Acral melanoma** is found usually on the hands and feet and can also sometimes have the KIT mutation.
- **Mucosal melanoma** can have either KIT or NRAS mutation.

Dr. Bastian reviewed the prevalence of these mutations and noted the fact that in most melanomas, various UV signature mutations are apparent.

He also presented new information about ocular melanoma. In his recent work, he has found that ocular melanoma does not harbour the same mutations as skin melanoma, but may have GNAQ (guanine nucleotide binding protein [G protein], q polypeptide) mutations. We now require markers for those mutations, and Dr. Bastian updated the conference on his team’s efforts to better delineate these. GNA-11 (guanine nucleotide binding protein, alpha 11) is one target he is trying to find. This work may help to find new molecules to block those mutations and treat metastatic ocular melanoma.

**SPINDLE CELL MELANOIMA**

Dr. Sébastien Labonté, Pathologist, Hôpital Hôtel Dieu de Québec, decided this year to present on a rare form of melanoma, called spindle cell melanoma. Most melanomas are of the epithelial type and are easier to differentiate, but desmoplastic melanomas often resemble fibroblasts or stroma-type cells and are therefore harder to diagnose and delineate. This becomes a problem when it comes time to evaluate the margins of the melanoma and presents a surgical challenge.

Great care is required in the pathologic diagnosis of these desmoplastic melanomas — especially if they are recurrent — because the cells tend to look like scars. Dr. Labonté suggests that the use of immunohistochemical stains like S1000 and HMV45 may help to differentiate desmoplastic melanomas from scars.

**MERKEL CELL CARCINOMA**

Dr. Nathalie Zeitouni, Chief of Dermatologic Surgery at the University of Buffalo, provided an overview of the situation with Merkel cell carcinoma, which we are seeing with increasing frequency in our practices.

Merkel cell carcinoma can be hard to diagnose. It is a small cell tumour that can look like small cell lung cancer. In the past few years, the literature has revealed an association between Merkel cell carcinoma and the polyoma virus. Monitoring the evolution of Merkel cell carcinoma usually requires imaging studies, most often with PET scan, which is also used for presurgical evaluation.

The standard of care involves sentinel lymph node biopsy and, in surgery, generally a 2 cm surgical margin and adjuvant radiotherapy on the surgical site. If a positive sentinel lymph node is obtained, there is still a debate over whether the patient should be treated with complete lymph node dissection alone, radiotherapy of the lymphatic basin alone, or a combination of lymph node dissection and adjuvant radiotherapy on the lymph node basin.

Merkel cell carcinoma is a changeable tumour and diagnosis requires a high degree of clinical suspicion. Pathologic examination and a special stain can improve diagnosis.

**LESS COMMON MELANOMAS**

Dr. Ezekiel Weis, from the Department of Ophthalmology at the University of Alberta, presented on diagnostic and therapeutic approaches to uveal melanoma, a rare and less well-known form of melanoma.

Dr. Tom Salopek, Director of Dermatology at the University of Alberta, presented on diagnostic and therapeutic approaches to the management of melanoma in situ of the lentigo maligna type, specially the modified Mohs technique and the so-called spaghetti technique.

Dr. Luc Thomas, Chairman of the Department of Dermatology at the Centre hospitalier Lyon Sud in France, is a world expert in the diagnosis of acral melanoma, which presents on either the nail or palms and soles. He reviewed the literature and clinical experience with various surgical approaches to the management of melanoma in situ of the lentigo maligna type, specially the modified Mohs technique and the so-called spaghetti technique.
**SENTINEL NODE BIOPSY**

**Dr. Merrick Ross**, a surgical oncologist at the University of Texas MD Anderson Cancer Center, and **Dr. Vern Sondak**, Chair of the Department of Cutaneous Oncology at the Moffitt Cancer Center, reviewed the importance of sentinel lymph node (SLN) biopsy in the management of patients with intermediate and thick melanomas. They recommended SLN biopsy for Breslow thickness above 1 mm, and in the presence of ulceration. For thinner melanomas, between 0.75 mm and 1 mm, they recommend SLN biopsy if there are signs of severity such as high mitotic rate or microulceration.

ASCO/SSO guidelines on SLN biopsy in melanoma are based on limited literature. Only one randomized clinical trial, the Multicenter Lymphadenectomy Trial I (MLST-1), has addressed whether patients with melanoma managed using SLN biopsy have better clinical outcomes than those managed any other way. ASCO/SSO guidelines recommend against routine SLN biopsy in small (<1 mm) tumours, and Drs. Ross and Sondak’s presentations supported this approach.

For melanoma above 4 mm, SLN biopsy is still recommended, but more for staging purposes and to facilitate regional disease control.

**STAGE-SPECIFIC MELANOMA**

**Dr. Ross** and **Dr. Carman Giacomantonio**, a surgical oncologist at Dalhousie University, covered the subject of local and in-transit metastases and reviewed the various options for management. These include intraluminal interleukin 2 injection, limb infusion or perfusion with melphalan. Further options are under development, including talimogene laherparepvec (T-VEC), which is a new vaccine, velimogene aliplasmid (Allovecin, for which phase III studies have been completed), and 10% Rose Bengal (PV-10, which has completed phase II studies).

**Dr. Steven O’Day**, a medical oncologist and Director of the Los Angeles Skin Cancer Institute at Beverly Hills Cancer Center, and **Dr. Michael Smylie**, medical oncologist at the Cross Cancer Institute, reviewed the treatment of metastatic melanoma. They pointed to the importance of immunotherapy with ipilimumab and presented treatment algorithms to manage the immune side effects of this therapy.

**Dr. Teresa Petrella**, a medical oncologist at Sunnybrook’s Odette Cancer Centre, presented a phase III multicentre trial of paclitaxel vs dacarbazine in 514 chemotherapy naive patients with stage IV cutaneous metastatic disease, but without current brain metastases. The primary endpoint was PFS validated by blinded radiology, and results showed paclitaxel to be superior to dacarbazine in this group.

**MOLECULAR PATHOLOGY OF MELANOMA**

**Dr. Alan Spatz**, Professor of Pathology and Oncology at McGill University, reviewed the importance of collaboration with pathology labs in the diagnosis of genetic markers as we enter the era of targeted therapies for melanoma. It is very important to use the most competent pathologic labs to find the various mutations — BRAF, KIT and NRAS — that are clinically important in the treatment of these patients with metastatic disease.

**Dr. Spatz** presented the situation with regards to BRAF testing in Canada and explained that in the near future we will have immunohistochemical detection of BRAF V600E mutation, which will be faster to obtain than the genetic testing we are doing right now.

**THE BRAF MUTATION**

Targeted BRAF inhibition is the main approach to the treatment of patients with metastatic melanoma with the BRAF mutation. This area was reviewed in detail by **Dr. Igor Puzanov**, a hematologist/oncologist from the Vanderbilt-Ingram Cancer Center. He examined the use of the BRAF inhibitors vemurafenib and dabrafenib. In future, we can expect these medications to be used in combination to avoid resistance. Often, this treatment is highly and quickly effective, but resistance appears after three to eight months. The proposed approach would be to combine an anti-BRAF medication with anti-CEK (nitrogen-activated protein kinase kinase) therapy in order to decrease side effects and prolong response.

Immunotherapy targeted to the CTLA (cytotoxic T-lymphocyte-associated protein 4) inhibitory signal with ipilimumab, and in the future also with anti-PD-1 (programmed death 1) therapy, is very promising. Ipilimumab was approved by Health Canada for the treatment of metastatic melanoma in February 2012. **Dr. Omid Hamid**, Director of The Angeles Clinic and Research Institute, reviewed new immunotherapy molecules like NTP1 and NPTLA1 that are in development now.

**Dr. Jeff Sosman** from the Vanderbilt-Ingram Cancer Centre looked at evolving strategies for treating patients who do not have the BRAF mutation. Options include vemurafenib or dabrafenib, immunotherapy, or patient selection to identify patients with NRAS and GNAQ mutations, which will be the next targets for metastatic ocular melanoma therapies. He also described the objectives of the SU2C-MRA (Stand Up To Cancer-Melanoma Research Alliance) Melanoma Dream Team in treating non-BRAF-mutated melanomas. This work is now at the feasibility trial stage.

My own presentation concerned vemurafenib, approved by Health Canada in February 2012 for the treatment of patients with with unresectable or metastatic melanoma that tests positive for the BRAF mutation. Its growing utilization allows for a better knowledge of its side effects. I reviewed common side effects and their management, including verrucous papillomas, hyperkeratotic peri-follicular rash, photosensitivity, alopecia and the development of keratoacanthomas (KA). Side effects can be managed with cryotherapy, excision of suspicious lesions, or moisturizing and topical steroids, without stopping vemurafenib. It is extremely important to emphasize the strong photosensitivity associated with this medication, and to recommend sunscreens with good UV protection.