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How I treat metastatic melanoma

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ABSTRACT

Tremendous progress in basic and clinical research has completely revolutionised the management of advanced melanoma, and this dramatic development is still ongoing. In this environment, state-of-the-art patient care is a major challenge. We describe how patient-centred medicine is organised in a leading referral centre that is also involved in early and late clinical trials and is part of a worldwide network for translational research.

A SHORT LOOK BACK

Treatment of melanoma has dramatically evolved over the last decade. Overseeing more than 3000 patients between 1995 and 2019 and witnessing the clash of the Gordon node with ipilimumab (ipi)[1] and vemurafenib (vemu) in 2010/2011,[2] I must confess that I had never expected this explosion of therapeutic possibilities. Before 2000, the brave and persistent community of melanoma researchers—basic and clinical, or both—have investigated every glimpse of hope, without any clear success.

During these desperate years of clinical research, many clinical scientists involved in melanoma trials have smelt that basic science achieves major breakthroughs, especially in the field of immunology and molecular cancer biology. Nobel Prize–winning researchers explored the rules to control the T cells and its relevance in autoimmunity. Subsequently, it became obvious that cancers high check these mechanisms to avoid powerful immune rejection mechanism. Therefore, a new promising treatment paradigm was born that was carefully and pertinently investigated, resulting in the development of checkpoint inhibiting monoclonal ab.[3]

Insights in the dysregulated wiring of signalling pathways in cancers have suspected the mitogen-activated-protein-kinase (MAPK) pathway to be essential in melanoma growth and survival. Another promising target arises. It was the merit of sophisticated pharmacological fine-tuning to create clinically useful small molecules inhibiting the MAPK pathway.

I am well aware of these circumstances and thankful that my patients with melanoma were among the first patients with cancer who profited from this research activity. Consequently, I am a strong believer that basic researchers will contribute to efficient therapies in the near future. I therefore use every opportunity to encourage research teams to focus on skin cancers with the promise to provide human samples from our biobank.[4]

PRINCIPLES OF MELANOMA PATIENT CARE IN AN ACADEMIC SETTING

'*The patient is the focus of treatment*' sounds like a self-evident statement—however, it presents the challenge of the first 60 min with a newly referred patient to understand her/his individual ideas, social situation,[4] goals as well as disease perception and expectations. On the other side, we need to explain our vision on the treatment plan and our commitment to apply the most promising regimen. We aim to contribute improving the therapeutic options but also our engagement in basic research. At the end, we wish to establish an open and reasonable relationship including regular skin examinations that facilitates an honest cooperation driven by serious communication. This is in general supposed to be rather direct and transparent with full access to all clinical data of the patient and our treatment algorithms (figure 1) to align the patient's perspective with the medical outlook. This endeavour is supported by educated so-called skin cancer nurses that repeat and re-explain medical information in the context of the social situation.

Our treatment strategy considers the latest knowledge and interdisciplinary expertise.[5 6] Since established guidelines typically take time to be updated, our team must participate in various international cancer conferences and specialised melanoma meetings and digest the trial results. More than 1 year before the approval of the recent adjuvant therapies, adjuvant dabrafenib/trametinib (dab/tra), nivolumab (nivo) and pembrolizumab (pembro) had substituted extensive surgery or irradiation therapy for locoregional lymph node metastases. Another example is the treatment of brain met patients: The preferred use of ipi/nivo as first line alone[7] or in combination

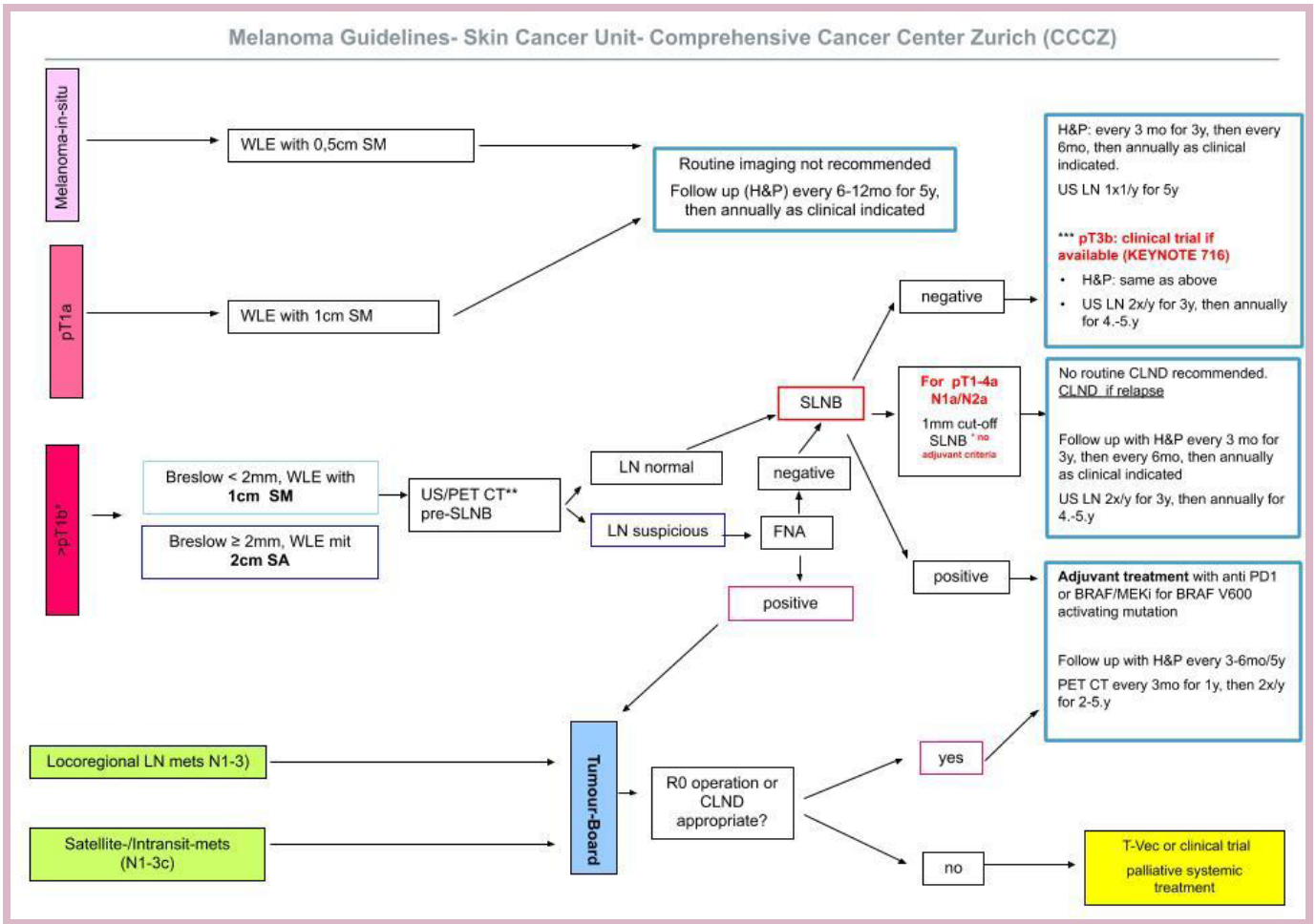

Figure 1 Staging and treatment algorithm for cutaneous melanoma as used in the Skin Cancer Center Zürich. CLND, complete lymph node dissection; FNA, fine needle aspiration; H&P, history and physical examination; LN, lymph node; mets, metastases; SLNB, sentinel lymph node biopsy; SM, safety margin; WLE, wide local expansion.
* Decision not the perform SLNB may be based on significant patient comorbidities, patient preference or other factors, in which case follow-up with regional basin US may be considered.
**PET CT for Breslow > 4mm.

with stereotactic radiotherapy was introduced within days after the presentation of the respective clinical trials. Whenever promising biomarkers are available, we aim to present them at our interdisciplinary tumour board. In order to decide the therapeutic strategy for a patient, it is essential to access medical information directly; all relevant images are presented and important routine laboratory tests such as LDH must be available. Today, we routinely reassess pathological diagnoses from other institutes and investigate a wide spectrum of molecular alteration including the mutational profile of the most important melanoma-associated genetic alterations such as mutations in oncogenes, tumour suppressors, mutational load and so on.

Clinical trials are preferred treatment options integrated in the treatment plan. Our centre has extensive experience in clinical research. We have been involved in various phase I and phase III clinical trials, which led to the establishment of targeted therapy (TT) and immunotherapy (IT) for stage III and IV metastatic melanoma.

Today, a number of prospective randomised trials are available which are important options for daily patient care are recommended by our interdisciplinary tumour board. In the adjuvant setting, we participate in a placebo-controlled clinical trial investigating pembro in high-risk patients without lymph node involvement (KEYNOTE 716 study—Adjuvant therapy with pembrolizumab vs placebo in resected high-risk stage II melanoma, a randomized, double-blind phase 3 study) (see figure 1).

Combination IT and combination TT are the established first treatment options for metastatic melanoma. However, in BRAF mutant patients, we do not yet understand whether sequence of the two treatment options matters, and if it would, in which patient population. Therefore, we are investigating three different options in a randomised multicentre clinical trial (SECOMBIT, a three-arm prospective, randomised phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) and combo target therapy (encorafenib/binietinib) in patients with

metastatic melanoma and BRAF mutation). In another trial, we had also investigated triple therapy using a PD-1 monoclonal antibody (mab) spartalizumab combined with combination targeted therapy dab/tra.

Education must be part of our daily work. We often welcome students and visitors from the whole world in the context of preceptorships and individuals such as physicians or nurses who are interested to be trained in dermato-oncology. Our tumour board is well attended by experienced physicians from the field of dermatology, oncology, ENT, plastic surgery, radio-oncology, neurosurgery and pathology and regularly includes short educational presentations.

TREATMENT DECISIONS—FROM STAGE I TO STAGE IV

Patients with low-risk primary melanoma (pT1a) are treated by non-disfiguring surgery, do not get imaging procedures and are typically followed by dermatologists in private offices lifelong.[8]

Sentinel lymph node biopsy (SLNB) is suggested to patients who are capable and motivated to undergo adjuvant therapy and a 5-year period of regular imaging procedures.

SLNB is the key for the next treatment and follow-up consequences, and therefore undergoes strict quality control.[4] The exact results of the primary tumour and the dimensions of the tumour load in the sentinel (SN) is essential to estimate the risk for relapse.[9]

The new American Joint Committee on Cancer classification (eighth version) is very helpful for defining the precise individual prognosis. During the discussion with the patient, the risk:benefit ratio is carefully analysed. In the context of anti-PD-1 immunotherapy, we always mention the low risk (approximately 1%) for developing lifelong damages that would necessitate ongoing drug therapy such as diabetes or hypothyroidism. In our point of view, immunotherapy and combination targeted therapy are reasonable options, nevertheless.

The available data for adjuvant TT[10] are more mature and include overall survival (OS) estimations.

Immunotherapy with nivo[11] and pembro[12] has only demonstrated effects on relapse-free survival, but its impact on OS can be delineated from the outcome in stage IV. In general, adjuvant IT is preferred in most patients.

This applies also for stage IV patients with a good performance status and normal LDH serum levels. These patients receive TT only if they suffer from a symptomatic metastatic disease including painful liver, bone or brain metastases.

As mentioned, large clinical trials supported by translational research are in general the preferred options. Whenever feasible, tumour material, blood and stool are collected and stored in our biobank. According to the trial protocols, treatment outcome is monitored by blood tests including LDH and S100 monthly and by imaging, mostly PET/CT quarterly. In case of mixed response or monolesional or oligo-lesional progress, associated with clinically meaningful disease control, the addition of surgery or irradiation therapy is considered.

Interdisciplinary management of brain metastases is challenging because they affect the quality of life in early stages and frequently cause death. Therefore, these patients need special care in specialised referral centres.[5 8]

Recent studies confirmed that the preferred systemic treatments TT and IT can be safely and efficiently applied in patients with brain metastasis (BM). Thus, four different treatment modalities may be used depending on the individual needs: neurosurgery, stereotactic radiosurgery (SRS), TT with BRAFi and MEKi combination and immunotherapies. Whole brain radiation therapy (WBRT) should be avoided whenever possible.[13]

Dab/tra combo therapy was investigated in a prospective multicentre, multicohort, open-label, phase II clinical trial in patients with good performance status. The response rate (RR) of 50% in BM is similar to the RR in other organ sites. However, PFS (median 6 months) seems to be shorter.

Ipi/nivo has demonstrated a RR of 50% in patients with asymptomatic BM with reasonable response duration. However, the inclusion criteria in these trials are strict and resulted in a selection of patients with low central nervous system tumour burden. These results suggest ipi/nivo as the preferred first-line option also in BRAF-mutated patients with asymptomatic BM.[7 14]

Since simultaneous use of multiple sessions of SRS is feasible in parallel to IT or TT systemic therapies, close disease monitoring by MRIs is recommended in order to add SRS if indicated.

Patients with brain metastases, whose local therapy had failed, and patients with neurological symptoms using dexamethasone or with leptomeningeal disease infrequently respond to ipi/nivo. Therefore, this population can be treated locally with irradiation. In case of leptomeningeal or very extensive disease, WBRT can be applied and even combined with systemic treatments such as hTT if BRAF mutant or temozolamid if wildtype. Nevertheless, the prognosis of this population is extremely poor.

After failure of systemic therapies with impact on survival, clinical trials with preferentially well-tolerated medications—see pasitreotide as an example[15]—or chemotherapy with taxane or platin derivates are *ultima ratio* possibilities, and a palliative care strategy needs to be tailored for the individual patient.

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