Developments in the treatment of advanced melanoma
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Discussion and future perspectives
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Introduction

The field of melanoma treatment has never before seen such a relative abundance of treatment strategies as today. This holds true for surgical management, locoregional treatments and systemic treatments alike. The rapid developments described in this dissertation have opened up new options for patients with intralymphatic metastasis, (neo)adjuvant treatment for (bulky) regional disease and (combined) treatment options with palliative or curative intent for disseminated disease.

In the upcoming decade on the surgical side we will see further refinement of minimally invasive techniques, intralesional therapies, and infusion and perfusion approaches, establishing whether there are patient groups for which less extensive curative and palliative procedures with less morbidity suffice. From the medical approach, advancement will come from sequencing therapies, identification of predictive biomarkers and combination treatment approaches. Our understanding of the disease will increase as we learn more about the interaction of aberrant and adaptive molecular pathways along with immune phenotypes; this will be balanced by the discussions on economic feasibility and utilizing positive and negative predictive biomarkers in making treatment decisions. Together these developments will lead to an approach that is more individualized than the current paradigms.

In surgery, less is more

In surgery, we are moving towards a more patient-centric, ‘less is more’ approach. After the proven benefit of wide excision margins and sentinel lymph node biopsy (SLNB) with completion node dissection, trials are now focusing on selecting for which patients excision margins can safely be reduced to 1 mm and which patients do not need a completion node dissection after SLNB.1-4 Moreover, the development of robotic and videoscopic surgical techniques allow for less invasive approaches.5-6 Time and trials will tell which patients and procedures benefit from these techniques.

In locoregional treatment: moving towards evidence for PFS/OS benefit

When metastatic melanoma is limited to the limb or liver, regional therapy is an important option to consider, especially the hyperthermic isolated limb perfusion (HILP), minimally invasive isolated limb infusion (ILI) and percutaneous hepatic perfusion (PHP) techniques.7-10 The benefits these procedures provide include a percutaneous approach that avoids the morbidity of open and complex surgical procedures, the ability to perform multiple treatments in the same patient and the ability to avoid or postpone systemic treatments.
which have more toxicity. HILP, ILI and PHP have demonstrated efficacy in achieving regional control of disease. Because of the readily accessible bypass circuit, real time pharmacokinetic data can be easily obtained. HILP and ILI also have the added feature of providing access to tumor tissue in the treated field during the entire time course of treatment via tumor biopsy of subcutaneous lesions with minimal morbidity. As more data become available, we will learn whether PHP provides PFS and OS benefits in addition to improved response rates. Intraläsional therapy is an attractive option for patients in in-transit disease when surgical resection to render a patient free of disease is not feasible. The ideal agent should have a low toxicity profile, be easy to administer, lead to fast responses and trigger a systemic immune response, thereby creating a bystander effect. Intraläsional injections are particularly attractive due to the fact that they are generally very well tolerated, they can be done during an outpatient procedure, and their ability to produce durable responses, albeit in a modest percentage of patients. The aforementioned bystander effect is mainly seen with PV-10 (rose bengal) and TVEC and makes these agents particularly attractive. TVEC is the first therapy to have shown an OS benefit in patients with stage IIIIB/IIIC and M1A disease.18

In systemic treatment: sequencing, biomarkers and quality of life
While the initial development of targeted therapy strategies was limited by a relative absence of therapeutic agents, the current challenge for both surgical and medical oncologists is to prioritize agents for systemic treatment when there are multiple physiological and pathological mechanisms to target. As there are growing examples of the critical nature of the degree of target inhibition, differences in pharmacokinetic properties and/or drug delivery methods are key issues, particularly in the development of systemic therapies for brain metastases. The achievement of durable clinical benefit requires an understanding of the mechanisms that underlie resistance in order to develop rational and effective strategies to prevent and/or overcome them. Recent melanoma exome sequencing efforts have failed to identify new frequently mutated kinase targets. New insights into the prognosis of people with metastatic melanoma might come from molecular profiling of the primary tumor and distant metastases, identifying the range of mutations along with the immunophenotype.

The availability of patient subsets surviving long term is another factor that will increase our understanding of melanoma biology. Before the introduction of the new wave of systemic treatments, less than 12% of patients were alive beyond five years and prospects for patients with brain metastases were even bleaker still. It is now seven years ago that the first BRAF inhibitor, vemurafenib, and the anti-CTLA-4 antibody ipilimumab were approved.20 Survival of patients treated with ipilimumab seems to plateau after three years at around 20%.20 For vemurafenib, long term survival has been observed as well, with 3- and 4-year melanoma specific survivals of 26% and 19% being reported.21 Anti-PD1 therapy offers even better prospects, with 35% of the phase 1 trial patients surviving after five years and a plateau being reached after four years.22 Research is focusing on combination therapies to further improve these outcomes and overcoming resistance. One area of research focuses on enhancing the effect of anti-CTLA-4 and anti-PD1/PD-L1 agents by adding immune stimulating antibodies such as TVEC or IDO inhibitors.23,28 However, improved outcomes may come at the price of higher toxicity, as seen with the ipilimumab/nivolumab combination.29,30 Quality of life must not be ignored and will factor into treatment decisions.

Increasingly: individualized cancer care
Individualized cancer treatment is an important cornerstone in the current treatment landscape. BRAF-targeted treatment is a beautiful example, where about 50% of patients harbor the BRAF V600E mutation.23 However, for anti-PD-1 therapy, this is not as clear cut. Although patient’s populations with high PD-L1 tumor expression typically have higher response rates and survival with anti-PD-1 therapies, patients with low PD-L1 tumor expression can still benefit from anti-PD-1 therapy.23,25 Better predictive biomarkers are needed for immunotherapy approaches. In addition, molecular alterations in the P13K pathway have not proven to be successful therapeutic targets in patients with advanced melanoma, indicating further work is needed. A better understanding of the pathways involved in melanogenesis and the increasing availability of next generation sequencing and other assays will lead to truly personalized medicine. Studies like NCI-MATCH (NCT02465060) and TAPUR (NCT02693535) signal a new era in precision medicine, where therapies are tailored to specific mutations as opposed to disease state.

In radiotherapy: highly focused technologies
Despite the historical concept of melanoma as a radiotherapy resistant tumor, new paradigms that employ radiation therapy (RT) to treat melanoma are rapidly emerging. The increasing understanding of the role of the immune system in regulating the response to RT and the recent development of a multitude of immuno-oncologic treatment modalities might change the role of RT in melanoma treatment. Highly focused RT including intensity modulated radiation therapy (IMRT), 3D conformal radiation therapy (3DCRT), stereotactic radiation therapy (SRT) and proton therapy, which will become available at the University of Groningen at the end of 2017, allow for dramatic dose escalation due to the ability of these techniques to improve the precision with which radiation therapy can be administered and avoid dose-limiting structures.37-39

And last but not least: cost of cancer care and the continued importance of primary prevention
Despite the large improvements that have been made in the medical and surgical management of patients with advanced melanoma, we must not forget that the majority of stage IV patients still succumb to their disease. Median overall survival rates for the nivolumab/ipilimumab combination are eagerly awaited, as are prospective overall survival data for anti-PD1 treated patients with brain metastases.20,21,23 An abundance of immune modulatory agents are now seen in pharmaceutical pipelines, which raises questions on how to optimize combinations,
sequencing and cost of cancer care. The financial burden of melanoma (and other cancer) treatments will likely rise.

Primary prevention is still an important part of the melanoma landscape and should not be overlooked. It is well known that smoking increases the risk for lung cancer and a recent study showed that smoking is also associated with an increased risk of experiencing lymph node metastasis in patients with melanoma.28 Furthermore, the importance of sun-protective behavior should continue to be stressed, especially for children and adolescents. 29

Taking all of these factors into account, treatment of melanoma has become increasingly complex and will continue to do so. Treatment requires an individualized and multidisciplinary approach. The ideal treatment should be tailored to the individual patient and based on the extent of disease, tumor characteristics, such as BRAF status and disease free interval, and patient characteristics including age and comorbidities. This will lead to a combination of injectable treatments, regional perfusions/infusions and systemic treatment. Imhotep’s treatment statement, “There is none”, finally stands defeated.

References

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