Defining optimal oncolytic virus treatment and diagnostics in high risk melanoma patients

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CHAPTER 1

General introduction and outline of the thesis

Cutaneous melanoma arise through malignant transformation of pigment producing melanocytes in the epidermis. This is the result of a complex interaction between genetic and environmental factors[1,2]. Important risk factors for cutaneous melanoma are the overexposure to ultraviolet light (from the sun or artificial) and subsequent sunburns (especially before the age of 35), the presence of atypical (melanocytic or dysplastic)- or numerous (more than 50) naevi, fair skin phenotype and family history of melanoma[3,4].

Worldwide incidence of melanoma has risen rapidly during the last decade and is still constantly increasing, mostly in fair-skinned populations[5]. In Europe, skin melanoma is the fifth most common diagnosed cancer in both men (after prostate, lung, colorectal and bladder cancers) and women (after breast, colorectal, lung and gynecological cancers)[6]. The Netherlands is one of the European countries with the highest incidence rate. In 2021, 7530 patients were diagnosed with melanoma, compared to 5203 in 2010[7]. This rising trend can be explained by increased and earlier detection, increased awareness, increased exposure to sunlight and less competing risks due to an increasing life expectancy[8].

Diagnostics in high risk melanoma

Staging and classification at initial diagnosis and upon recurrence of disease is currently done with the eighth AJCC American Joint Committee on Cancer (AJCC). This cancer staging system relies upon assessments of the primary tumor (T1a-4b), regional lymph nodes (N1a-3c), and distant metastases (M1a-d). Stage II disease according to the 8Th AJCC is defined by the presence of a primary melanoma with a Breslow thickness >1.1mm with ulceration or with a Breslow thickness >2.1mm without ulceration. Stage III disease is defined by the presence of lymph node involvement and/or satellite/in-transit metastases (ITM), in the absence of distant metastases[9]. Satellite metastases and ITM are locoregional recurrences confined to the superficial lymphatics and develop in approximately 4-8% of patients. Lesions can be cutaneous or subcutaneous, isolated or widespread, and can occur with or without synchronous nodal and/or distant disease[10].

In routine practice in the Netherlands, in clinical stage IIB-C (T3b-4b) melanoma no routine imaging (US, CT or PET-CT) is performed prior to lymphoscintigraphy (LSG) and sentinel lymph node biopsy (SLNB). In patients with recently discovered stage III disease, a whole body PET/CT is performed in order to rule out more metastases.

Treatment of stage III melanoma

The SLNB is a surgical staging procedure used to determine whether cancer has spread beyond a primary tumor into the lymphatic system. The sentinel node

(SN) is the first draining lymph node from the primary tumor and is considered a surrogate indicator to predict the risk of further (micro-)metastatic spread. This procedure is used worldwide for patients with newly diagnosed primary melanomas, as many studies have proven it's prognostic value[11]. The Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1) also tested if the procedure had a therapeutic value (if the early removal of the SN and subsequent completion lymph node dissection (CLND) could potentially prevent further spreading of disease and thereby improve survival), but no statistical significant survival benefit was found when comparing the procedure to nodal observation[12,13].

Until recently, all patients with a positive SN underwent a CLND, a procedure in which all remaining lymph nodes in the SN positive lymph node basin are removed, with the hope of preventing recurrence or disease progression. However, two randomized controlled trials (MSLT-II and DeCOG-SLT) set out to assess the value of CLND for patients with sentinel-node metastases and concluded that immediate CLND was not associated with improved melanoma-specific or distant metastasis-free survival when compared to sequential nodal observation using ultrasound[14,15]. Therefore, CLND after detection of SN metastases stopped being standard of care and therapeutic lymph node dissections (TLND) are now only performed in patients with recurrent, clinically detectable lymph node metastases. Nevertheless, the SLNB remains an important staging tool, especially with the arrival of adjuvant systemic immunotherapy.

After resection (by SLNB, LND or resection of ITM) of micro- or macroscopic disease, patients with stage III melanoma still have a high risk of developing recurrence. Depending on the number of affected lymph nodes and the presence of satellite- and/or in-transit metastases, survival rates range from 32% to 93% (8th AJCC)[9]. Fortunately, due to successful advances in systemic treatments for unresectable stage III-IV disease, not long ago, trials were set up to investigate the same systemic agents in adjuvant setting for resected high-risk melanoma.

The EORTC 18071 trial was the first to show a significantly improved recurrence-free survival (RFS) in completely resected stage III melanoma for adjuvant high-dose ipilimumab (10 mg/kg) when compared to placebo (3-yr RFS of 46.5% vs. 34.8%, respectively). However, toxicity rates were high: 5 patients died and 54% experienced grade 3/4 adverse events[16]. These results have since been surpassed by two studies investigating anti-PD1 agents. The CheckMate 238 study examined adjuvant nivolumab versus high-dose ipilimumab in resected stage IIIB-IV disease. At 12 months, this study showed a 10% recurrence benefit for the nivolumab arm and 14% of the nivolumab group experienced 3/4 adverse events compared to 45.9% of the ipilimumab group[17]. Most recent was the study by Eggermont et al., which reported a significantly longer 1-year RFS for patients treated with

pembrolizumab (75%) versus placebo (61%) with an adverse event rate of 15%[18]. For BRAF-mutated melanomas, the COMBI-AD trial compared the combination of dabrafenib and trametinib with placebo in resected stage III disease. The 3-year RFS rates were 58% for the combination arm compared to 39% for the placebo arm ($p<0.001$) after a median follow-up of 2.8 years and 41% of patients experienced grade 3/4 adverse events[19].

Talimogene Laherparepvec

Oncolytic virus therapy has emerged as new therapeutic option for patients with injectable tumors. In these viruses, tumor regression is mediated through a dual mechanism of action. First, viral infiltration of tumor cells causes cell lysis, which in turn can infect surrounding tumor cells, propagating a local effect. Secondly cell lysis also causes the release of tumor-derived antigens, thereby generating systemic anti-tumor immunity[20]. Talimogene Laherparepvec (T-VEC, previously known as OncoVEX$^{GM\text{-}CSF}$) was the first oncolytic virus to demonstrate a clinical benefit in patients with cancer. It was designed to selectively replicate- and induce oncolysis only in tumor cells, thus avoiding normal cells[21].

More specific, T-VEC is a genetically modified oncolytic immunotherapy derived from the herpes simplex virus-1 (HSV-1). T-VEC is based on a JS-1 strain, in which the genes ICP34.5 and ICP47 have been completely disabled and the coding sequence for human granulocyte-macrophage colony-stimulating factor (GM-CSF) has been inserted. Deletion of ICP34.5 provides tumor selective virus replication and deletion of ICP47 prevents the blocking of antigen presentation, thereby restoring the anti-tumor immune response. Deleting ICP47 also increases expression of the HSV US11 gene, which allows US11 to further enhance the degree of viral replication and oncolysis of tumor cells. Finally, expression of GM-CSF leads to the recruitment and stimulation of dendritic cells and thus antigen presentation[22].

In 2006, a phase I study investigating T-VEC in 30 patients with cutaneous or subcutaneous solid tumors (breast, colorectal, melanoma, and head and neck cancer) showed it was well tolerated. The most common side effects were local inflammation, erythema and febrile responses[22]. Subsequently, a phase II trial assessed the efficacy of T-VEC in 50 patients with stage IIIC and IV melanoma. They reported an overall response rate (ORR) by RECIST of 26% in both injected as well as uninjected distant (including visceral) lesions and 92% of these responses lasted for 7 to 31 months. For patients with a partial response (PR), complete response (CR) or surgical CR (CR after additional resection of disease) as best response, the 1-year survival rate was 93%. A limited toxicity profile was seen again[23]. These results led to the pivotal randomized controlled phase III OPTiM trial. In the OPTiM, 436 patients with unresectable injectable stage IIIB-

IV melanoma were randomly assigned to intralesional T-VEC or subcutaneous GM-CSF, at a 2:1 ratio. The overall- and durable response rate (DRR) were significantly higher in the T-VEC arm (ORR: 26.4% vs. 5.7%, p<0.001; DRR: 16.3% vs. 2.1% respectively, p<0.001). Also the overall survival, although barely not-statistically significant, favored the T-VEC arm (23.3 months vs 18.9 months, p=0.051). Efficacy was most pronounced in the patients with stage IIIB, IIIC or IVM1a disease (AJCC 7th edition) and treatment-naive patients. Again, T-VEC had a tolerable safety profile and most common adverse events included fatigue (50%), chills (49%) and pyrexia (43%). Thirty-six percent of patients had a grade 3 ≥ AEs and there were no treatment-related fatal events[24]. Based on the results of the OPTiM trial, T-VEC was approved by the Food and Drug Administration (FDA) for treatment of patients with metastatic melanoma that cannot be surgically removed, in October 2015. Shortly after, T-VEC was also approved by the European Medicines Agency (EMA) for patients with early metastatic disease (stage IIIB-IVM1a), as they achieved the best outcomes.

Despite this, many health care players in different countries across the world struggle to assess T-VEC, to which patients have limited access except in a few selected countries, as reimbursement is not provided in many other countries. Since its approval, T-VEC has been examined in multiple real-world studies and there is an increasing amount of clinical data that supports the efficacy in melanoma patients[25-28].

Aims and outline of the thesis

This thesis aims to improve treatment of patients with stage III melanoma. We mainly focus on accurate patient selection for successful treatment with T-VEC, by evaluating the efficacy and safety, identifying clinical prognostic factors and focusing on use in clinical practice. Further aims are to assess the value of surveillance- and screening imaging in high-risk melanoma.

The first part of this thesis mainly focuses on several aspects regarding treatment with T-VEC. **Chapter 2** focuses on prognostic factors for a CR to T-VEC and presents a nomogram for predicting CR in patients, allowing a more accurate selection of patients for T-VEC monotherapy. **Chapter 3** externally validated this nomogram in an independent cohort. **Chapter 4** reviews the current literature on T-VEC and presents a meta-analyses of efficacy data from the included studies. False positive FDG uptake in locoregional lymph nodes of patients treated with T-VEC was described in **chapter 5**. **Chapter 6** is a pilot study investigating dermoscopy as response evaluation tool for cutaneous metastases treated with T-VEC.

In the second part of this thesis, **chapter 7 and 8** evaluate the role of surveillance- and screening imaging in high-risk stage II and III melanoma.

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