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Combining surgery and systemic therapy in metastatic melanoma

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Chapter 1

General introduction and thesis outline

1

GENERAL INTRODUCTION

Melanoma is a malignant tumor originating from melanocytes. The most common type is cutaneous melanoma, located in the skin. The incidence of cutaneous melanoma has been increasing over the past decades, with a global incidence of 324.635 in 2020.[1] The age-standardized rates in the Netherlands were 27.0 per 100.000 in 2020, which is the fourth highest in the world, with Australia and New-Zeeland having the highest rates.[2] Melanoma is an aggressive disease and prognosis is strongly dependent on the stage of the disease, which depends on Breslow thickness and ulceration status (T-stage); presence of in-transit and/or nodal metastases (N-stage); or distant metastases (M-stage). Tumor staging is described according to the American Joint Committee on Cancer (AJCC) classification: majority of patients present with localized disease (stage I and II), but a proportion of patients either present with, or progress to stage III (regional metastases) or stage IV (distant metastases) disease.[3,4]

Treatment of primary melanoma

Surgery is the cornerstone of treatment in localized disease. After diagnosis of primary melanoma, wide local excision (WLE) is recommended to resect potential microsatellites. The clinical safety margin of the WLE depends on the Breslow thickness: 0.5 cm in melanoma in situ, 1 cm in melanomas ≤2 mm, and 2 cm in melanomas >2 mm.[5] Additionally, in stage T1b and higher, guidelines recommend to combine WLE with a sentinel lymph node biopsy (SLNB).[6,7] If tumor cells are found in the first draining lymph node, i.e. a positive SLNB, patients are classified as having stage III melanoma.

Surgery in stage III melanoma

As described in the previous paragraph, SLNB is recommended for T1b melanomas and above. The important prognostic value of this procedure was described by Morton et al., in the MSLT-1 trial.

In this trial, patients with primary melanoma were randomly assigned to either WLE with nodal observation, or WLE with SLNB. Patients with a negative SLNB showed a significantly better melanoma-specific survival (85%) than patients with a positive SLNB (62%). In patients with a positive SLNB a completion lymph node dissection (CLND) was performed. No survival differences were seen between the nodal observation and SLNB (± CLND) groups.[8] This led to a successive trial: the MSLT-2, which randomized patients with positive SLNB between nodal observation and CLND.[9] Since both this trial and the similar DeCOG-SLT trial failed to show a survival benefit, CLND is no longer recommended by guidelines in patients with a positive SLNB.[10]

Although lymph node dissections are no longer performed in this patient population, this is still the main treatment in patients with clinical/imaging detected (macroscopic) nodal metastases. In this situation, the procedure is described as a therapeutic lymph node dissection (TLND).[5,11]

Despite the surgical efforts described above, recurrences and progression to stage IV disease are common in patients with stage III melanoma after surgery alone.

Systemic therapy for melanoma

Over the past decades, drastic developments have taken place in the systemic treatment of melanoma patients. Both immune checkpoint inhibitors (ICI) and targeted therapy (TT) have improved the prognosis of patients with advanced melanoma drastically. Inhibitors targeting immune checkpoints PD-1 or CTLA-4 can be applied as either monotherapy or combination therapy and have shown durable responses.[12-18] Targeted therapy directed at tyrosine-kinases BRAF and MEK is available to treat patients with BRAF V600-mutated melanoma, approximately 50% of patients, and shows rapid and high response rates, but has shown to induce resistance.[19-21] These therapies were first introduced in stage IV melanoma patients and showed clear survival benefits compared to chemotherapy or best-supportive care. Due to these encouraging results and the observation that a substantial proportion of patients with stage III melanoma treated with surgery alone develop a recurrence in due course, the indications for these new systemic therapies have broadened.

Due to the high risk of recurrence after surgery in stage III melanoma, adjuvant therapies have been a topic of interest in melanoma research over the past decades. Interferon-α-2b (IFN) was the first adjuvant treatment approved by the Food and Drug Administration, because it had shown recurrence free (RFS) and overall (OS) survival benefits in the ECOG 1684 trial, with a limited sample size.[22] However, in Europe IFN has never been approved due to conflicting results of the subsequent EORTC 18592 and EORTC 18991 trials, which did not show an OS benefit.[23-25]

The development of both TT and ICI have brought new options for the adjuvant treatment of stage III melanoma patients. High-dose anti-CTLA-4 ipilimumab (10 mg/kg) was the first to show a RFS and OS benefit, however, at the cost of very high toxicity rates.[26,27] Both anti-PD-1 agents nivolumab and pembrolizumab have shown encouraging results in improving RFS compared to ipilimumab or placebo, respectively, but have yet to show an OS benefit.[28-31] The BRAF/MEK inhibitor combination dabrafenib and trametinib has also shown an RFS benefit compared to placebo.[32]

This has caused the standard of care to shift from WLE + SLNB, followed by a CLND in case of a positive SN to currently no longer performing adjuvant surgery, but rather offering adjuvant systemic therapy to these patients.

As both TT and ICI have shown to improve recurrence free survival in patients with resected stage III melanoma, the following topic of interest is optimally selecting patients who benefit the most from these therapies.

The success of adjuvant therapy has shown the value of combining surgery and systemic therapy. This collaboration will be explored further in other patient populations: using

systemic therapy to pave the road to surgery in unresectable advanced melanoma, surgery after initial treatment with systemic therapy in metastatic melanoma, or neoadjuvant therapy in patients with macroscopic lymph node metastases to prevent recurrences.

OUTLINE OF THIS THESIS

The aim of this thesis is to create insight in combining surgery and systemic therapy to enhance melanoma treatment. In **chapter 2** and **chapter 3**, results of the REDUCTOR trial are discussed, which investigated the use of a short-term induction with BRAF/MEK inhibition in unresectable locally advanced melanoma. Chapters 4 and 5 focus on adjuvant therapy in stage III melanoma: **chapter 4** is a review on current adjuvant trials and **chapter 5** describes a biomarker study to select patients who will benefit from adjuvant therapy. The following chapters 6 and 7 are population-based studies, using data from the Dutch Melanoma Treatment Registry (DMTR). **Chapter 6** describes the appliance of surgery after a response to systemic therapy in advanced melanoma. **Chapter 7** focusses on the retrospective value of SLNB once patients have progressed to advanced disease.

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