Immunotherapy for metastatic melanoma and beyond = immunotherapie voor gemetastaseerd melanoom en verder

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English summary
Nederlandse samenvatting

ENGLISH SUMMARY

The research described in this thesis focusses on novel treatment modalities with cellular and non-cellular (immuno)therapies for patients with advanced melanoma and non-melanoma skin cancer. The introductory **chapter 1** provides an overview of the etiology and the rapidly evolving therapeutic landscape for (advanced) melanoma, with the development of immune checkpoint inhibitors, adoptive cellular therapies (ACT), targeted therapies and oncolytic viral immunotherapy. In addition, the importance of timing of treatment is highlighted. Furthermore, the rationale and outline of this thesis are described.

Part I – Cellular immunotherapies for melanoma

The main part of this thesis, **Part I**, addresses multiple aspects of ACT for patients with advanced melanoma, including prospective clinical trials with T cell receptor T cell (TCR-T-cell) therapy and treatment with tumor-infiltrating lymphocytes (TIL). First, in **chapter 2**, a more detailed background on ACT in melanoma is given, describing its development over the years and future possibilities. ACT comprises the intravenous adoptive transfer of either modified peripheral blood or tumor resident immune cells and can be subdivided into three different methods. In ACT with TCR-T-cell therapy, autologous peripheral blood T cells are isolated and genetically modified *ex vivo* with novel T cell receptors that target specific tumor antigens. Multiple trials have been conducted in patients with advanced melanoma and although this treatment method holds the potential to form large pools of tumor-specific T cells, many targeted antigens are also present on normal tissue, often resulting in 'on-target, off-tumor' adverse events. A second method of ACT with chimeric antigen receptor (CAR) modified T cells consists of peripheral blood T cells modified with an artificial receptor. These CAR T-cell therapies have achieved a breakthrough in the treatment of hematological malignancies. Lastly, ACT with TIL comprises the *ex vivo* isolation and expansion of tumor-resident T cells. The first clinical evidence in patients with advanced melanoma was obtained in 2002, after which many phase I/II clinical trials, reaching similar high response rates, followed. For all three methods, patients are pretreated with a lymphodepleting, non-myeloablative chemotherapy and in TIL and some TCR-T-cell therapies, patients are also treated with interleukin-2 (IL-2) following the adoptive transfer of the *ex vivo* expanded autologous T cells.

Chapter 3 reports on the results of a dose-finding clinical phase I/IIa trial with TCR-T-cell therapy conducted between October 2012 and October 2017 using a novel production method in 12 treatment-refractory advanced melanoma patients. In this production method, autologous peripheral blood T cells were modified to express a MART-$1_{(26\text{-}35)}$-specific 1D3 TCR and cultured in IL-7 and IL-15 to generate a less differentiated phenotype. For all 12 patients with unresectable stage IIIC-IV cutaneous (n=7) or uveal (n=5) melanoma,

generation and administration of a highly potent cell product was feasible and persistence of transduced T cells corresponded with the infused cell dose. The highest tolerated cell dose was $1.0x10^8$ cells, with dose-dependent 'on-target, off-tumor' toxicity presenting as uveitis, dermatitis and hearing loss. A partial response was seen in 2/11 (18%) evaluable patients. This trial demonstrated the feasibility of a novel production method for TCR-T-cell therapy, but further development was limited by severe dose-dependent toxicity.

Chapter 4 of this thesis reviews the development and clinical experiences with TIL therapy in patients with advanced melanoma from earlier conducted phase I/II clinical trials, including its three treatment components with a preparative lymphodepleting regimen, TIL production methods, IL-2 administration and its related toxicity. In addition, the possible role of TIL in other solid tumor types than melanoma and the timing of TIL treatment are addressed.

As noted earlier, many clinical phase I/II trials have been conducted with TIL in patients with advanced melanoma. In **chapter 5**, the results are presented of the first multicenter, randomized, clinical phase III trial with TIL in solid tumors conducted between September 2014 and March 2022 at the Netherlands Cancer Institute, Amsterdam, the Netherlands, and the National Center for Cancer Immune Therapy (CCIT), Herlev, Denmark. This trial aimed to evaluate the efficacy, safety and quality-of-life (QoL) in 168 patients with unresectable stage IIIC-IV melanoma treated either with TIL or standard of care ipilimumab. Patients were randomized 1:1 between both treatment arms, with no differences in baseline characteristics and the majority of patients (86%) was PD-1-refractory. At a median follow-up of 33 months, TIL treatment demonstrated to be superior above standard ipilimumab in the intention-to-treat population, with a median progression-free survival of 7.2 months compared to 3.1 months (hazard ratio for progression or death, 0.50; 95% CI, 0.35-0.72; $p<0.001$), respectively. The response rate was also significantly higher in patients treated with TIL compared to ipilimumab, with 49% of TIL patients and 21% of ipilimumab patients reaching an objective response, with 20% and 7% complete responses, respectively. Even though there was no significant overall survival (OS) benefit for TIL, patients treated with TIL had a median OS of 25.8 months, compared to 18.9 months in patients treated with ipilimumab. Grade ≥3 adverse events (AEs) occurred in all TIL-treated patients, mainly associated with chemotherapy-induced pancytopenia, and 57% of ipilimumab-treated patients. TIL-treated patients scored better on global QoL and physical and emotional functioning than ipilimumab-treated patients. Based on these findings, TIL treatment has become a reimbursed second-line treatment option for this patient population in the Netherlands since January 2023.

Part II – Non-cellular (immuno)therapies for melanoma and non-melanoma skin cancer
The second part of this thesis concentrates on innovative treatment strategies with non-cellular (immuno)therapies is patients with (non-)melanoma skin cancer, shining a light on neoadjuvant treatment for melanoma and treatment for patients with advanced cutaneous squamous cell carcinoma (CSCC).

In **chapter 6**, the outcome is discussed of a single center, single-arm clinical phase II trial evaluating the potency of short-term neoadjuvant targeted therapy with dabrafenib and trametinib to allow for radical surgical resection in 21 patients with locally advanced stage IIIC or oligometastatic BRAF-mutated melanoma treated between August 2014 and March 2019. The treatment approach for these patients is usually that of stage IV melanoma patients, as upfront radical resection is deemed unfeasible. This trial has shown however, that a radical resection was possible in 81% of patients after 8 weeks of neoadjuvant treatment with dabrafenib and trametinib. Half of the patients that underwent surgery developed recurrent disease. In these cases, recurrence tended to occur shortly after surgery, with a median recurrence-free survival of 9.9 months, providing a window for fitted adjuvant treatment in future research. This trial has demonstrated an additional feasible treatment option for this patient population who would otherwise be treated as patients with metastatic disease.

In **Chapter 7,** a study protocol for a single center, single-arm, clinical phase II trial is presented. In this NIVEC trial, 24 patients with resectable stage IIIB – IVM1a melanoma will be treated with neoadjuvant combination therapy with nivolumab and talimogene laherparepvec (T-VEC), an oncolytic viral immunotherapy, with the aim to show an improved major pathologic complete response (pCR) rate. It is hypothesized that intralesional T-VEC in combination with systemic treatment with nivolumab can heighten the immune response in neoadjuvant setting and treated patients will be evaluated for efficacy and safety.

Chapter 8 reports on a retrospectively analyzed cohort of 65 patients with advanced CSCC treated with cemiplimab in a named patient program in three centers in the Netherlands. An earlier conducted pivotal clinical phase I/II trial demonstrated a high response rate upon treatment with cemiplimab in this patient population with otherwise limited treatment options. In this real-world cohort of patients with either locally advanced or metastatic CSCC, similar results were observed, with 52% patients achieving a tumor response, of whom 22% reached a complete response. Grade ≥3 AEs occurred in 22% of patients and six patients discontinued treatment due to AEs. This study confirms the role of cemiplimab for the treatment of, often frail, patients with advanced CSCC.

Part III – Concluding remarks

In this final part, **chapter 9** provides a general discussion of the results obtained in this thesis, how these translate into daily clinical practice and offers insights for future prospectives for the treatment of, and further research opportunities for, patients with melanoma and non-melanoma skin cancers.