GENERAL INTRODUCTION
Chapter 1

Background

A decade ago, new targeted therapies and immune checkpoint inhibitors revolutionized anti-tumor treatment.\(^1\,^2\) Increasing numbers of targeted therapies have become available due to the improved understanding of tumor biology, e.g., identification of genetic alterations in cancer cells. These targeted therapies target an oncogenic protein or enzyme. Compared to conventional chemotherapies, targeted agents can have improved efficacy, rapid response onset, and fewer side effects. However, targeted therapies are only effective in patients that harbor the specific mutation the agent targets. Examples of targeted therapies are BRAF/MEK-inhibitors for melanoma patients with a \(BRAF\)-mutation and EGFR-inhibitors to treat \(EGFR\)-mutated non-small lung cancer (NSCLC). Immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab, atezolizumab, or ipilimumab) are monoclonal antibodies that target immune-regulatory checkpoints (e.g., PD-(L)1 or CLTA-4). By targeting these immune checkpoints, the inhibitory immune signal is interrupted, resulting in the activation of the immune system and subsequent anti-tumor responses. Anti-tumor responses with immune checkpoint inhibitors are often durable and make long-term survival possible for patients with advanced cancers.

The availability of targeted therapies and immune checkpoint inhibitors revolutionized the management and prognosis of various advanced cancers, including melanoma and NSCLC.\(^3\,^4\,^6\) In advanced melanoma, the 5-year overall survival was 5-19% before 2010, whereas nowadays, the 5-year overall survival is 26-52% in patients treated with immune checkpoint inhibitors.\(^7\,^10\) The 5-year overall survival was, historically, as poor as 5% in patients with advanced NSCLC.\(^11\) Similar to melanoma, NSCLC survival improved with the availability of effective treatments, and the 5-year overall survival can now be as high as 25% and 40-50% in subgroups of NSCLC patients with high PD-L1 expression or an \(ALK\)-mutation (a mutation amenable to targeted therapy), respectively.\(^12\,^14\)

The improved treatment outcomes, including the potential of long-term survival, resulted in research largely concentrating on anti-tumor treatment. This focus on achieving long-term survival, however, may distract from giving adequate attention to supportive and palliative care needs of patients and their caregivers, while not all patients will achieve long-term survival. Supportive and palliative care focus on maintaining or improving the quality of life of the patients with cancer and their informal caregivers.\(^15\,^16\) Supportive care initially focused on managing side effects of anti-tumor treatments, such as chemotherapy-induced nausea and vomiting, and later expanded to the management of long-term effects of cancer and its treatments, referred to as survivorship care.\(^17\) When palliative care emerged around 1970, it primarily focused on end-of-life/hospice care.\(^18\) However, over the last decade, evidence emerged that initiation of palliative care earlier in the disease course can improve patient care.\(^19\,^22\) Early palliative care leads to clinically meaningful improvements in a patient’s quality of life, psychological issues, satisfaction with care, and less aggressive care near death. Therefore, the World Health Organization (WHO) definition of palliative care changed in 2002.
to include early integration of palliative care. The 2002 WHO definition states: “palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, and is applicable early in the course of the illness, in conjunction with other therapies that are intended to prolong life”.23

In the current treatment era of tumors sensitive to targeted therapies and immune checkpoint inhibitors, there are patients with advanced cancers who experience durable responses, while those not responding to treatment may rapidly deteriorate and die from their disease. For those experiencing durable responses, adequate survivorship care is essential. For those dying from their disease, providing support and comfort in the last phase of life and enabling patients to die at their preferred place of death are of critical importance. During the treatment phase and when the prognosis is still uncertain, physical, psychosocial, and existential issues also merit clinical attention. To ensure that patients' and caregivers' supportive and palliative care needs are met throughout the disease trajectory, supportive and palliative care should be integrated with effective anti-tumor treatment.

In summary, the introduction of effective treatment options remarkably improved the survival for patients with cancers sensitive to targeted therapies and immune checkpoint inhibitors. By entering this improved treatment era, new clinical challenges were introduced regarding the optimization of anti-tumor treatment while still addressing palliative care needs. By addressing those clinical challenges, this thesis aimed to describe, analyze, and improve the care of patients with tumors sensitive to immune checkpoint inhibitors across the disease trajectory. The overall aim is to eventually improve the integration of supportive and palliative care into the anti-tumor treatment from diagnosis to long-term survival or death. The clinical questions regarding anti-tumor treatment and supportive and palliative care addressed in this thesis are described below.

The efficacy of immune checkpoint inhibitors was first explored in recurrent and metastasized cancers.1 The favorable outcomes in the advanced setting triggered the investigation of immune checkpoint inhibitors in earlier treatment lines. Adjuvant immune checkpoint inhibitor treatment is already approved in, for example, melanoma and NSCLC to reduce the risk of developing distant metastases.24 Currently, many studies on neoadjuvant immune checkpoint inhibitors are ongoing.25,26 Neoadjuvant immune checkpoint inhibitors have the potential to 1) induce a broader systemic immune reaction compared to adjuvant treatments, 2) diminish the need for extensive and debilitating localized treatments, and 3) provide research opportunities into biomarkers (factors that can predict which patients can benefit from treatment). In melanoma, large clinical trials are ongoing, and these studies may not only be relevant to patients with melanoma. Other advanced non-melanoma skin cancers (Merkel cell carcinoma (MCC), cutaneous squamous cell carcinoma (cSCC), and basal cell carcinoma (BCC)) are also sensitive to immune checkpoint inhibitors.27–29 The current standard of care of early stage non-melanoma skin cancers are localized, sometimes debilitating, treatments, which may be averted by neoadjuvant immune checkpoint
inhibitors. However, the translation of immune checkpoint inhibitor treatment from the advanced to the neoadjuvant setting in non-melanoma skin cancers is hampered by the rarity of these skin cancers in the advanced stage and the older, more frail patient population affected with these diseases. The implementation of immune checkpoint inhibitor treatment in non-melanoma skin cancers can be advanced by the knowledge already obtained regarding efficacy, toxicity, and study design in melanoma. Therefore, a critical review was performed and presented in chapter 2. This review aimed to describe the transition of immune checkpoint inhibitor treatment from the metastatic to the neoadjuvant setting in melanoma, MCC, cSCC, and BCC. The knowledge obtained in melanoma can be used to help navigate the immune checkpoint inhibitor implementation in non-melanoma skin cancers. All FDA-approved immune checkpoint inhibitors indications for melanoma, MCC, cSCC, and BCC were identified. Furthermore, PubMed and ClinicalTrials.gov were searched to extract published and ongoing immune checkpoint inhibitor clinical trials in patients with MCC, cSCC, and BCC in the adjuvant and neoadjuvant settings and in patients with melanoma in the neoadjuvant setting only.

The efficacy of immune checkpoint inhibitors has not only resulted in their application in earlier disease settings, but also in those with tumors that previously lacked effective systemic treatment options. This is, for example, the case in patients with melanoma brain metastases, which occur in up to 50% of patients with metastatic melanoma. Due to the lack of systemic effective treatment options, the historical survival was only 4-5 months with neurosurgery and radiotherapy. Nowadays, with the availability of targeted therapies and immune checkpoint inhibitors, patients with melanoma brain metastases have effective systemic treatment options and the possibility of long-term survival. For this reason, brain MRI-scans are increasingly used to detect brain metastases at an early time point and to closely monitor patients for intracranial disease progression. However, evidence to support rational use of brain MRI-scans in the management of melanoma is lacking. As a result, the use of brain MRI-scans varies widely in clinical practice. At the University Medical Center Groningen (UMCG), we advise 6-monthly screening MRI-scans to detect brain metastases and 3-monthly follow-up MRI-scans in patients with known brain metastases to inform localized and systemic treatment decisions. To get better insight into the impact of these scans in chapter 3, a retrospective study was performed that aimed to determine how frequently asymptomatic melanoma brain metastases were diagnosed by screening MRI-scans and the number of treatment strategy changes after follow-up MRI-scans in patients with melanoma brain metastases. Patients diagnosed with melanoma without brain metastases at the time of diagnosis and patients diagnosed with melanoma brain metastases between June-2015 and January-2018 were included. The impact of screening MRI-scans was evaluated in the first two years after metastatic melanoma diagnosis, and the impact of follow-up MRI-scans was determined in the first year after the brain metastases diagnosis.
Due to the durable tumor responses that can be achieved using immune checkpoint inhibitors, long-term treatment toxicity has become increasingly relevant to patients with tumors sensitive to immune checkpoint inhibitors. Most immune checkpoint inhibitor toxicities are acute in nature and resolve with adequate treatment. However, some toxicities, such as endocrine and rheumatological toxicities, may be long-lasting or permanent. Furthermore, radiotherapy for brain metastases may also cause significant toxicity (e.g., decreased neurocognitive function or symptomatic radionecrosis). These toxicities can significantly impede a patient's quality of life and their ability to participate in work, hobbies, or socialize. Next to these more somatic sequelae, patients were diagnosed with an initially life-limiting disease. This, in itself, can also cause psychological issues, such as anxiety, depression, existential distress, and fear of recurrence. Most of the research related to these matters was performed prior to the implementation of immune checkpoint inhibitors. Therefore, more insight into long-term treatment toxicity (including neurocognitive functioning), psychosocial, and existential issues in the current treatment era is needed.

A cross-sectional study in melanoma, NSCLC, and urogenital cancer survivors at least two years after treatment with immune checkpoint inhibitors was performed. In that study, patient's and caregiver's quality of life, patient's neurocognitive functioning, psychological well-being, perceived sexual functioning, and physical fitness were evaluated, and the persistency of immune-related adverse events was determined. Patients completed self-report questionnaires and a neuropsychological test battery, muscle strength, and walking test were performed. Additionally, caregivers were asked to complete a questionnaire evaluating their quality of life. In chapter 4, we included a preliminary report of this study reporting the quality of life, neurocognitive functioning, and psychological well-being outcomes in patients and caregivers that were included at the UMCG between October-2018 and November-2021.

To better understand neurocognitive impairment in cancer patients, also in those actively receiving treatment, a study (chapter 5) to evaluate the frequency of neurocognitive impairment and neurocognitive concerns and associated factors in patients with metastatic NSCLC was performed. Outpatient patients with metastatic NSCLC were included between October-2018 and June-2019 at the Princess Margaret Cancer Centre (Toronto, Canada). Eligible patients completed neuropsychological tests and questionnaires related to neurocognitive concerns, neurobehavioral symptoms, psychological issues, and physical symptoms.

Existential distress may also impede a cancer patient’s quality of life across the disease trajectory. The confrontation with the inevitability of one's death may cause distress about death and dying (death anxiety). In patients with metastatic NSCLC, the diagnosis of brain metastases and the presence of neurocognitive decline may also heighten death anxiety because of the link with disease progression. Chapter 6 describes the study performed to determine the relationship between psychological, physical, and disease-related factors
with death anxiety in patients with metastatic NSCLC. This study was performed in the same study cohort as chapter 5.

While long-term survival is the ultimate goal, not all patients benefit sufficiently from targeted therapies or immune checkpoint inhibitors. The availability of treatments with intracranial efficacy has resulted in increasing numbers of patients with melanoma brain metastases receiving anti-tumor treatment. It is unknown to which extent these treatments are provided near death and insight into this can inform the development of care pathways for patients with melanoma brain metastases with integrated supportive and palliative care in the current treatment era. Therefore, the anti-tumor treatments provided and healthcare consumption in the last three months of life of a cohort of patients with melanoma brain metastases were analyzed and reported in chapter 7. The cohort consisted of patients diagnosed with melanoma brain metastases between June-2015 and June-2018 in the UMCG and who died before November-2019.

In those that eventually die of their disease, death at home is most preferred by patients and their caregivers. Patients are regularly admitted to the hospital to evaluate new or progressive symptoms. When it is deemed that no further treatment options are feasible or available, some patients enter the terminal phase. Because most patients wish to die at home, these patients can be discharged home with end-of-life care at home. These discharges of terminally ill patients are complex but have hardly been explored. Structured analyses of hospital discharges will identify areas of potential improvements to ensure high-quality discharges and improve the quality of care for vulnerable, terminally ill patients. In chapter 8, we describe a method to systemically evaluate hospital discharge procedures of terminally ill patients and we subsequently used this method to evaluate the UMCG discharge procedures. The evaluation method assessed the cooperation between the hospital and community nurses, the required and provided care, and assessed how the community nurses evaluated the discharge handovers. The hospital discharges of terminally ill patients in the UMCG were evaluated between June and November-2014.

In the current treatment era, there are patients that respond to treatment and achieve long-term survival and patients who do not respond and die of their disease. Unfortunately, accurate prediction of who will benefit from the treatments is not yet possible. Therefore, it is important to both acknowledge and prepare for the possibility of an unfortunate outcome (i.e., death) while still working towards long-term survival. This duality may especially be relevant to patients with brain metastases. Minimal intracranial progression can provoke rapid neurological deterioration, including personality changes and impaired decision-making. The integration of early supportive and palliative care, including advance care planning and survivorship care, with anti-tumor treatment might be critical for these patients. Advance care planning relates to anticipatory conversations about potential symptoms and patient’s wishes regarding received care. Care pathways can support the integration process of supportive and palliative care into oncological care. The European
Pathway Association defines care pathways as a complex intervention aiming to improve the organization and quality of care for a well-defined group of patients during a well-defined period. By using such an intervention, the care process of patients with brain metastases might be modified so that effective anti-tumor treatment is provided together with adequate attention to supportive and palliative care needs. In chapter 9, our study in which we evaluated the current care of patients with melanoma and NSCLC brain metastases and subsequently developed and implemented a supportive and palliative care pathway for these patients is described. The care pathway was developed according to the “7-phase method to design, implement, and evaluate care pathways” of the European Pathway Association. The preliminary report described the evaluation of care and the development and implementation of the care pathway.
Chapter 1

References


Chapter 1


General introduction