New approaches and consequences for elderly cancer patients with focus on melanoma

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Chapter 9

Summary

For optimal treatment of an individual cancer patient, it is important to gain a maximum of useful information in order to optimally predict the result of a certain therapy. Specific tumor and patient characteristics are an important part of this so-called personalized therapeutics. In this thesis, the efficacy and toxicity of cancer treatment is evaluated with focus on melanoma, renal cell carcinoma and gastro-intestinal stromal tumor patients. Special attention is paid to subgroups like elderly patients.

Chapter 1 consists of the general introduction and outlines the thesis.

In **chapter 2**, current and emerging therapies for renal cell carcinoma are reviewed concerning efficacy, toxicity and complication risk for the elderly subgroup of patients. Approximately 50% of the patients with renal cell carcinoma consist of elderly. They differ from their younger counterparts in a higher incidence of multimorbidity and reduced organ function. Over the last decade several novel effective drugs have become available for the metastatic setting targeting angiogenesis and mammalian target of rapamycin. Immune checkpoint blockade with a programmed death 1 antibody has recently been shown to increase survival and further studies with immune checkpoint inhibitors are ongoing. Since age negatively influences outcome of surgery, age has to be taken into account the decision-making process in elderly patients eligible for cytoreductive nephrectomy. With multiple systemic treatment options available, instruments rating clinical benefit are highly relevant. For this purpose, the National Comprehensive Cancer Network (NCCN) developed evidence blocks, European Society for Medical Oncology (ESMO) developed a magnitude of clinical benefit scale (MCBS) and American Society of Clinical Oncology introduced a value framework. However, these tools are created for the entire patient population and are not necessarily applicable to elderly. We present modified evidence blocks for elderly metastatic renal cell carcinoma patients. Where possible, evidence-based recommendations for treatment choices in elderly patients with metastatic renal cell carcinoma are provided.

Chapter 3 reviews the current treatment options and drugs in development for metastatic melanoma with a special emphasis on the effects in the elderly subgroup of patients. Melanoma is a tumor type of all ages. On one hand, it is one of the most prevalent tumor types in adolescents and young adults. On the other hand, ~50% of newly diagnosed melanoma patients are above 65 years of age. New effective classes of drugs are available in the metastatic setting. The monoclonal antibodies targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibit immune checkpoints lead to prolonged overall survival and can result in long-term disease control. In addition, BRAF and MEK inhibitors, which target protein products of gain-of-function mutations in oncogenes, result in high response rates. Changes in the immune system occur during aging. Also, tumor driver-mutation profiles are age-specific in melanoma. Confronted with an aging population, there is a clear need to incorporate age-specific clinical information into treatment decisions within the new treatment landscape for metastatic melanoma. Historical data demonstrates that biological behavior of melanoma is unfavor-

able for elderly. Age-related changes of the immune system and an aged microenvironment can contribute to a poorer outcome for elderly. The aging population has led to an increasing need to incorporate age-specific clinical data in the decision-making process concerning anti-tumor therapy choices for elderly with metastatic melanoma. Although underrepresentation of elderly in clinical trials still endures, it is encouraging that in recent years an increasing number of (very) old patients are included in metastatic melanoma studies. A notable exception is the trial studying ipilimumab in the adjuvant setting, in which over 80% of the participants were younger than 65 years of age. Efficacy in elderly with metastatic melanoma is demonstrated for all Food and Drug Administration (FDA) approved treatments. It is exciting that – in contrast to results of vaccination for infectious diseases – activation of the immune system in elderly can be achieved with immune checkpoint inhibitors resulting in antitumor efficacy. Unfortunately, age-specific toxicity data is scarce. Interestingly, the outcome for many newly registered melanoma therapies obtained high scores for clinical effect in the NCCN value blocks and ESMO MCBS. This indicates a meaningful clinical benefit of several drugs and underscores the relevance to seriously consider these novel treatment approaches in the elderly. In the future, several approaches can afford better insight into the effects of the novel melanoma drugs on elderly patients. For example, reports of real-world data from expanded access trials and compassionate use programs can contribute to age-specific knowledge. In addition, the FDA and European Medicines Agency pharmacovigilance databases can be interrogated for age-related side effects. The FDA has implemented an initiative named Drug Trials Snapshots in which data from clinical trials is made transparent regarding age, gender and ethnicity of the participants. In addition, differences in efficacy and toxicity for the same demographic subgroups will be provided.

The biological behavior of melanoma in elderly is unfavorable compared to young patients. Recent studies with immune checkpoint inhibitors identified T cells as prominent actors in the immune response against melanoma. In **chapter 4**, the hypothesis that differences in T cell response might be an underlying factor in the discrepancy in biological behavior between young and elderly melanoma patients is tested. The circulating T cell repertoire of 34 metastatic melanoma patients is compared to that of 42 healthy controls. They were either qualified as young (< 50 years of age) or elderly (≥ 65 years of age). Absolute numbers of CD4+ T cells were decreased in young and old melanoma patients when compared to the age-matched control groups. Percentages of naive and memory CD4+ T cells were not different when comparing old melanoma patients to age-matched controls. Percentages of memory CD4+ T cells tended to be increased in young melanoma patients compared to young controls. Proportions of naive CD4+ T cells were lower in young patients than in age-matched controls, and actually comparable to those in old patients and controls. This is accompanied with increased percentages of memory CD4+ T cells expressing HLA-DR, Ki-67 and PD-1 in young melanoma patients in comparison to the age-matched controls, but not in old patients. The percentage of CTLA-4 expressing CD4+ T cells was similar in melanoma patients and controls. Proportions of FOXP3+Helios- regulatory T cells were increased in young and old melanoma patients when compared to their

9

age-matched controls, whereas those of FOXP3+Helios+ regulatory T cells were similar. We observed no clear modulation of the circulating CD8+ T cell repertoire in melanoma patients. In conclusion, the CD4+ T cell compartment of young melanoma patients shows strong signs of activation, whereas these signs are lacking in CD4+ T cells of old melanoma patients. These findings might explain the unfavorable behavior of melanoma in the elderly.

The immune checkpoint inhibitor ipilimumab induces apart from anti-tumor efficacy also autoimmune mediated side effects. Since autoimmunity is associated with older age and female gender, **chapter 5** describes the efficacy and toxicity profile of ipilimumab in the elderly melanoma patient population and examines the effect for gender. Patients participating in the Dutch Named Patient Program in 2010 and 2011 in 7 centers were included in the study. Response assessment was performed and side-effects were recorded. In addition, to evaluate reported real world side-effects the public pharmacovigilance FDA database was analyzed. Of the 172 patients with a median age of 55 years, 29.7% were ≥ 65 years and 43.0% were women. Median overall survival was 6.7 months (95% CI 4.7–8.7) in patients < 65 years and 10.4 months (95% CI 6.3–14.6) in patients ≥ 65 years. Grade 3–4 bowel toxicity was observed in 8.3% of patients < 65 years and 9.8% of patients ≥ 65 years. Discontinuation because side-effects occurred in 7.6% of the younger versus 8.3% of the older patients. No difference in efficacy and toxicity profile was observed between genders. 3,771 serious side-effects were reported as of November 2015 to the FDA database without major differences in toxicity profile between ages. In conclusion, treatment with ipilimumab for metastatic melanoma is equally effective in elderly and younger patients, is safe in patients ≥ 65 years and has similar efficacy and toxicity for both genders.

Gastrointestinal stromal tumors (GIST) are rare neoplasm of the gastrointestinal tract. First line treatment of metastatic or irresectable disease consists of imatinib, a tyrosine kinase inhibitor. A minority of the patients has primary resistance to this therapy. Recognition of these primary resistant patients with reliable upfront or early predictive biomarkers would enable early switch to effective treatment. In patients with chronic myelogenous leukemia treated with imatinib, development of hypophosphatemia was associated with response. In **chapter 6** is evaluated whether hypophosphatemia or hypocalcaemia are predictive biomarkers for GIST patients treated with imatinib. GIST patients treated with imatinib between 2004–2007 at the University Medical Center Groningen formed the test cohort. We longitudinally measured calcium, phosphate and parathyroid hormone levels before and during imatinib treatment. The efficacy of imatinib was defined as time to progression with response assessment by computed tomography. Results were validated in an independent patient cohort treated at the Erasmus University Medical Center between 2002–2007. All patients gave written informed consent. In the test cohort (n = 35 patients) imatinib initiation led to a significant decrease in the serum concentration of calcium corrected for albumin and phosphate in, while parathyroid hormone concentrations increased. Patients who developed hypophosphatemia had a shorter time to progression (median 8.4 months) than patients who did not develop hypophosphatemia (median 25.3 months), p = 0.016. In the validation cohort (n = 31) a similar decrease in plasma calcium

and phosphate was found, but a difference in time to progression between patients with and patients without hypophosphatemia could not be confirmed. In conclusion, development of hypophosphatemia early during imatinib treatment does not predict treatment efficacy.

Approximately 20–55% of patients with stage IV melanoma will die due to brain metastases. **Chapter 7** described a study that was set up in 2000 to evaluate whether prophylactic brain irradiation could help prevent or postpone the occurrence of brain metastases in patients with metastatic melanoma responding to systemic treatment with chemo-immunotherapy. It was the first study evaluating prophylactic irradiation in metastatic melanoma. Thirty patients with histologically confirmed distant metastatic melanoma were included and initially treated with dacarbazine, carboplatin and interferon-α. Sixteen patients showed non-progressive disease on systemic treatment and were offered to receive prophylactic brain irradiation. Thirteen patients actually received prophylactic brain irradiation. Patients who responded to chemo-immunotherapy, therefore eligible for prophylactic brain irradiation, survived longer (median 16.9 versus 6.9 months) and developed more often brain metastases (5 versus 2 patients) than the non-responders to chemo-immunotherapy. Of the patients treated with prophylactic brain irradiation, two developed clinical brain metastases within 10 months (12.5%, 95% CI 0–31%). Most common side-effects were headache and alopecia. This study was performed prior to general availability to BRAF inhibitors and novel immune boosting therapy. Also, currently we are more aware of long-term toxicity from whole brain irradiation. The future of prophylactic brain irradiation is therefore unsure. As the perception of radio-resistance for melanoma is changing, as well as the finding that melanoma cells are heterogeneously radio-responsive, analysis of optimal brain irradiation schedules is warranted. Given the growing systemic treatment arsenal available, the optimal time-window for prophylactic brain irradiation will remain challenging.

Chapter 8 consists of five subchapters, all describing a notable case report. **Chapter 8a** describes a patient with the first documented brain metastases harboring a BRAF V600R mutation that was treated to vemurafenib and it responded favorable. **Chapter 8b** described a patient with metastatic melanoma who developed disseminated intravascular coagulation induced by vemurafenib. Pharmacovigilance databases were proven to give insight in the existence of adverse events not reported in conventional literature. **Chapter 8c** describes a patient with metastatic melanoma who successfully managed her disease in an unconventional way by intermittent use of her anti-tumor therapy. Preclinical evidence suggests that her intermittent use of vemurafenib might be beneficial over the standard continues use. **Chapter 8d** describes a phenomenon named pseudo-progression, which can be seen after immune checkpoint blockade. Knowledge of this phenomenon may have impact on treatment choices. **Chapter 8e** describes the first case of a patient that developed a rabid granulomatosis with polyangiitis after a single dose of pembrolizumab. It is the first documented vasculitis case after a PD-1 antibody. Moreover, this case gives insight in the pathophysiology of anti-neutrophil cytoplasmic antibody-associated vasculitis.

Chapter 9 and **chapter 10** summarize this thesis in English and Dutch, respectively.

9