Targeted therapy, molecular imaging and biomarkers in cancer treatment

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Chapter 1

General Introduction

BACKGROUND

Until 2001 chemotherapy and hormonal therapies were the mainstays of systemic treatment of solid tumors. In 2001 it was shown that activation of the mutated c-Kit receptor in gastrointestinal stromal tumors (GIST) could be blocked by imatinib, a c-KIT tyrosine kinase inhibitor. This was one of the first successes of targeted therapy in solid tumors apart from the already long existing anti-hormonal therapy. The objective response rate in metastatic and unresectable GIST went from 0-5% for chemotherapy up to 38% for imatinib [1]. In recent years, more and more drugs specifically targeting diverse tumor characteristics have been developed. Unfortunately, not all targeted agents were as successful and in most cases, the effect of targeted agents is temporarily and often only seen in a subgroup of patients.

A major challenge in oncology is to identify patients that will benefit from various targeted agents. Eventually, this should lead to 'personalized medicine': a specific drug to treat a specific tumor with specific molecular or genetic characteristics in a specifically selected patient. Molecular profiling of tumor tissue is important in this regard, but there may also be a role for molecular imaging in selecting patients and predicting tumor responses. The advantage of molecular imaging is that it is non-invasive and all tumor lesions can be assessed which addresses tumor heterogeneity and circumvents sampling errors.

Another application of molecular imaging may be the (early) assessment of tumor responses. Treatment with targeted drugs may not always lead to a direct volume response of the tumor. Response assessments based on tumor diameter such as RECIST criteria for solid tumors on CT scans may therefore underestimate the anti-tumor activity of targeted agents [2]. In brain tumors, response assessment is especially difficult due to the blood brain barrier. Disruption or normalization of the blood brain barrier by the treatment complicates the evaluation of contrast enhanced MRI imaging [3]. Targeted drugs can block or reactivate pathways in tumors and modify the tumor microenvironment. This can potentially be visualized by molecular imaging with labeled drugs or labeled markers of pathway and microenvironment alterations.

As anticancer treatments are becoming more effective, attention also needs to be paid to side effects of treatment and care for long term cancer survivors. Prognostic markers for toxicity due to anticancer treatments are therefore warranted. Early recognition of susceptibility for toxic effects of anticancer therapy can lead to early treatment adaptations and more specific follow up.

The aim of this thesis is to provide novel insights in targeted drugs and the use of molecular imaging and biomarkers in anticancer treatments.

OUTLINE OF THE THESIS

Currently, the most frequently used way of systemic anticancer treatment is still DNA damage induction via chemotherapy. This DNA damage leads to apoptosis of tumor cells via the intrinsic apoptotic pathway. However, tumor cells often have mutations in this pathway, resulting in resistance to chemotherapy [4]. In addition, chemotherapy does not selectively affect tumor cells, but also induces damage to normal cells. Another way of inducing cell death is by targeting

the extrinsic pathway in tumor cells that induces apoptosis. One of the potentially interesting ways of doing this is via the TRAIL-R1 and TRAIL-R2 death receptors. Agonistic antibodies and recombinant TRAIL (rhTRAIL) can activate these receptors. In preclinical studies, it was found that these drugs can induce apoptosis and can enhance apoptosis in combination with chemotherapy and radiotherapy [5-7]. In **chapter 2**, a literature review was performed concerning the results of the phase 1 and 2 studies with the different agonistic antibodies against the TRAIL receptors and recombinant TRAIL.

When the first studies with imatinib in GIST patients were conducted, a decrease of ^{18}F-fluorodeoxyglucose (FDG) uptake on PET scans was noted within days of starting imatinib therapy. It was suggested that this could be used as an early marker of therapeutic response in these patients [8]. Approximately 15% of GIST patients show primary resistance to imatinib, defined as progressive disease at first CT evaluation after 2 months [9]. In **chapter 3** we retrospectively analyzed FDG-PET scans before start of imatinib and after 1 week of treatment initiation in 36 patients and compared the results with the outcome on CT scan after 2 months of treatment. We investigated whether early changes in tumor FDG uptake can predict primary imatinib resistance.

In brain tumors, the use of FDG-PET scans is hampered by the high uptake of glucose in normal brain tissue. However, accurate assessment of response to standard therapy with MRI imaging in glioblastomas is extremely difficult. Progressive lesions may not represent tumor growth, but rather a treatment effect that subsides in time without a change of therapy. This phenomenon is called pseudoprogression and seen in up to 64% of the patients with progressive disease on MRI directly after radiotherapy [10]. The difficulty to distinguish recurrent tumor growth (true progression) from pseudoprogression complicates the clinical decision making in these patients: in case of pseudoprogression, standard treatment with adjuvant temozolomide should be continued, whereas in case of true tumor progression, other treatment modalities or palliative care would be more appropriate. ^{18}F-fluorothymidine (FLT) is a PET tracer that is taken up by proliferating cells and therefore it may be possible to use FLT-PET scans to discriminate true progressive tumors from pseudoprogression as in the latter less proliferation would be expected. In **chapter 4** we prospectively investigated the capability of FLT-PET scans in discriminating between pseudoprogression and true progression in patients with newly diagnosed glioblastoma treated with radiotherapy and temozolomide. In 30 patients, FLT-PET scans were performed before start and 4 weeks after completion of concomitant radiochemotherapy. MRI scans were performed at these two time points and after 3 cycles of adjuvant TMZ. Pseudoprogression was defined as progressive disease on MRI after radiochemotherapy, with stabilization or improvement of enhancing lesions after 3 cycles of adjuvant TMZ. Changes in FLT uptake were compared between patients with true progression and pseudoprogression.

Another challenge in the management of malignant gliomas is the lack of effective standard therapy for recurrent disease, despite numerous studies with targeted agents and chemotherapeutics conducted in recent years. One reason for this might be that the blood-brain barrier hampers the uptake of targeted agents in brain tumors. An important target in high grade

gliomas is TGF-β, since it was shown that TGF-β functions as a tumor promoter in advanced cancer and is involved in glioma development [11,12]. In **chapter 5**, we describe a clinical study in which patients with recurrent high grade gliomas were treated with fresolimumab, a monoclonal antibody against TGF-β. To investigate whether the antibody actually reached the tumor, patients underwent a PET scan with ^{89}Zirconium labeled fresolimumab before start of treatment.

Testicular cancer patients are mostly treated with a combination of bleomycin, etoposide and cisplatin (BEP) chemotherapy. The cure rate is very high in this patient group. But about 10% of the patients treated with BEP develop bleomycin induced pulmonary toxicity and in up to 3% of the patients this is fatal [13]. TGF-β is involved in many cellular physiological and pathological processes in the body including the immune response, wound healing and fibrosis [14]. In preclinical studies, TGF-β is implicated as an important factor in the development of bleomycin induced pulmonary toxicity [15]. An early marker that can predict which patients will develop this toxicity is not available. In **chapter 6** we investigated the prevalence of abnormalities that were suspect for bleomycin-induced pulmonary changes on post chemotherapy restaging CT scans and whether TGF-β1 and GDF15 (a member of the TGF-β superfamily) and Hs-CRP levels in plasma can be used as biomarkers for the occurrence of these changes in testicular cancer patients treated with bleomycin containing combination chemotherapy. In **chapter 7** the thesis is summarized and future perspectives are given. **Chapter 8** provides a summary of the thesis in Dutch.

REFERENCES

[1] Cohen MH, Farrell A, Justice R, and Pazdur R, Approval summary: Imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors, Oncologist. 14 (2009) 174-180.

[2] Eisenhauer EA, Therasse P, Bogaerts J*, et al*, New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), Eur. J. Cancer. 45 (2009) 228-247.

[3] Brandsma D and van den Bent MJ, Pseudoprogression and pseudoresponse in the treatment of gliomas, Curr. Opin. Neurol. 22 (2009) 633-638.

[4] Vousden KH and Lu X, Live or let die: The cell's response to p53, Nat. Rev. Cancer. 2 (2002) 594-604.

[5] Ashkenazi A, Pai RC, Fong S*, et al*, Safety and antitumor activity of recombinant soluble Apo2 ligand, J. Clin. Invest. 104 (1999) 155-162.

[6] Chuntharapai A, Dodge K, Grimmer K, Schroeder K, Marsters SA, Koeppen H, Ashkenazi A, and Kim KJ, Isotype-dependent inhibition of tumor growth in vivo by monoclonal antibodies to death receptor 4, J. Immunol. 166 (2001) 4891-4898.

[7] Ichikawa K, Liu W, Zhao L*, et al*, Tumoricidal activity of a novel anti-human DR5 monoclonal antibody without hepatocyte cytotoxicity, Nat. Med. 7 (2001) 954-960.

[8] Abhyankar SA, Nair N. Highlighting the role of FDG PET scan in early response assessment of gastrointestinal stromal tumor treated with imatinib mesylate., Clin Nucl Med. 33(3) (2008) 213-214.

[9] Demetri GD, von Mehren M, Blanke CD*, et al*, Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors, N. Engl. J. Med. 347 (2002) 472-480.

[10] Fink J, Born D, and Chamberlain MC, Pseudoprogression: Relevance with respect to treatment of high-grade gliomas, Curr. Treat. Options Oncol. 12 (2011) 240-252.

[11] Massague J, TGFbeta in cancer, Cell. 134 (2008) 215-230.

[12] Kjellman, Olofsson SP, Hansson O, Von Schantz T, Lindvall M, Nilsson I, Salford IG, Sjogren HO, and Widegren B, Expression of TGF-beta isoforms, TGF-beta receptors, and SMAD molecules at different stages of human glioma, Int. J. Cancer. 89 (2000) 251-258.

[13] Simpson AB, Paul J, Graham J, and Kaye SB, Fatal bleomycin pulmonary toxicity in the west of scotland 1991-95: A review of patients with germ cell tumours, Br. J. Cancer. 78 (1998) 1061-1066.

[14] Blobe GC, Schiemann WP, and Lodish HF, Role of transforming growth factor beta in human disease, N. Engl. J. Med. 342 (2000) 1350-1358.

[15] Li M, Krishnaveni MS, Li C*, et al*, Epithelium-specific deletion of TGF-beta receptor type II protects mice from bleomycin-induced pulmonary fibrosis, J. Clin. Invest. 121 (2011) 277-287.