University of Groningen

PET imaging and in silico analyses to support personalized treatment in oncology

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

Link to publication in University of Groningen/UMCG research database

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Summary and future perspectives

Summary

Over the last decades many molecules and key pathways in cancer were identified, which facilitated a shift in anticancer drug development from DNA-damaging chemotherapy to a more personalized approach with targeted antibody therapeutics.[1] Moreover antibodies have been reshaped and modified in order to improve their efficacy.[2] For instance antibody-drug conjugates, and several types of bispecific antibodies, including bispecific T-cell engager (BiTE) antibody constructs and dual-affinity re-targeting antibodies, have been developed. To date, 34 antibodies including five antibody-drug conjugates and one BiTE antibody construct are approved by the U.S. Food and Drug Administration and/or European Medicines Agency for oncological indications.

A major challenge in oncology is to identify those patients that will benefit from targeted antibody therapeutics. Eventually this should lead to "personalized medicine" in which a specific drug is used to treat a tumor with specific molecular or genetic characteristics in a specifically selected patient. Therefore, it is important to assess tumor selective expression of molecular targets. Nowadays this can be done by performing immunohistochemistry (IHC) or quantitative polymerase chain reaction on serum and/or tumor samples. However, there may also be a role for molecular positron emission tomography (PET) imaging in selecting patients and predicting tumor responses. The advantage of molecular imaging over conventional methods is that it is non-invasive and enables whole-body assessment of tumor lesions, thereby addressing tumor heterogeneity and circumventing sampling errors. For these reasons, molecular antibody imaging can be a valuable tool in drug development, and patient enrichment strategies.

With a plethora of targeted agents becoming available to treat patients with cancer, broad knowledge concerning frequency of target expression across tumor types is of importance to fully exploit therapeutic options. Performing large-scale, golden standard, IHC analyses for many drug targets is time-consuming and demands many resources. Moreover standardized protocols for IHC staining are rarely available which has a strong impact on IHC results.[3] Alternatively one could use *in silico* functional genomic mRNA profiling (FGmRNA profiling) to predict target overexpression at the protein level across a broad range of tumors.[4] Although mRNA data should be interpreted with some caution, e.g. mRNA transcripts might not always be translated to the protein or proteins may not end up on the cell membrane, predicted overexpression rates have all been obtained with exactly the same methodology.[5] This approach allows researchers to directly compare predicted overexpression rates between tumor types and tumor subtypes.

The research performed in this thesis aimed to gain insight into antibody behavior in cancer patients, thereby focusing on novel bispecific T-cell engager antibody constructs, using early clinical development studies and molecular PET imaging. In addition, we aimed to contribute to a more personalized anti-cancer treatment approach by predicting overexpression rates of various drugable targets across a plethora of tumor types using FGmRNA profiling.

Chapter 1 provides a general introduction of the topic and outlines the thesis. In **chapter 2** we present an overview of theranostic approaches using antibodies and antibody-related therapeutics visualized with molecular PET imaging, in both the preclinical and clinical setting. We reviewed the available literature on PubMed and explored ongoing clinical trials on ClinicalTrials.gov.

We identified 24 different antibodies and antibody-related therapeutics used for theranostic purposes across 58 PET imaging studies in patients with cancer. The most frequently investigated antibody and radionuclide are respectively trastuzumab (n = 14; serum half-life several days) and zirconium-89 (^{89}Zr) (n = 18; physical half-life 78.4 hours). For theranostic PET approaches to become integrated in standard care, further standardization with respect to procedures involved is required.

Despite the highly dynamic field of drug discovery in cancer, there remains an urgent need for new therapeutics to improve survival in patients who have derived no or only minor benefits so far. In **chapter 3** we present data from a phase I study using ~55 kDa AMG 211, a carcinoembryonic antigen (CEA) and cluster of differentiation 3 (CD3) directed BiTE antibody construct. In this 3+3 dose-escalation dose-expansion study the safety, tolerability, immunogenicity, pharmacokinetics, and preliminary signs of clinical efficacy of single agent AMG 211 were determined in patients with advanced gastrointestinal adenocarcinomas. Moreover, pharmacodynamics including plasma inflammatory cytokines and CEA expression on tumor cells were studied in paired biopsies. Via central venous access, AMG 211 was administered as continuous intravenous infusion for 24 hours per day for either 7 or 14 consecutive days in 28-days cycles, or 28 consecutive days in 42-days cycles. At the start of each cycle, patients were admitted to the hospital for at least 48 hours. Afterwards, treatment was continued in the outpatient setting. Patients visited the outpatient clinic at least once a week for safety monitoring according to The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 criteria.[6] Blood was drawn for regular laboratory tests, and to study antibody-drug antibodies, pharmacokinetics, and inflammatory markers. Response evaluation with diagnostic CT was assessed at

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baseline and after every 2 cycles according to the immune-related response criteria.[7] Finally, mandatory archival and optional freshly gained biopsies were used to study CEA expression on tumor cells and the tumor microenvironment.

Forty-four patients with adenocarcinomas of the gastrointestinal tract were treated with AMG 211 for a maximum of 7 cycles (median 2) across 8 dosing cohorts. The maximum evaluated dose was 6,400 µg/day for 14 consecutive days in 28-days cycles, and 12,800 µg/day for 28 consecutive days in 42-days cycles. Dose limiting toxicities were not observed. Adverse events reported in > 20% of patients were fatigue (54.5%), pyrexia (38.6%), nausea (36.4%), abdominal pain (34.1%), and diarrhea (29.5%). Cytokine release syndrome, a well-known phenomenon of T-cell stimulating therapies, occurred in two patients (4.5%).[8] The study was discontinued after observation of anti-AMG 211 antibody formation in all patients treated at high doses of > 3,200 µg/day resulting in a drop in AMG 211 exposure with high anti-AMG 211 antibody titers. Pharmacokinetic steady-state concentrations were reached within 2 days of dosing and maintained throughout treatment, and dropped rapidly afterwards. Longest half-life was 15.2 hours in the two patients receiving AMG 211 12,800 µg/day for 28 days. Best response was stable disease, which occurred in 6 patients (13.6%) and ranged between 14 to 38 weeks. Nineteen of 22 available tumors expressed CEA on IHC analyses, while CEA transcript expression by NanoString was detected in all samples analyzed. This study showed that AMG 211 continuous intravenous infusion was generally well tolerated but did not lead to objective antitumor efficacy.

With modified bispecific antibodies, the potentially different binding affinity for the target of each of the arms might affect biodistribution. However, knowledge about biodistribution in patients of bispecific antibodies including BiTE antibody constructs is largely unknown. Therefore, we performed in **chapter 4** a first-in-human, two-center molecular PET imaging study with [89]Zr-labeled ~55 kDa AMG 211 as tracer. We aimed to study whole-body biodistribution of [89]Zr-AMG 211 in healthy tissues and tumor lesions before AMG 211 treatment and/or immediately after the end of the second AMG 211 treatment period of 28 days ("during AMG 211 treatment") as described in **chapter 3**. [89]Zr-AMG 211 was produced in the University Medical Center Groningen under good manufacturing practice conditions. Patients with relapsed or refractory gastrointestinal adenocarcinomas eligible for the phase I study received 37 MBq [89]Zr-AMG 211 intravenously with or without cold ("unlabeled") AMG 211. Subsequently patients were admitted for observation of side effects, which were graded according to NCI CTCAE v 4.03.[6] PET scans were performed at 3, 6, and 24 hours after completion of the tracer injection. Standardized uptake values (SUVs) were calculated for healthy tissues and tumor lesions and were compared within and between patients. At each

PET scan time point blood samples were collected to study tracer pharmacokinetics, tracer integrity, and tracer binding to immune cells.

Nine patients were enrolled. Before AMG 211 treatment, the optimal imaging dose was 200 µg ^{89}Zr-AMG 211 + 1,800 µg cold AMG 211. At 3 hours, the highest blood pool SUV_{mean} was 4.0, and tracer serum half-life was 3.3 h. CD3-mediated uptake was observed in CD3-rich lymphoid tissues like spleen and bone marrow (SUV_{mean} 3.2 and 1.8, respectively), and the SUV_{mean} decreased slower than in other healthy tissues. ^{89}Zr-AMG 211 remained intact and mainly unbound as measured in plasma, and was excreted predominantly via the kidneys in degraded forms. 37 out of 43 visible tumor lesions were PET quantifiable, with a SUV_{max} of 4.0 (interquartile range 2.7 – 4.4) at 3 hours using the optimal imaging dose. The tracer uptake differed 5-fold between tumor lesions and 9-fold between patients. During AMG 211 treatment more tracer was present in the blood pool, which is reflected by a longer serum ^{89}Zr-AMG 211 half-life of 16.4 h, while tumor lesions were not visualized, possibly indicating target saturation. This study demonstrated that imaging with ^{89}Zr-AMG 211 is very informative about the CEA/CD3 BiTE antibody constructs whole-body biodistribution and tumor targeting. We showed CD3-specific tracer accumulation in lymphoid organs and clear tumor uptake that was highly heterogeneous, both within and between patients.

In the era of personalized medicine, identification of novel drugable targets to increase therapeutic possibilities in cancer patients is of great value. The membrane-bound heparan sulfate proteoglycan glypican 3 is currently exploited as a novel drug target because it is a highly specific tumor marker. In this respect, it is critical to have good insight into its overexpression across several tumor types. In **chapter 5**, we aimed to predict glypican 3 protein overexpression across 60 different tumor types and subtypes with FGmRNA profiling. This technique was applied to expression profiles of 18,055 patient-derived tumor samples to predict glypican 3 overexpression at the protein level with healthy tissues as reference. In addition, we compared our predictions with IHC staining of a breast cancer tissue microarray containing 391 tumor samples with an average of 2.74 assessable cores per tumor, and historical IHC data in literature derived from a systematic search on PubMed.

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Predicted glypican 3 overexpression was observed in 77% of hepatocellular carcinoma samples, 45% of squamous cell lung cancer samples, 19% of head and neck squamous cell cancer samples, and 18% of squamous cell esophageal cancer samples. The overexpression found in head and neck squamous cell cancer was not yet reported with IHC analysis in the literature. In breast cancer, predicted glypican 3 overexpression was receptor status dependent with 13% for estrogen receptor (ER)-

positive, 7% for human epidermal growth factor receptor 2 (HER2)-positive, 14% for ER-positive/HER2-positive, and 8% for triple negative breast cancer. Since IHC glypican 3 overexpression in breast cancer subgroups based on receptor status was not yet reported in literature, we compared our predictions with IHC staining measured with a breast cancer tissue microarray. This analysis showed glypican 3 overexpression in 13% of ER-positive, 17% of HER2-positive, 12% of ER-positive/HER2-positive and 13% of triple negative breast cancers. For 34 tumor types and subtypes FGmRNA profiling data could be compared with IHC data showing a relative difference of $\leq$ 10% for 28 out of 34 tumor types. This study provides a data-driven prioritization of tumor types and subtypes for future research with glypican 3 targeting therapies.

In **chapter 6** we reviewed available literature and ongoing clinical trials concerning antibody-drug conjugates, both marketed and in clinical development, and the targets to which they are directed. We subsequently aimed to define the landscape of predicted antibody-drug conjugate target overexpression across a broad range of 60 different tumor types, which could be helpful to guide clinicians and drug developers in deciding which antibody-drug conjugate is of potential interest for further evaluation in which tumor type. We therefore applied FGmRNA profiling to expression profiles of 18,055 patient-derived tumor samples to predict, per tumor type, the antibody-drug conjugate target overexpression rate at the protein level, using healthy tissue samples as reference.

We identified 87 antibody-drug conjugates directed against 59 unique targets. In frequently diagnosed breast cancer, 31 of these 59 antibody-drug conjugate targets had a predicted overexpression rate $\geq$ 10% of samples, including 23 antibody-drug conjugate targets in triple negative breast cancer. A predicted overexpression rate of $\geq$ 10% of samples for multiple antibody-drug conjugate targets was also observed for other high incidence tumor types like colorectal cancer (n = 18), lung adenocarcinoma (n = 18), squamous cell lung cancer (n = 16), and prostate cancer (n = 5). In rare tumor types we observed, amongst others, a predicted overexpression rate of 55% of samples for cluster of differentiation 22 and ectonucleotide pyrophosphatase/phosphodiesterase 3 in adrenocortical adenocarcinomas, 81% for cluster of differentiation 74 and fibroblast growth factor receptor 3 in osteosarcomas, and 95% for c-MET in uveal melanomas. In conclusion, our data provides clinicians and drug developers with an instrument that facilitates further evaluation.

Discussion and future perspectives

Bispecific T-cell engager antibody constructs in cancer patients

Tumor development resembles micro-evolution, and the concept of cancer immune-editing is now widely accepted as a mechanistic basis consisting of the three subsequent phases elimination, equilibrium, and escape.[9] During elimination, the innate and adaptive immune system successfully recognizes and destroys tumor cells. However, relatively less immunogenic tumor cells can remain undetected for years, and finally escape immune surveillance and grow into clinically relevant tumors.[10] Specific recognition and subsequently killing of tumor cells is mostly accomplished by the adaptive immune system and in particular by cytotoxic T-cells.[11] Currently several therapeutic approaches that utilize the cytotoxic potential of T-cells to destroy tumor cells have successfully entered the clinic including adoptive T-cell therapy, and immune checkpoint inhibitors.

CD19/CD3 directed blinatumomab has provided clinical proof of concept for the BiTE platform in hematological tumors.[12,13] More recently the application of BiTE antibody constructs in solid tumors has been explored. The CEA/CD3 BiTE AMG 211 was generally well tolerated in our phase 1 study in patients with advanced gastrointestinal adenocarcinomas, but objective responses were not seen. In a phase 1 study with EpCAM/CD3 directed solitomab in patients with refractory solid tumors, significant target-related adverse events such as an increase in liver parameters and severe diarrhea prevented dose escalation to therapeutic levels.[14] Future research has to elucidate whether solid tumors can respond to BiTE molecules. Approaches are ongoing to prolong drug circulation time by increasing its size, for instance via albumin-fusion, Fc-fusion, or glycosylation.[15,16] This could facilitate sustained tumor drug exposure and accumulation, as has been shown for a CEA/CD3 single chain diabody in mice bearing CEA-positive tumors.[17] For the full-size CEA/CD3 antibody CEA-TCB preliminary results of two ongoing phase 1 studies in patients with advanced colorectal cancers report metabolic partial response, assessed with ^{18}F-fluorodeoxyglucose PET at week 4-6, in 28% of patients when applied as single agent and 60% when combined with the programmed cell death ligand-1 antibody atezolizumab. This suggested the relevance of simultaneously targeting CEA on tumor cells and CD3 on T-cells.[18] As seen from this study, concomitant administration of BiTE antibody constructs with other anti-cancer therapeutics might also be of interest. Preclinically, the combination of AMG 211 and immune checkpoint inhibition resulted in a more potent cytotoxicity towards CEA-positive tumor cells.[19] In patients, such an approach is being investigated for blinatumomab. In an ongoing phase 1 study in patients with acute lymphoblastic leukemia, blinatumomab is combined with nivolumab or with ipilimumab (ClinicalTrials.gov identifier NCT02879695).

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Molecular PET imaging using radiolabeled bispecific antibodies

It is well acknowledged that the development of bispecific antibodies like BiTE antibody constructs for clinical use has been more challenging compared to the low hanging fruit comprising conventional monoclonal antibodies.[20] In bispecific antibodies, the two arms differ in binding affinity for targets, which might consequently affect tissue distribution and accumulation in patients, as has already been shown in mice and monkeys.[21-23] However, little is known about biodistribution of bispecific antibodies in patients.[24,25] Molecular PET imaging can be used as tool to expand our knowledge concerning whole-body target expression, biodistribution, and tumor accessibility for targeted antibody therapeutics including bispecific antibodies. This approach can support rational trial design for such innovative antibody targeting strategies. In the PET scan study **(chapter 4)**, we demonstrated that imaging with [89]Zr-AMG 211 was very informative regarding CEA/CD3 directed AMG 211 whole-body biodistribution and tumor targeting. We showed high specific [89]Zr-AMG 211 accumulation in CD3-rich lymphoid tissues like the spleen and bone marrow, as well as a clear but heterogeneous tumor uptake both within patients and between patients.

Comprehensive lesion assessment via non-invasive molecular PET imaging might provide useful support in treating patients. For instance, because of heterogeneity in tumor target expression patterns, some tumor lesions will be effectively targeted by the drug, while others remain untreated and will contribute to poor clinical outcomes. Lesions with low uptake may benefit more by local treatment. Alternatively, extensive lesion assessment via conventional methods like IHC could be used, but are burdensome to patients, given the invasive techniques involved, especially when repeated assessment is required. Pretreatment imaging of HER2 targeting, combined with early metabolic response assessment using ^{18}F-fluorodeoxyglucose PET, showed heterogeneity in target expression and was able to accurately predicted morphological response to therapy.[26] This therefore holds great promise for improving the understanding of tumor heterogeneity in metastatic HER2-positive breast cancer and for selecting patients who will or will not benefit from HER2 directed therapy with the antibody-drug conjugate trastuzumab emtansine.[26] More recently, the additive value of molecular PET imaging with [89]Zr-labeled programmed cell death ligand-1 directed atezolizumab was reported. Tumor responses correlated better with tumor uptake at baseline PET than with IHC determined programmed cell death ligand-1 status.[27] The lack of responders in the AMG 211 phase 1 study hindered our ability to establish molecular PET imaging associations with response.

Although molecular PET imaging is a valuable tool to study antibody biodistribution and tumor uptake, future studies are needed to confirm their role

as a biomarker in a larger patient population. Performing larger studies will require harmonization and standardization of radiolabeling and imaging procedures, as well as access to the required radionuclide. Large multicenter studies using [89]Zr probably will be feasible, as tracer sharing is easy given the relatively long physical half-life enabling transportation to other centers.

Functional genomic mRNA profiling to predict target overexpression for targeted therapeutics in cancer patients

We showed the potential of *in silico* FGmRNA profiling as screening tool to predict overexpression for the highly specific tumor target glypican 3, and for 59 unique antibody-drug conjugate targets across 60 tumor types and tumor subtypes. In the clinic, IHC analyses are most often used to assess protein presence. However, gaining insight into a broad range of tumors using IHC screening for the presence of various drugable targets is time consuming and demands many resources. Our studies showed that FGmRNA profiling provides "an educated guess" to answer questions concerning antigen target overexpression across tumors in a more efficient manner than large-scale IHC analyses. Nevertheless, some pitfalls concerning FGmRNA profiling must be considered. For example, mRNA is not always translated to protein and a protein does not always end up on the cell membrane and therefore mRNA data must be interpreted with some caution.[5] In addition, FGmRNA profiling does not inform about target heterogeneity and it cannot distinguish between tumor cells and non-tumor cells as source of target overexpression. Subsequent IHC validation or results might therefore be warranted. On the other hand, with IHC, major heterogeneity in staining antibodies, scoring methods and cut-off boundaries hamper direct comparison of results. It has clearly been illustrated that standardized protocols are critical in order to use IHC results for validation.[3]

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