Targeted therapy in oncology: mechanisms and toxicity

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General discussion

Targeted therapy

Conventional chemotherapeutical agents act by creating toxic effects on all dividing cells, frequently resulting in severe damage of normal tissues leading to side effects like myelosuppression, alopecia, or gastrointestinal problems. The optimum goal is to find a treatment modality that specifically kills malignant cells and causes little or no side effects. Targeted therapies were developed to target key elements that play a role in tumor development and tumor growth.

There is not one unanimous definition for the term 'targeted therapies'. In theory all therapies are 'targeted', so the term 'targeted therapies' is artificial when not used by a certain definition.[1] One common definition, and used in this thesis, is 'Targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with rapidly dividing cells (e.g. with traditional chemotherapy)'. There are various ways to categorize targeted agents, including categorizing by mode of inhibition of a signaling pathway, e.g. small molecule vs. antibody or by type of receptor that is blocked, e.g. EGFR, VEGFR, c-KIT etc. Another way of categorizing targeted agents is by effects in the tumor development, e.g. angiogenesis inhibitor, apoptosis inducer etc.

Trastuzumab (Herceptin®) is an excellent example of a targeted agent in the category of the monoclonal antibodies and is directed against the Her2 (EGFR2) receptor. In the category of targeted small molecules, imatinib (Gleevec®/Glivec®) was the first agent that was successfully developed. The results of imatinib in GIST, a tumor that is poorly affected by chemotherapy and radiotherapy, were astonishing and lead to a boost in research of small molecule tyrosine kinase inhibitors in solid tumors.[2,3] Also, the prognosis of Her2 positive breast cancer patients has improved significantly since the development of trastuzumab.[4,5]

On the contrary, most targeted agents do not meet up to the high expectations. The hope was that when crucial receptor and downstream signaling could be inhibited, proliferation of cancer cells was blocked and cancer could subsequently become a chronic illness. However, it becomes more and more clear that proliferation of cancer cells, in general, cannot be stopped by blocking only one or two signaling pathways.

Drug-development and patient selection in the treatment with targeted agents

Alterations should be made to the conventional phases of drug-development in oncology. In my opinion, maximum tolerated dose (MTD) can no longer be the only end-point

in oncological phase I studies, since targeted agents have limited side effects and MTD might never be reached. Instead, phase I studies should aim at identifying the maximum biological active dose, i.e. the dose that creates the maximum target inhibition. In our phase I study with telatinib, a small molecule angiogenesis inhibitor, we performed additional measurements with DCE-MRI, and plasma VEGF and s-VEGFR levels. Biomarker analyses showed dose-dependent increase in VEGF levels and decrease in sVEGFR-2 levels, with a plateau at 900 mg bid. A decrease in tumor blood flow (K_{trans} and $IAUC_{60}$) was observed with DCE-MRI. These results, together with the PK results were the main factors in determining the recommended phase II dose of a drug with limited side effects.

In phase II/III studies, instead of response rate, other endpoints should be chosen, like time to progression, while with targeted agents it might take some time before stabilization of the disease occurs. When agents like telatinib or danusertib are evaluated in phase II trials these changes to, in my opinion, 'old' trial designs should be made.

The observation that the efficacy of most targeted agents is limited in unselected patients warrants studies aiming at selecting subgroups of patients for which these drugs are beneficial. Exploration of predictive receptor polymorphisms or specific tumor subtypes with specific overactivity of certain signaling pathways may help to achieve this goal. In phase III studies, selection of the study population should be made based on biogenetics of the tumor, and investigations should also include pharmacodynamic analysis of target inhibition. In previous large phase III trials in unselected patients, targeted agents were incorrectly judged to be ineffective, and research of an effective drug has incorrectly been stopped.

In the studies reported in this thesis we aimed at selection of the best patient groups. In sarcomas we searched for EGFR and Her2 expression to select those patients who could benefit from EGFR/Her2 directed therapies. With pharmacogenetic studies we aimed to select those patients treated with the aurora kinase inhibitor danusertib or the small molecule VEGF inhibitor telatinib who would benefit most from those targeted agents without experiencing unnecessary side effects.

Toxicity of targeted agents

Unexpectedly, the toxicity of these new and specific agents is sometimes severe and may be unrecognized by the treating physician due to lack of experience. One example is the difference in monitoring of cardiovascular toxicity of trastuzumab and sunitinib, both known for their cardiotoxic side-effects. Trastuzumab has been part of the therapeutic arsenal far longer then sunitinib. In the five major randomized adjuvant trials, the use

of trastuzumab combination therapy resulted in severe congestive heart failure (New York Heart Association class III or IV) in 0-3.9% of patients treated in the trastuzumab arms versus 0-1.3% in the control arms. Ejection fraction decline of ≥10- 15% was reported in 3-34% of trastuzumab treated patients in these trials.[6] For sunitinib, data on cardiovascular toxicity are more recent, however in some reports the rate of congestive heart failure and reductions in ejection fraction are even higher then with trastuzumab treatment.[7,8]

As new therapies become available, new side effects emerge. Physicians have to be aware of those new side effects and monitoring for newly emerging side effects should be optimalized. Ongoing research should include studies on side effects of new and older agents, and studies to prevent or limit these toxicities. Clinical studies with translational research on mechanisms of toxicity and pharmacogenetic investigations have expanded the insight of and experience with selected targeted anti-cancer drugs.

This thesis focusses on hypertension, a specific side effect that is frequently seen in the treatment with VEGF inhibitors. The relevance of hypertension monitoring and treatment during anti-angiogenic treatment in cancer is often underestimated by clinicians. Acute rises in blood pressure caused by VEGF inhibitors may cause posterior leukoencefalopathy syndrome, with high morbidity and even mortality, which may be prevented by in time regulation of blood pressure.[9] Even more, multiple trials have shown that poorly controlled hypertension can lead to serious cardiovascular problems.[10,11] A long-term rise in diastolic blood pressure of 5-6 mm Hg is associated with 35-40% more stroke and 20-25% more coronary heart disease within 5 years.[12] We have shown that treatment with bevacizumab and telatinib, a monoclonal antibody against VEGF and a small molecule VEGF tyrosine kinase inhibitor, both result in decreased capillary density. This decreased capillary density is probably the basis for the VEGF-inhibitor induced hypertension. We could also show that the changes in capillary density are reversible after discontinuation of the VEGF-inhibitor. These studies increase the knowledge on the mechanisms of action of angiogenesis inhibitors and on angiogenesis induced side effects.

Future directions

In the coming years the use of targeted agents will probably expand even more rapidly. The indications might expand to almost all tumor types, to advanced and adjuvant therapy settings, and to combinations of multiple targeted agents or combinations of a targeted agent with conventional chemotherapy. Many clinical trials are already initi-

ated to explore which (combination of) agents in specific patient groups have the most potential and should be further investigated. The final position of certain targeted drugs in anti-cancer treatment will become more clear in the next decades. Agents will be registered for use when a clear survival benefit is observed for a certain indication, first in advanced stages of disease and then in the adjuvant setting. Moreover, new targeted agents directed at new pathways important in angiogenesis, apoptosis, cell division, and many others will hopefully be found.

This thesis reports a few of many trials that will increase the knowledge on targeted agents, on how to use them, whom to give them and hopefully increase the life expectancy and quality of life of future cancer patients.

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