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Editorial Comment

Targeted therapy – How successful has it been?

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The notion of 'targeted' for the actual and future antitumour therapeutic principle implies that the therapy of the past was undirected or lacking targets. This would be to overemphasise what medical oncologists are capable of doing now. Furthermore, it has to be admitted that the therapeutic approaches of the past were not target-less.

Most agents of conventional chemotherapy target tumour-cell DNA synthesis or repair as general principles, exploiting thereby the often only marginal advantage of the relative smaller proliferation rate of many non-malignant transformed cells in comparison to cancer cells. Many alkaloids, derived from plants or of marine origin, function mainly via interference with microtubules and have a negative impact on the functioning of the spindle apparatus. In highlighting the 'target-directed' approach, we base our concept of malignancy on the newer understanding of cancer as a genetic disease with mutations that produce oncogenes, with dominant gain of function, and tumour suppressor genes, with recessive loss of function. Therapeutically, the mutated genes, their gene products such as receptors, or even comprehensive signal-transduction pathways and networks, may be targeted. As with conventional chemotherapy, the absence or the low expression of such genes, their products or entire networks in normal tissues provide the basis for specific tumour targeting.

A model of the physiological circuits of normal cell regulation has been provided by Hanahan and Weinberg [1] in their seminal 'The hallmarks of cancer'. According to Carbone [2], 'hitting a specific target is not therapeutically meaningful unless the tumour depends on the target and equally important, the host does not'. The paradigm of a targeted therapy we are most familiar with is (anti-)hormone therapy, especially in breast cancer. Although it is one that goes back more than a hundred years, we learned only very recently (in 1996) that there exists more than a single receptor mediating the action of oestrogens [3]. Similarly, how to profit from anti-oestrogen therapy even with incomplete knowledge of its mode of action until today, although, in comparison to others, the steroid hormone pathway is among the simplest of the cell's physiological circuits known so far. Nevertheless, it took decades: (1) to determine the target patient population; (2) to standardise the method of determining/measuring the hormone receptor level with various detection methods; (3) to assess the putative therapeutic impact on palliative, curative or adjuvant treatment and prevention. And there are still many open questions to be determined/answered, among them a definitive explanation of its mode of action.

The paradigm of an oncogene-targeted cancer therapy is all-*trans* retinoic acid (ATRA) in acute promyelocytic leukaemia (APL); a condition that is induced by a t(15,17) translocation that generates a PML/RARα fusion protein. ATRA causes degradation of PML/RARα, thereby overcoming the dominant negative effect of this translocation product, ultimately inducing differentiation. ATRA single-agent therapy yields remissions in 87%, among them 81% complete remissions, lasting a median of 12 months. In previously treated patients, complete remissions were observed in 77% [4]. Nevertheless, since combining ATRA with conventional chemotherapy yielded superior survival, only the combination of this highly selective targeted therapy with conventional chemotherapy became state-of-the-art treatment for this rather rare disease [5].

Exactly a 100 years ago, Paul Ehrlich, the founder of chemotherapy, used the term 'magic bullets' for antibodies attacking only the pathogen, thereby leaving the healthy organism unaffected [6]. Rituximab (Mabthera®) was the first (chimeric anti-CD20) monoclonal antibody introduced successfully in haematology; it

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yielded 48% remissions, among them 6% complete remissions, in relapsed and/or refractory patients with indolent and follicular lymphoma [7]. Nevertheless, the treatment of these in principle incurable subentities of the lymphomas with this highly targeted approach has not changed the overall outcome of the disease. Clinical trials to combine the monoclonal antibody with conventional therapies are now envisaged. The ultimate established indication for the drug until now is in the treatment of elderly (i.e., >60 years) patients with diffuse large B-cell lymphoma, where it yields statistically significant longer survival ($P = 0.007$) when added to/combined with conventional chemotherapy in form of the CHOP regimen [8].

The first therapeutically successful humanised monoclonal antibody in solid tumour oncology, trastuzumab (Herceptin®), is directed against the extracellular domain of the transmembrane glycoprotein receptor HER-2. It yielded an objective response rate of 15% (4% complete remissions; based on an intent-to-treat analysis; 95% confidence interval, 11–21%) in a cohort of patients with breast cancers over-expressing HER-2 and progressing after chemotherapy, with a median duration of response of 9.1 months [9]. HER-2 over-expression has a direct role in the pathogenesis of this malignant disease; thus its expression is directly linked to the prognosis of breast cancer. Experimental data suggest that trastuzumab's effect on downregulating HER-2 and/or HER-2-mediated signal transduction are more critical to the clinical activity of the antibody than any effects on antibody-mediated cell killing by activated immune effector mechanisms. The objective response rate of less than 20% led the targeted molecule to be added to conventional chemotherapy, resulting in significantly superior results for the combination with regard to objective response, duration of response, time to progression and survival [10].

The chimeric monoclonal antibody cetuximab (Erbitux®) blocks the binding of the natural ligands, epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) to the extracellular domain of the EGF receptor (EGFR), thereby increasing receptor internalisation and inhibiting receptor phosphorylation/activation as well as cell proliferation. The objective single-agent activity in patients with metastasised EGFR-expressing colorectal cancer who were resistant to chemotherapy with irinotecan was 11% [11]. Valuable definite survival results from adding cetuximab to chemotherapy in colorectal cancer are not available as yet; time to progression was significantly longer when cetuximab was combined with irinotecan compared to its use alone. In a prospective randomised phase III study in patients with head-and-neck cancer, no significant advantageous impact of adding cetuximab to cisplatin has yet been found with regard to time to progression or survival [12].

The humanised monoclonal antibody bevacizumab (Avastin®) directed against vascular endothelial growth factor (VEGF) was the first representative of the category of anti-angiogenic/antivascular agents proved to have significantly superior results regarding objective response, duration of response, disease-free survival and median survival when combined with standard chemotherapy in general, and with irinotecan/fluorouracil/leucovorin in previously untreated patients with metastasised colorectal cancer in particular [13]. No comparable advantageous effect on survival was found when bevacizumab was compared prospectively with placebo in metastatic renal cell cancer; nevertheless, time to progression was significantly increased [14]. In a prospective randomised phase III study in patients with breast cancers who had failed prior therapy with an anthracycline and a taxane and who were treated with capecitabine alone or in combination with bevacizumab, no advantageous effect on the primary study aim, progression-free survival, was observed for the combination [15].

Let us focus now on the evaluation of the small molecules that were developed as targeted therapies and that have already become available in the clinic. The outcome of a targeted approach is indirectly determined by the identification of an ideal therapeutic target. In this respect, there is probably no better target identified so far than BCR–ABL. It is expressed in the majority of the patients with chronic myelogenous leukaemia (CML) and it has been shown to be the cause of the underlying disease. The BCR–ABL fusion protein functions as a constitutively activated tyrosine kinase and mutagenic analysis has shown that this activity is essential for the transforming function of the protein.

Imatinib mesylate (Glivec®) was developed primarily as an inhibitor of platelet-derived growth factor receptor (PDGFR). It also inhibited all ABL tyrosine kinase variants and c-KIT, the receptor for stem-cell factor (SCF), but no other protein tyrosine kinases. Very recently, it proved to be statistically significant superior to the established combination chemotherapy consisting of interferon-α plus cytarabine with regard to haematological and cytogenetic responses as well as progression to accelerated-phase or blast crisis-free survival [16]. There exist therapeutic limitations to using imatinib in the treatment of the various forms of CML. Several differing mechanisms of resistance can be activated. Therefore, various pharmacological approaches may be, alone or in combination, adequate to tackle this phenomenon. From the clinic, we had to learn that advanced BCR–ABL-positive leukaemias develop DNA mutations at high frequency and dispose on a reduced role for DNA repair. Therefore, preventing resistance from occurring is of utmost importance. Similarly successful was the development of imatinib for the treatment of patients with gastrointestinal stromal tumours (GIST). The constitu-