

Preface

Drugs for HER-2-positive Breast Cancer: A Major Approval for Translational Cancer Research

Research over the last 2–3 decades in the fields of cell and molecular biology as well as biomedicine has tremendously improved our understanding of the mechanisms of malignant transformation and progression. A lot of knowledge gained from these findings could already be transferred to clinical application and has led to a number of major advances in the early diagnosis and treatment of cancer. This applies especially to breast cancer. Development of molecular-targeted drugs nowadays is characterized by several key features. In the first step, promising molecular targets have to be identified. The ideal cancer drug target – albeit not often found – should represent a molecule that is absolutely required for the proliferation and survival of the transformed cell. In other words, it should be a molecule to which the tumour cell is “addicted” (the “Achilles heel”). Consequently, the choice of drug targets is based on and driven by a profound knowledge about the cellular and molecular biology of the crucial regulatory processes that are significantly aberrant in malignant cells. In the second step, promising chemical lead structures are identified or a panel of antibodies is produced. Therefore, whereas classical cytotoxic drugs were previously identified by more or less random screening of large libraries of (natural and synthetic) compounds, novel molecular-targeted drugs are usually identified by a more rational approach that takes into account several aspects such as the physical–chemical properties of the aimed target domain and the therapeutic compound. These agents are then screened for optimal therapeutic indexes (maximal treatment effects with concurrent minimal side effects).

Tamoxifen was the first molecular-targeted drug ever in use in clinical oncology. It has been and is still being used for the management of oestrogen receptor-positive breast tumours. This drug – originally developed as an oral contraceptive – was not successful for that indication. However, “by chance” it was found that tamoxifen potently blocks the growth of oestrogen receptor-positive breast cancer cells [1]. In contrast to tamoxifen, development of the anti-ErbB2 antibody trastuzumab

against ErbB2-positive metastatic breast cancer was “hypothesis-driven” according to the above-mentioned criteria. Thus, trastuzumab became the first clinically available oncogene-targeted therapeutic agent for the treatment of solid tumours (see chapter by Bartsch and Steger). The first kinase inhibitor for application against malignant diseases was imatinib. It inhibits the ABL kinase, which is rearranged and hyperactive in chronic myelogenous leukaemia. Notably, recent encouraging data indicate that the reversible dual-specific EGFR/ErbB2 kinase inhibitor lapatinib is still effective in ErbB2-positive breast cancer patients who have already developed resistance to trastuzumab. In conclusion, breast cancer belongs to that type of solid tumours, in which molecular-targeted therapies were most efficient and yielded most clinical benefits so far (e.g. tamoxifen, trastuzumab, lapatinib). Unfortunately, however, despite these improvements, breast cancer is still a major life-threatening disease for women in industrialized as well as developing countries, and there are several significant detriments when using ErbB-targeted therapies against mammary cancer. First, only a proportion of ErbB2-positive breast cancers are actually sensitive to trastuzumab (*a priori*, primary resistance). Moreover, almost all ErbB2-positive, trastuzumab-sensitive breast cancers become resistant within 1 year of trastuzumab treatment (acquired, secondary resistance) (see chapters by Morgillo et al., Bianchi and Gianni, von Minckwitz and Pirvulescu). In recent years, it has become increasingly evident that signalling pathways are by no means linear cascades of signal processing; they rather represent intensely interwoven regulatory networks that communicate with each other via several relay proteins that function as signalling hubs (see chapter by Köstler and Yarden). Thus, even if a highly specific drug such as trastuzumab potently silences its intended target ErbB2, the cell still might be capable of avoiding the growth-inhibitory pressure by rerouting the signal to other growth-promoting cascades leading to resistance after a certain treatment period. Therefore, targeted cancer treatment should seek to specifically neutralise the hub proteins, which control a number of signal pathways that are crucial for cancer cell growth and survival (the “Achilles heel” of cancer). Another possibility is to use kinase inhibitors with broader specificity in order to neutralize more than one signalling protein. Novel treatment strategies usually apply more than one targeted inhibitor or antibody, or they combine target-specific blockers with classical cytotoxic drugs. Moreover, therapeutic efficiency may be further increased by using inhibitors that bind covalently instead of reversibly by hydrogen bonds to their respective substrates and thus permanently neutralise the target. Such second-generation, irreversible, multi-specific kinase inhibitors are currently in clinical development (see chapter by Solca et al.).

In summary, the recent developments in targeted therapy for breast cancer and of other neoplastic diseases have already considerably improved cancer treatment. Moreover, this era is characterized by an intense, fast and bi-directional flow of knowledge between basic science and clinical application. This type of research is growing very rapidly and has created an entirely new field of research known as “translational research”, which is located right at the interface between basic science and clinical medicine. Milestone achievements during the last decade

suggest that we are currently just at the beginning of a revolutionary and exciting era of cancer research, which almost certainly will tremendously improve future options for diagnosis, classification, individualisation and treatment of cancer.

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Reference

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