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Paediatric Update

Commentary

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Thanks to progress in basic and clinical research, there has been a remarkable improvement in the survival rates of children with cancer over the past 30–40 years. Advances in histopathological and molecular diagnostics have led to improved treatment stratifications. Technical improvements have spawned more specific radiological diagnostics, and enhanced surgical and radiation options. In addition, knowledge of the cytotoxic mechanisms of chemotherapeutic drugs has grown constantly. This growth has led to the development of standardised and consistently optimised polychemotherapies, and the corresponding regimens of supportive care. Both developments have resulted in better tumour control a substantial reduction in treatment-related toxicities, thus allowing larger boundaries of dose intensification for systemic treatment. Nevertheless, antitumour activity, especially against primary brain tumours and neuroblastoma, has often been rather modest. This constraint is probably due to various cellular survival mechanisms that still have to be elucidated.

Conventional cytotoxic chemotherapy was developed on the assumption that excessive rates of cell division are responsible for the genesis and progression of cancer. It therefore involves the use of agents capable of interrupting cell division. Mechanisms of action such as the inhibition of microtubule formation and/or the induction of DNA damage, by leading to errors in mitotic events as well as in DNA transcription and RNA translation, result in primarily apoptotic methods of cell death with their inevitable side-effects. The problem is that these are non-specific actions; they affect all rapidly dividing cells.

Half a century of cancer research has now generated a rich and complex body of knowledge. It has revealed that the production of human cancer is a multistep process with an age-related incidence reflecting a succession of genetic changes. These changes confer various types of growth advantage that drive the progressive transformation of normal cells into invasive, highly malignant derivatives. However, we must admit that despite all the recent advances in research and therapy, the ultimate problems of paediatric cancer have not been solved, especially those of non-response due to the successful survival mechanisms intrinsic to tumour cells, and of dose-limiting side-effects due to damaged normal cells.

How are we to incorporate all this acquired knowledge into future treatments without adding further layers of complexity to a body of scientific knowledge that is already complex beyond measure? Perhaps our unremitting search for the origin and treatment of the disease has reached a point where we might benefit from a conceptual change in both scientific and therapeutic approaches, by moving the science from complexity towards simplification in order to change the therapy from 'killing' towards control.

Our faith in such a change of strategy arises directly from cell biology. We know a small subset of acquired cellular properties is essential and shared by most, if not all, types of human tumour because these properties are in some sense fundamental to cancer. Examples include: self-sufficiency in relation to growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, sustained angiogenesis, limitless replicative potential, and tissue invasion and metastasis (reviewed in Ref. [1]), all of which represent promising targets for more selective types of therapy.

In their Update in this issue of the *European Journal of Cancer* [2], Drs. Brown and Small have chosen a very intriguing instance of one of these mechanisms, uniquely acquired by cancer cells, which is self-sufficient

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growth signalling. Normal cells require mitogenic growth signals before they can move from a quiescent to an active proliferative state. The corresponding signalling cascades are regulated by the activation of transmembrane receptors. These, in turn, activate the appropriate apparatus of cellular growth, primarily through their association with distinctive classes of signalling molecules, such as growth factors (e.g. transforming growth factor-α), survival factors (e.g. insulin-like growth factor-1), hormones (e.g. oestrogen), cytokines (e.g. interleukins-3 and-6), extracellular matrix components and cell-to-cell adhesion/interaction molecules [3]. Indeed, most growth factors and cytokines bind to their specific receptors and exert their effects by inducing kinase-mediated phosphorylation of downstream proteins [3]. To the best of our knowledge, no normal cell type can proliferate in the absence of such stimulatory signals, and only the orderly function of their corresponding pathways provides a balanced assemblage of eukaryotic cell proliferation, differentiation and death.

We also know that many oncogenes act by mimicking normal growth signals, a process that results in neoplastic transformation. Of particular interest are those oncogenes with constitutive kinase activity [4]. These proteins are products from genes such as *c-ABL*, *FLT3*, *c-KIT*, *c-FMS* and *PDGFRβ*, each of which is normally involved in the regulation of cell proliferation. The kinase activity of the oncogene is constitutively activated by mutations that remove the inhibitory domains of the molecule or induce the kinase domain to adopt an activated configuration [5]. The mechanisms of acquired growth-signal autonomy specific to malignant cells have become an attractive target for specially designed monoclonal antibodies or enzyme inhibitors.

In their review, Drs. Brown and Small comprehensively summarise the current literature on the molecular mechanisms of the FMS-like receptor tyrosine kinase 3 (FLT3), a member of the class III tyrosine kinase family. In assessing the potential impact of various promising FLT3 inhibitors on the treatment of both adult and childhood cancers, they correctly focus on the importance of the molecular background by explaining in detail the several potentially leukaemogenic signalling pathways differentially induced by different types of FLT3-activating mutations and the aberrant expression of wild-type FLT3. However, they also point out that more functional studies are urgently required to understand and make best use of the biochemical backdrop. The dynamics of the target and corresponding up- and down-stream proteins affected by specific inhibitors should be correctly characterised before any drawing conclusions, especially from potentially misleading descriptions of their levels of inert expression.

Aside from the targeted cancer therapies summarised in this review, other novel approaches have emerged. To name but a few such approaches, the inhibition of proteasome-dependent protein degradation [6] or of angiogenesis [7], the induction of tumour cell differentiation by histone deacetylase inhibitors [8], and specific alterations of the activities of cell-cycle regulatory proteins and transcription factors [4] have all proved promising. But, while aspiring to design agents that modulate these 'specific' pathways, we must continue to consider several critical factors, as follows:

1. Possible toxicity of the targeted therapy: because most of the targeted pathways are activated to a significantly greater degree in malignant than in normal cells, their partial inhibition may be sufficient to interfere with malignant cell growth while sparing normal tissue. But these pathways also have a pivotal role in normal cellular function, so careful studies on potential toxicity to normal cells by their inhibition are needed, as well as on designing targeted treatment regimens that provide sufficient selectivity.
2. From another perspective, we should not simply focus our experimental attention on the genetically altered cancer cells, but also continue to investigate cell-to-cell growth signalling: the apparently 'normal bystanders' such as fibroblasts and endothelial cells may have key roles in driving tumour cell proliferation.

The difficulties of target validation must be reiterated. Drs Brown and Small point out that, excepting the product of the *BCR-ABL* fusion gene in the rare children with chronic myeloid leukaemia, and in those with Philadelphia chromosome-positive forms of acute lymphoblastic leukaemia and acute myeloid leukaemia, most of the currently studied target proteins and their inhibitors have been investigated in adult haematological malignancies rather than in the paediatric solid tumours. Therefore, other points for consideration in designing inhibitors are (a) their cell-type specificity and (b), the evolutionary conservation of the targeted molecules. Our fluctuating hopes for gene and immunotherapy, for example, should remind us that not every basic biological observation can easily be transferred from mice to men, from cell line to tissue, from adults to children, or from haematological malignancies to solid tumours.

The fact that each cellular signalling pathway is a substantial part of a complex, concentrated network of interconnecting cascades, resulting in a certain amount of redundancy and overlap, is an additional, crucial challenge. A better understanding of this complexity, even though it might now be provided by high-tech equipment, will probably not be achieved only by global studies on gene and protein expression, which often leave the clinical scientist alone with, at first sight, mainly non-specific profiles. As already mentioned, basic biochemical and molecular approaches that provide

functional monitoring in addition to descriptive analyses of single target proteins, in addition to their specific role within normal and abnormal cell-cycle regulation, should be fundamental to cancer research in general and to future study designs. A *rapprochement* in these different approaches should encourage basic and clinical scientists to collaborate even more closely, with each discipline exercising its specific skills, but sharing knowledge and developing improved concepts of and conduits for translational research from bench to bedside and *vice versa*.

Future research on targeted cancer treatment should therefore encourage us to proceed towards a change in the general therapeutic paradigm. Until now, we have primarily focused upon eradicating cancer. But, through understanding the complexity of paediatric cancer in terms of a small number of underlying principles, some of them not yet identified, and with having the continuing technical progress in molecular cancer research at our side, we should be allowed to ask the following question: Why should we not re-define the term 'cure', with all its acute and long-term sequelae, as a process through which cancers are conquered by keeping the cancer cells under control rather than by simply killing them? Modulation of the major molecular or biochemical 'hot spots' contributing to cellular dysfunction could be a promising approach, already remarkably successful in the treatment of patients with diabetes and acquired immunodeficiency syndrome (AIDS).

'Collecting, structuring, analysing—being a modest servant dedicated to the house of knowledge to better deal with the circle of life'[1] may be a realistic route to greater success in paediatric cancer research and therapy.

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[1] Ich sammle, ich ordne, ich teile ein, ein bescheidener Diener im Haus des Wissens; ich deute und versuche, die Gestalt der Dinge darzustellen und ihren Lauf zu verzeichnen [9].