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A new era in cancer therapeutics?

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The 14th EORTC–NCI–AACR Symposium *Molecular Targets and Cancer Therapeutics* (Frankfurt, Germany; 19–22 November 2002) is the foremost meeting in the cancer field to focus specifically on molecular targets and their exploitation in the discovery and development of selective cancer therapeutic agents.

The meeting consisted of a series of plenary lecture sessions given by acknowledged leaders in the field. Other sessions took the form of keynote lectures, workshops, posters and proffered papers. A sizeable number of exhibitors, mainly from the pharmaceutical and biotechnology sectors, were also represented at the meeting.

Crucial issues

The conference programme attempted to address the following central issues in cancer therapeutics: (1) What were most likely to be important targets for therapeutic intervention, and (2) What were the major advances in cancer drug discovery and development during the past year or so? Put another way, if 2001 was the year of Glivec® (Novartis AG; http://www.novartis.com) and tyrosine kinase inhibition, what was making the news this year?

This question, however, proved rather complex to answer because several advances in a variety of areas hold great promise for ultimately improving prospects for cancer patients. The main themes of the meeting were:

- EGF-receptor targeting – clinical achievements
- Cytokines and angiogenesis in cancer biology and treatment
- Therapy prevention interface
- Pharmacogenetics
- Transcription factors and related pathways
- Chromatin modelling
- Cell cycle modulation
- Genomic integrity and DNA damaging process.

One of the main messages from this conference was that further advances in our understanding of cancer cell biology at the level of the individual tumour type (and increasingly at the level of the individual patient) continue to drive efforts to develop selective therapeutic agents. Much of the discussion during the meeting centred around the key question of what are the best targets to pursue for therapeutic application (target validation).

A key question discussed was whether the most successful cancer drugs in the near future will be agents that are selective for a specific molecular target affecting a single (or few) signalling pathway(s) – for example, EGFR tyrosine kinase inhibitors – or agents acting against a target simultaneously modulating several oncogenic lesions (e.g. Hsp90). Strategies for the intelligent combination of therapeutic agents targeting a single molecular defect with established chemotherapeutics (e.g. cytotoxic agents) to produce an efficacious response and overcome mechanisms of drug resistance were also a feature of discussion; Stanley B. Kaye, Royal Marsden Hospital, http://www.royalmarsden.org).

Tyrosine kinase inhibitors

Clearly, Glivec® is still an agent of tremendous promise for the treatment of other tumour types, in addition to the original indications (targeting Bcr–Abl oncoprotein in chronic myelogenous leukaemia and c-kit in gastrointestinal stromal tumour). New results on Glivec® show that its ability to inhibit platelet-derived growth factor (PDGF) receptor signaling increases the tumour uptake of cytotoxic agents several-fold through PDGF antagonist-mediated reduction in tumour interstitial fluid pressure (Arne Östman, Ludwig Institute of Cancer Research; http://www.licr.org). For example, treatment studies with Glivec® in combination with either of the cytotoxic drugs 5-fluorouracil (5-FU) or paclitaxel, or with the tubulin inhibitor epothilone B, produced superior antitumour effects in animal models than the single agent alone, without any signs of increased toxicity. An update on progress on the related epidermal growth factor receptor tyrosine kinase inhibitors, a number of which are in clinical development, was provided by several speakers (Manuel Hidalgo, The Sydney Kimmel Cancer Center at John Hopkins, http://www.skcc.org).

In general, these agents [e.g. Iressa® (AstraZeneca; http://www.astrazeneca.com) and Tarceva® (OSI Pharmaceuticals; http://www.osip.com)] are well tolerated in Phase I studies, and pharmacological results demonstrate adequate oral absorption and the achievement of biologically relevant plasma concentrations. Subsequent data from non-comparative trials (Phase II/III) indicated objective responses and prolonged stable disease in a substantial number of

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patients accompanied by improvement of symptoms. Disappointingly, however, the preliminary data from the first large randomized Phase III clinical trial of Iressa in non-small-cell lung carcinoma were negative.

Future issues to be addressed in this area include whether or not patients should be selected for disease-orientated studies based on the expression of the receptor, a problem exacerbated by the lack of robust and well-standardized methods to assess receptor expression, as well as suitable tissues for analysis in most patients. Results from future clinical studies with agents of this class are eagerly anticipated.

Chromatin modelling and secondary DNA structures

One particularly interesting issue arising from the meeting is the re-emergence of DNA structures, deemed unfashionable in some quarters in recent years, as an anticancer therapeutic target. For example, new work providing evidence for the formation of a G-quadruplex structure in the c-myc oncogene promoter region and its targeting with a small molecule to repress c-myc transcription were presented by Laurence H. Hurley (University of Arizona and Arizona Cancer Center; http://www.azcc.arizona.edu). The formation of similar G-quadruplexes in promoter regions of other growth regulatory genes (such as PDGF-A, c-myb and Ki-Ras) suggest that this might be a more general phenomenon in genes associated with growth and proliferation.

The role of histone methylation in both positive and negative regulation of transcriptional control, and the progress in elucidating the mechanisms by which such modifications regulate transcription, was reported by Tony Kouzarides (Wellcome/CRC Institute; http://www.welc.cam.ac.uk). A potential therapeutic application of DNA cytosine methylation inhibitors, such as 5-aza-2′-deoxycytidine, in causing rapid changes in the state of chromatin modification and resulting in the activation of silenced genes (e.g. tumour suppressor genes) was also described, by Peter A. Jones (University of Southern California, Norris Comprehensive Cancer Center; http://128.125.190.120/).

Other topics

Genetic polymorphisms, or rare mutations of proteins involved in metabolism, transport and action, can fundamentally alter the efficacy and toxicity profile of anticancer drugs. It is clear that these interindividual differences in response to therapy (e.g. through variability of cytochrome P450 expression) will assume increasing importance in future years and, appropriately, this topic formed the subject of a plenary session by speakers including Michel Eichelbaum (Dr Margarete Fischer-Bosch-Institut für Klinische Pharmakologie; http://www.ikp-stuttgart.de).

Gratifyingly, the subject of cancer chemoprevention was the theme of a plenary session, with notable contributions on the subject of dietary chemopreventatives (Andreas Gescher, Department of Oncology, University of Leicester; http://www.le.ac.uk), breast cancer chemoprevention (Andrea Decensi, European Institute of Oncology; http://www.ieo.it), and endpoint biomarkers in chemopreventative agent development (Scott Lippman, M.D. Anderson Cancer Center, University of Texas; http://www.mdanderson.org).

Progress in the development of angiogenesis inhibitors and cell cycle modulatory agents was also reported, and are areas of great promise that will feature in this type of meeting for years to come.

Summary

The conference as a whole gave a broad and contemporary overview of the inter-related fields of molecular targets and cancer therapeutics. Important advances are undoubtedly being made in this field that will ultimately translate into more selective and efficacious agents for patients. It is reasonable to expect that new validated targets for therapeutic exploitation at the individual tumour/patient level will be uncovered at an ever-accelerating rate driven by technological advances (e.g. gene expression profiling, presentation by Louis Staudt, Center for Cancer Research, National Cancer Institute; http://www.nci.nih.gov), giving drug discovery scientists unprecedented opportunities for novel therapies and new combination strategies in the clinic. It is clear that we are heading in the right direction and that the future holds great promise. The question of how long we might take to realise our ambitions, particularly against the most common solid tumours, is rather more difficult to answer.

The organising bodies, the EORTC (European Organisation for the Research and Treatment of Cancer; http://www.eortc.be), NCI (US National Cancer Institute; http://www.nci.nih.gov) and AACR (American Association for Cancer Research; http://www.aacr.org) represent the largest cancer research organisations in Europe and the USA, and their annual coming-together for this Symposium has been an important event in the cancer research calendar since 1999, alternating between Europe and the USA. The abstracts from all presentations can be found in a supplementary issue of the *European Journal of Cancer* (2002) Vol. 38, Suppl. 7.