Pergamon

European Journal of Cancer Vol. 32A, No. 1, pp. 39–40, 1996

Printed in Great Britain
0959-8049/96 $15.00+0.00

0959-8049(95)00629-X

Meeting Highlight

On the Threshold of Success? Report on ECCO8, 29 October–2 November 1995, Paris, France

D.C. Purves and I.R. Hart

British Postgraduate Medical Federation, 33 Millman Street, London WC1N 3EJ; and Richard Dimbleby Department of Cancer Research, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, U.K.

ATTEMPTING TO précis and review an International Meeting which attracted over 7 500 participants and lasted 5 days is clearly an impossible task. The numerous session overviews, plenary lectures and symposia covered the spectrum of activities and topics of interest to anyone involved in the treatment of, or research into, neoplasia.

If one major theme did emerge from this conference, it was that the remarkable expansion of knowledge in cell and molecular processes involved in tumour development, which has occurred over the past decade, is now providing us with novel targets for therapeutic intervention. As was pointed out by Dr Verweij (Rotterdam, The Netherlands), there are currently more than 50 new compounds in phase I trials, many of which are new chemical entities rather than adaptions of established pharmaceuticals, with novel targets and mechanisms of action.

While some of these agents, such as the antimetabolite Gemcitabine and the thymidylate synthase inhibitor Tomudex, are entering routine clinical practice, others are in more preliminary phases of development. For example, Professor Pinedo (Amsterdam, The Netherlands) indicated that future targets for cancer therapy, already under preclincal evaluation, include the *RAS* oncogene, signal transduction pathways, the enzyme telomerase, angiogenesis and many others. Selective inhibition of *RAS* genes, which are mutated and activated in many tumours, has proven possible in laboratory experiments using receptor or non-receptor tyrosine kinase inhibitors. Equally, MAP kinase inhibitors, which block downstream events, may terminate the proliferation signals generated by such activated oncogenes. Compounds which affect these targets have already been identified in the laboratory and, though they still have some way to go before they reach the clinic, provide promising new avenues for exploration.

Similarly, telomerase is an enzyme involved in DNA replication which functions to maintain telomeres at the terminal end of chromosomes. Telomeres, which consist of repeated TTAGGG DNA sequences, shorten with each cell division so that, after approximately 100 divisions, the cell senesces and becomes incapable of further division. Telomerase utilises its internal RNA component as a template to synthesise the TTAGGG telomeric sequence directly on to the ends of chromosomes and, by stabilising the telomeres, serves to act as an immortalising enzyme. It is the lack of telomerase in normal cells which regulates and inhibits indefinite cell growth, which is a hallmark of cancer cells. It has been shown that telomerase is expressed in more than 85% of all cancers, but, while it is also expressed in stem cells, the enzyme is not found in normal proliferative cells. Therefore, telomerase may provide a therapeutic target which is specifically present in the malignant cell. It is hoped that selective blocking of this enzyme activity could push the cancer cells into an ageing pathway and thereby stop proliferation.

The concept of re-routing cancer cells to pathways which result in regulated or controlled cell death (i.e. apoptosis) or to terminal differentiation, was emphasised by Sir Walter Bodmer (London, U.K.) in his plenary lecture. Reversal of imbalances in cell division, differentiation and cell death, which occur in malignancies as a result of accumulated mutations, may be a way of controlling tumour growth without the requirement to actually destroy all the neoplastic cells. Sir Walter stressed the central role that molecules which regulate normal cell–cell and cell–substratum adhesion have to play in maintaining differentiation pathways. Since disruption of these interactions is, or can be, such an important component of tumour development, it might be that agents which cause the re-expression of the appropriate adhesion molecules could regulate oncogenesis.

Equally, it may not be necessary to direct therapies to the neoplastic cells *per se*, since adjacent or interposed stromal cells in the tumour mass might serve as potential targets for therapy. Attacking the tumour by inhibiting the formation of new blood supplies, for example, may provide good anti-tumour efficacy and have the advantage that field-effects might be expected. Current anti-angiogenic mechanisms under evaluation include agents which inhibit the proliferation of endothelial cells (AGM-1470, PF-4, thalidomide), agents which bind and neutralise endothelial growth factors (suramin, monoclonal antibodies) and agents which inhibit

the proteolysis of extracellular matrix (inhibitors of metalloproteinase activity). These anti-angiogenic substances were briefly reviewed by Professor Pinedo (Amsterdam, The Netherlands).

Professor Paul Nurse (London, U.K.) in his Pezcoller Foundation award lecture, ably took us through the intricacies of the regulation of the cell cycle. Pioneering work in the fission yeast identified the cyclin dependent kinases (CDKs) as important checkpoint control elements in regulating the cell cycle. In the fission yeast, a single CDK $p34^{cdc2}$, encoded by *cdc2*, is required both for the initiation of S-phase and mitosis, two major events in all eukaryotic cell cycles. Biochemical analysis of the regulation of this protein kinase has revealed a series of interactions responsible for these precise sequential and temporal events. These mechanisms include the regulated availability of cyclin-B (to form an active complex with $p34^{cdc2}$), tyrosine phosphorylation at the active site of the enzyme (which functions to inhibit activity), specific phosphatases and the action of a protein inhibitor. As Professor Nurse stated, since these checkpoint control systems basically appear to be similar in all eukaryotic cells, the possibility exists that their dysregulation may not only have an impact on tumour development, but also may serve as targets for compounds aimed at disrupting cell proliferation.

Though the potential of many of these experimental discoveries has yet to be realised, their introduction into the clinic is an important event since it signals the fact that increased comprehension of tumour development mechanisms can result in new approaches and new compounds. Already some clinical trials are proceeding using novel approaches and giving cause for cautious optimism. Dr Riva (Cesena, Italy) presented results showing that the use of intralesional monoclonal antibodies against tenascin for malignant glioma, including recurrent disease, resulted in a response of 38%, with a median survival of 18 months. Monoclonal antibodies were also used in radio-immunoguided surgery for colorectal cancer, and Dr Schneebaum (Tel Aviv, Isreal) presented results showing that the use of an anti-TAG (tumour-associated glycoprotein) labelled with radioactive iodine permitted the intra-operative localisation of otherwise unidentified occult lesions in 45% of patients, which changed their surgical plan. The production of a vaccine to human papilloma virus for the treatment of advanced cervical cancer was described by Dr Adams (Cardiff, U.K.), where DNA containing the E6/E7 reading frames for HPV16 and 18 were incorporated into a vaccinia vector. Of the 8 patients given this vaccine, 2 produced an increased cytotoxic T-lymphocyte response to HPV, and 1 patient, who had had several recurrences, was clear of disease. New trials with CIN3 volunteers are now being initiated. The use of intratumoral β-interferon as a radiosensitiser for the treatment of solid tumours inaccessible for local treatment was presented by Dr Wildfang (Hannover, Germany), where there were responses in 11/20 patients, lasting 29–192 weeks.

New chemotherapeutic drugs were evident, and some seemed to produce promising if not totally convincing results. Tomudex, a thymidylate synthase inhibitor, was shown in a phase III randomised trial to produce a non-significant increased response compared with treatment with 5-fluorouracil and leucovorin, with less toxicity and simpler scheduling. Two different topoisomerase I inhibitors in phase II studies had some activity in pretreated small cell lung cancer, Topotecan producing responses in 25% and CPT-11 producing responses in 21% of patients. Gemcitabine, an antimetabolite, was shown to have activity in ovarian, breast and small cell lung cancer, but the most impressive results were produced with non-small cell lung cancer, where single agent therapy produced a response rate of 20–22%, lasting 8 months, and when combined with cisplatin, it produced responses of 36–58%. Professor Cavalli (Bellinzona, Switzerland) described results of fludarabine and 2-chlorodeoxyadenosine, both purine analogues, in malignant lymphoma, which produced responses in 75–80% of patients. He predicted that the future therapy of this disease would comprise high-dose conventional chemotherapy to destroy proliferating cells, followed by fludarabine to kill the bulk of the non-proliferating cells, and followed finally by biological therapy to eliminate any remaining cells.

Professor van Oosterom (Edegem, Belgium) summarised the current status of therapy with the taxanes, which are antimitotic compounds, affecting the microtubules of the mitotic spindle. While the number of studies conducted with paclitaxel is higher than that with docetaxel, both produce similar response rates of around 45% in first-line therapy of breast cancer. In second-line therapy of ovarian cancer, the average response rate with paclitaxel from eight studies was 23% and with docetaxel from three studies was 34%. In terms of other malignancies, Professor van Oosterom indicated that the spectrum of antitumour activity for these two drugs is quite different, as is their pharmacology and toxicology, and therefore they should be treated as two separate compounds rather than as if interchangeable. He also stressed the point that is should not be the pharmaceutical companies and their aggressive marketing techniques which define the use of these drugs, but rather scientists and clinicians should determine the most appropriate application of these compounds through experimentation and clinical trials.

In addition to the extensive laboratory and clinical programme, other sessions focused on epidemiological data across Europe, such as the Eurocare study, and there were also symposia on chemoprevention, and problems of drug development and registration. There was also a parallel nursing oncology programme, which centred on patient communication, quality assurance and quality of life aspects.

The number of participants at ECCO-8 appeared to support the cynical aphorism that "There are more people living off cancer than die of it"! If the promise of the new discoveries and approaches to cancer treatment discussed in ECCO-8 are realised, perhaps by ECCO-14 that criticism will no longer be applicable.