Something old and something new: taking cancer therapy forward

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The recent Management Forum meeting, *The Treatment of Cancer: An Update on Novel Approaches* (17–18 September 2001, London, UK), saw several excellent speakers and ~40 delegates convene to discuss existing and novel ways to treat cancer.

The recent biotechnology boom could at last promise some realistic alternatives for cancer treatment that are less invasive than surgery, and more specific, effective and less toxic than conventional radio- and chemotherapy regimes. The focus of this meeting was the development, particularly in clinical phases, of new anti-cancer agents, and the speakers and delegates included representatives from industry, research institutes, academia and the healthcare sector.

Issues with cancer therapy

Alan Barge, Global Product Director at AstraZeneca (Macclesfield, UK), kick-started the conference with a general overview of development, regulatory issues and marketing considerations for anti-cancer drugs. He summarized the criteria for determining clinical benefit in oncology as:

- the direct effect of treatment on the disease (duration, time to progression and survival); and
- the effects on other clinical consequences of the disease and its treatment (reduction of symptoms and treatment toxicity).

Barge also covered the ethical considerations that make cancer clinical trials so challenging. For example, the genotoxic nature of anti-cancer treatments must be taken into consideration when making treatment decisions; although Hodgkin's disease (HD) is regarded as a cancer with a good cure rate, a significant number of patients go on to develop leukaemia as a result of their treatment[1]. It is also generally impossible to study cancer drugs in healthy volunteers, and cancer trials must be designed to ensure that patients are not put through a bad trial. Many cancer patients are eager to enter into trials, often out of desperation or an altruistic desire to help others. Barge emphasized that investigators need to think about what they are expecting patients to go through when designing their study.

In another presentation, Pablo Fernandez (Pharmanet, Princeton, NJ, USA) said that global clinical trials are essential for the global benefit of therapies to patients, and also to ensure that drug development is comprehensive. A heterogeneic population, the specialist skills and knowledge of investigators and 'live' integrated data capture to ensure feedback to and from ongoing studies were among the requirements deemed essential for a successful global trial.

David Webb (Great Ormond St Hospital, London, UK) emphasized this further when he discussed difficulties encountered with paediatric trials, particularly in the light of recent media attention surrounding tissue storage and informed consent, and concluded that high standards of conduct are increasingly expected and that international trials are the future for childhood cancers.

Where and what should we target?

Barge continued with an excellent presentation on the current 'hot' pathways and targets in anti-cancer drug discovery and development. He commented that research concentrating on the metastasis of tumours is better than identifying early stage targets, such as those involved in cell cycle control, because by the time a tumour is diagnosed, early stage therapies will be of little use.

Several classes of anti-cancer drugs that are currently being investigated were discussed by Barge, including anti-proliferatives [e.g. growth-factor tyrosine-kinase receptor (GFR) antagonists such as Herceptin® (Genentech, South San Francisco, CA, USA)], anti-angiogenics [e.g. anti-vascular-endothelial growth-factor receptor (VEGFR) antibodies], anti-invasives [e.g. drugs that target the matrix metalloproteases (MMPs)] and work directed at improving the use of cytotoxics. The MMPs have been a particularly disappointing target class, according to Barge, who explained that, to date, drugs that target MMPs have shown no benefits in clinical trials and have yielded no information for further research [British Biotech (2001) Reports of clinical studies with matrix metalloprotease inhibitors in cancer. *Press Release* 13 February][2,3].

Barge illustrated his presentation with the drug development story of Gleevec™ (ST1571), the tyrosine-kinase inhibitor that has been hailed as a wonder drug for treating chronic myeloid leukaemia. This drug is so successful, Barge said, because it targets the sole oncogenic event early in the disease. Work is now under way to study whether Gleevec is a suitable drug for other targets, such as the stem cell factor, c-kit, which is mutated in gastrointestinal stromal tumours.

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Drug targeting and resistance remain the greatest challenge to anti-cancer agents, but Barge pointed out that new technologies such as positron electron tomography (PET) will help us to understand how drugs exert their effects and enable us to use combination therapies more effectively. He added, however, that with recent advances in biotechnology, our ability to clone cells and molecules has outstripped our ability to understand the underlying biology.

In 2000, cancer was second only to cardiovascular disease as the disease with the highest morbidity rates in the Western world (http://www.who.int/whr/). Barge envisaged a future where we do not have oncology doctors, but rather, people who treat specific genetic disorders. He suggested that the ultimate combination of: (1) the identification of the molecular pathology of all cancers; (2) the development of improved diagnostics and imaging; (3) improved drug discovery; and (4) cancer patients being genetically profiled, could lead to cancer being relegated nearer to the bottom of the morbidity 'league table' in the 21st century.

Gene targeting

A promising area of cancer drug discovery is the development of agents that target genes involved in cancer pathogenesis[4]. David Thurston (University of London School of Pharmacy, London, UK) gave a detailed overview of this exciting field, and described potential gene targets (e.g. oncogenes, drug resistance genes, DNA processing and repair enzymes and genes involved in metastasis). He also described some of the strategies available for targeting at the gene level (the antigene approach), such as designer proteins, peptide nucleic acids (PNAs) and triple-helix-forming oligonucleotides (TFOs), in addition to the RNA level (the antisense approach, e.g. ribozymes and oligonucleotides).

Although macromolecular approaches are highly selective for their target genes and have provided promising *in vitro* data, Thurston pointed out that there are issues with the cost, stability, delivery and pharmacokinetics of these agents. An alternative is to use small molecules to avoid the problems associated with macromolecules.

Thurston and colleagues have been developing small-molecule agents that interact within the minor groove of DNA, most of which are based on naturally occurring heterocyclic molecules derived from *Streptomyces* species. Thurston described a particular class of antitumour antibiotics, the pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs), which form an aminal bond with a guanine base thus resulting in a DNA adduct. Thurston's group is now using solid-phase and combinatorial approaches to design and synthesize different forms of PBDs extended in length so that they can recognise and bind to unique sequences in specific genes thus down-regulating or ablating expression of the targeted gene. It is hoped that this combinatorial chemistry based platform technology will have widespread use not just in cancer but in other diseases where single genes can be usefully targeted (i.e. novel antibacterials and antivirals etc). At present, effort is concentrated on optimizing sequence-specificity and structure–activity relationships. However, one candidate molecule, SJG136, with relatively modest sequence selectivity (i.e. spanning six base pairs), is expected to enter Phase I clinical trials in both the USA and UK in 2002. This study will be the first to attempt to link the sequence specificity of an agent of this type to its antitumour activity, and will use DNA microarray analysis technology to measure gene expression profiles in patients' tumour cells as a pharmacodynamic endpoint in the Phase I trial.

Development of novel therapies

Risa Harman (GlaxoSmithKline, Ware, UK) gave a detailed presentation on the many preclinical tests that are required for progression of a cytotoxic anti-cancer drug through early development, and highlighted issues that needed to be considered when testing combination therapies. Harman's presentation initially dealt with small molecules, but she went on to discuss the special requirements needed in the development of biopharmaceuticals, using gene-directed enzyme prodrug therapy (GDEPT) as an example.

The development of biopharmaceuticals was discussed further by Heinz Zwierzina (University of Innsbruck, Innsbruck, Austria) who considered new initiatives for the development of drugs that will treat molecular abnormalities rather than the whole disease, including new measurements that should be determined in early phase trials and surrogate markers as alternatives to tumour response endpoints.

Continuing with the biopharmaceuticals theme, Gunnel Hallden (Imperial Cancer Research Fund, Imperial College, London, UK) discussed gene therapy using viral vectors, with particular reference to the use of *dl*1520 (ONYX-015). *Dl*1520 is an adenovirus in which the *E1B-55kD* gene has been deleted, which means that the virus can only replicate and cause toxicity in p53-deficient cancer cells. Hallden described a Phase I/II clinical development strategy for the use of *dl*1520 for head and neck cancer, both as a single agent and in combination with cisplatin and 5-fluorouracil. The data presented suggest a promising future for this type of therapy.

Cancer in the clinic

Peter Harper, Consultant Medical Oncologist at Guy's, King's and St Thomas' Cancer Centre (London, UK) provided an overview of the difficulties encountered in cancer clinical trials, with particular reference to lung cancer, and highlighted the increasing need for supportive therapies to improve the quality of life of patients. This was further emphasized by David Webb, who explained how supportive care for childhood

cancer patients greatly improved because of the creation of a national network of children's cancer centres across the UK.

Harper was among others at the meeting to predict that cancer will become a chronic disease, and highlighted the potential use of CNS treatments for severe fatigue, erythropoietin to prevent haemoglobin depletion and appetite stimulants to counteract the debilitating effects of chemo- and radiotherapy. Maintenance of haemoglobin levels during radiotherapy has actually been correlated to an improved prognosis for disease[5]. Harper suggested that more funding in the future should focus on palliative care rather than on finding cures for cancer alone.

New paradigms for cancer therapy

During his keynote lecture, Karol Sikora (Global Clinical Expert – Cancer, AstraZeneca, Macclesfield, UK) discussed the global explosion of technology that will hopefully lead to many new effective therapies. He listed the cancers that are most curable (e.g. Hodgkin's disease, acute lymphoblastic leukaemia and testicular cancer) as only 5% of all cancer cases. However, Sikora added, the number of anti-cancer drugs in preclinical and Phase I trials has increased dramatically within the last decade, mainly because of the advent and development of technologies such as sequencing and bioinformatics, expression vectors, three-dimensional structural biology, HTS, combinatorial chemistry and platform approaches to drug discovery. These have resulted in a huge increase in potential drug targets and Sikora predicted an explosion in investigational new drugs (INDs) in the next five years.

Sikora concluded the keynote with a consideration for the unmet medical need of developing countries. He commented that we need a 'McDonald's' type solution to cancer therapy in underprivileged countries, using the analogy that a hamburger tastes the same in any country even though its price might differ greatly. However, the question remains as to who will fund such a solution when the costs associated with ameliorating the side effects of cancer treatment are often more than the chemotherapy itself.

References

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