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Questions and Answers

Question: Do you envisage the goals of anticancer therapy changing with the introduction of these new therapeutic agents?

Dr Eric Rowinsky: It is clear that we have focused too much on some, albeit very laudable, treatment goals – increasing cure rates and survival – and in the process have made little clinical headway apart from some extraordinary gains in the management of the more rare and atypical cancers (e.g. leukaemia, lymphoma, germ cell malignancies, etc.). The pursuit of such goals has come at a high price, with toxicity and low therapeutic indices being features of the majority of chemotherapeutic agents used against the solid malignancies. I believe that many rationally targeted therapeutics may be associated with less troublesome toxicity and the ability to delay tumour progression; consequently, I see therapeutic goals shifting towards increasing the time spent free of symptoms of disease progression or drug toxicity. Patient cure rates and survival will continue to improve slowly as this alternative objective is pursued and as new molecular targets are discovered.

Question: Given the potential of these agents to be used at all stages of disease and either as monotherapy or in combination with chemotherapy or radiotherapy, what in your opinion will be the pattern of usage for the management of solid tumours?

Dr Rowinsky: The current approach of progressively expanding therapeutic applications from more advanced disease to early-stage disease, to adjuvant use and finally to prevention, which we have seen for cytotoxic agents, will most probably also be applied to target-based therapeutics. In the process, it is of course possible that some therapeutics with major clinical potential will fall at the first hurdle and be judged ineffective in patients with advanced disease.

Since rates of major disease reduction are likely to be low with many novel therapeutics, the requirement for rapid cytoreduction in patients with advanced disease provides the rationale for combining novel therapeutics with standard cytotoxic agents. However, such combination regimens will obviously display toxicity comparable to that of current cytotoxic regimens. It is critical that clinical evaluations should proceed quickly so that new therapeutics can be applied in the early-disease setting and that new treatment paradigms should be developed for advanced disease, such as initial cytoreduction with combinations of cytotoxic agents/radiation and novel therapeutics, followed by long term therapy with the novel therapeutic to control disease progression.

Question: Can a subset of cancers most likely to respond to epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitors be defined at the present time?

Dr Eric Raymond: A number of tumours that are known to frequently express EGFR are more likely to respond to EGFR-TK inhibitors. These tumours include non-small cell lung cancer (NSCLC), ovarian cancer, head and neck cancer, prostate cancer, colon cancer, and a variety of other carcinomas. In future, measurement of the expression of EGFR in individuals prior to initiating treatment with EGFR-TK inhibitors is likely to be mandatory in selecting the patient population likely to respond to such treatment. This will be prospectively validated in clinical trials.

Question: In view of the multiplicity of signal transduction pathways, is an approach based on the targeting of multiple pathways likely to produce more effective anticancer therapies in the future?

Dr Raymond: The combination of multiple agents that simultaneously inhibit several signal transduction kinases is likely to be required to

actively control the proliferation of cancer cells. This will require an ability to identify which signalling pathways are critical in individual patients. The tailoring of treatment based on the expression of target proteins and/or critical signalling pathways in cancer cells will be required for the use of specific signal transduction inhibitors.

Question: Can examples be given of the types of tumours being treated with the various agents in clinical trials, and which drugs are being used for the comparator arms in the phase III trials?

Professor Fortunato Ciardiello: The types of tumours that have been tested in clinical trials so far are mostly head and neck cancers, NSCLC, renal cancer, colorectal cancer, prostate cancer, and breast cancer. I should say that although tumours have been selected on the basis of overexpression of EGFR, it is not absolutely certain that overexpression is needed for the drugs to show activity.

Combinations of cisplatin and C225 and of radiotherapy and C225 are being tested. Combinations of cisplatin plus gemcitabine and ZD1839, and of carboplatin plus paclitaxel and ZD1839 are also being tested in clinical trials. The primary endpoint of these studies will be an increase in overall survival compared with placebo.

Question: Can some further explanation be given as to why the small molecule approach may be more attractive than or superior to other approaches?

Prof. Ciardiello: Small molecule approaches with the EGFR-TK inhibitors (EGFR-TKIs) could have the following advantages compared with other selective anti-EGFR approaches: EGFR-TKIs can be given orally to allow convenient long term treatment of cancer patients that does not require ambulatory or hospital administration; EGFR-TKIs can inhibit the EGFR that is mutated and constitutively active in the tyrosine kinase enzyme; EGFR-TKIs do not elicit antibody formation or potential allergic reactions that are typical of chimeric or murine monoclonal antibodies, although fully humanised antibodies should not elicit an allergic response. C225 is chimeric and antibodies against C225 have been detected.

Also, monoclonal antibodies are large molecules and it is possible that they may not penetrate into a bulky tumour, especially if they have high affinity and are bound tightly to the superficial cells in the tumour mass. There should be no such penetration problem with a small molecule.

Question: Are any further details regarding the drug's pharmacokinetics available? For example, how is ZD1839 ('Iressa')[1,2] eliminated – are the processes mainly renal or hepatic? What is the volume of distribution?

Dr Steven D. Averbuch: The pharmacokinetics of ZD1839 have been studied extensively in healthy volunteers and patients with advanced cancer. The primary route of elimination is hepatic with <4% elimination by the renal route. Following oral administration, exposure, as measured by maximum plasma concentration and area under the plasma concentration-time curve, was proportional to the dose; however, interpatient variability in exposure within a dose group was 2.5- to 7-fold. Intrapatient variability after continuous administration appears to be low. The terminal half-life in patients ranged from 24 to 85 hours and there was no evidence of any change in half-life with increasing dose.

Question: Why are 2 different doses being used in phase III trials, and when might we expect the first results from the phase II/III trials in NSCLC? Which other types of cancer are being considered for investigation in phase II/III trials?

Dr Averbuch: The observation of antitumour activity across a broad range of doses well below the maximally tolerated dose did not allow for a single dose to be chosen for phase II/III trials in NSCLC. Therefore, 2 doses within this range are being evaluated in order to select the optimal dose to provide the most favourable therapeutic index.

A broad range of tumours are being considered for further investigation, especially prostate, gastric, breast, and colorectal, among others.

1 'Iressa' is a trade mark of the AstraZeneca group of companies.

2 Use of a trade name is for product identification purposes only, and does not imply endorsement.