Anti-Cancer Drugs 1999, **10** (suppl 1):S1–S3

Increasing options in cancer therapy: current status and future prospects

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Comprehensive reviews of current options in the treatment of a wide range of common solid tumors, including those of the colon and rectum, lung, breast, cervix, ovary, and head and neck, are covered in this volume. Although concentrating on single-agent and combination chemotherapy using a variety of new and established agents, exciting data on adenovirus-mediated p53 gene replacement therapy is also presented.

The topoisomerase I inhibitors are briefly reviewed. The majority of the early work with irinotecan was in metastatic colorectal cancer and it is in this indication that recent randomized phase III studies have demonstrated the most striking evidence of benefit. In one such trial, 36% of patients assigned to irinotecan were alive at 1 year, compared with only 14% of patients in the control group receiving best supportive care.[1] In a complementary trial of irinotecan versus best infusional 5-fluorouracil (5-FU)-based chemotherapy, the 1-year survival rate was again significantly higher in patients assigned to the topoisomerase I inhibitor (45 versus 32%).[2]

In an attempt to further increase activity, the combination of irinotecan with other agents has been undertaken. Data presented in this volume demonstrate that irinotecan plus 5-FU, irinotecan plus raltitrexed and irinotecan plus oxaliplatin are among the dual-agent regimens holding promise. With the latter combination, objective response rates in the region of 50% have been reported in advanced colorectal cancer.[3] Looking further into the future, the use of irinotecan in three- and even four-drug combinations appears feasible. If such complex regimens can demonstrate improved survival when given first-line in advanced disease, their use in the adjuvant and neoadjuvant settings should be considered.

There is clear interest in the development of oral formulations, in an effort to improve the therapeutic index of cytotoxic agents, and formulations of oral irinotecan, topotecan and 9-nitrocamptothecin may assume importance.

Among the newest agents, DX-8951 has strong topoisomerase I inhibitory activity and a broad spectrum of anticancer activity.

Promising phase II activity of irinotecan in small cell and non-small cell lung and cervical cancers, alone and in combination with cisplatin, is also presented. There are indications that irinotecan plus cisplatin can achieve higher response rates than traditional cisplatin combinations in the first-line treatment of stage III/IV non-small cell lung cancer, for example.[4,5] However, it may well be that the focus of the next decade will be the activity of topoisomerase inhibitors in other epidermoid tumors such as those of the head and neck, and esophagus. There will also be interest in the activity of topotecan in hematological malignancies, and there is potential in an agent such as TAS 103 which combines inhibition of topoisomerase I and II.

A further element in the future of chemotherapy will be attempts to predict response to individual agents, allowing therapy to be tailored to the circumstances of specific patients. The identification of tumors with p53 mutations, thymidilate synthase overexpression, the topoisomerase I gene and replication errors will be equally important in enhancing the efficacy of therapy with agents such

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as the topoisomerase I inhibitors, raltitrexed and oxaliplatin.

In metastatic breast cancer, docetaxel appears to be the most active single agent and is the only drug so far shown to have significantly greater activity than the previous gold standard of doxorubicin.[6] Docetaxel is also the only agent yet demonstrated by controlled trial to prolong survival in patients with advanced disease already treated with anthracyclines.[7] Encouragingly, the combination of docetaxel with doxorubicin appears relatively free of the cardiotoxicity.[8,9] Given docetaxel's high level of activity and the feasibility of its use with an anthracycline, the current randomized trials of docetaxel-containing regimens in the adjuvant setting are timely and their results eagerly awaited.

Traditionally, there have been far fewer treatment options of proven benefit in non-small cell lung cancer than in cancer of the breast. However, this situation is beginning to change following the randomized phase III trial of docetaxel versus a reference arm of ifosfamide or vinorelbine.[10] When data were censored at subsequent chemotherapy (to counter the dilution effect due to informal crossover of patients to docetaxel), patients assigned initially to docetaxel showed a significant survival advantage and this was accompanied by important evidence that quality of life was better preserved in patients randomized to docetaxel than in controls. The meeting also heard promising initial results (with response rates of greater than 50%) in patients with advanced disease treated with docetaxel/platinum combinations.[11–13]

The combination of docetaxel with cisplatin (and 5-FU) is also showing some promise in cancer of the head and neck. To date, combination chemotherapy bringing together cisplatin, 5-FU and methotrexate has not increased survival when compared with monotherapy in metastatic/recurrent disease, and new therapeutic options are clearly needed. Studies with single-agent docetaxel produced response rates ranging from 23 to 42%, which led to combination studies with docetaxel in head and neck cancer.[14] Response rates of 25–1000% were observed in the latter series of combination studies.[14] Based on these exciting results, phase III combination studies are ongoing and studies in the neoadjuvant setting have been initiated.

Similarly, little increase in survival has been observed in advanced ovarian cancer, even though the last few years have seen clear progress in this disease, brought about primarily through the combination of paclitaxel with cisplatin or carboplatin. Phase I and II studies with docetaxel as a single agent or in combination with the platinums showed interesting results.[15] Combining docetaxel with carboplatin seems to offer a safe and convenient outpatient therapy with the possibility of little neurotoxicty and promising potential activity. Randomized trials of docetaxel plus the platinum compounds versus paclitaxel plus platinums are now underway.

While incremental improvements in chemotherapy have brought effective palliation and a degree of survival benefit in several common tumors, it is understandable that radically different approaches to treatment should stir the imagination. The identification of genetic lesions which cause a cell to become malignant presents us with the opportunity of using gene therapy directly to target and hopefully correct the cause of cancer itself.

Although clinical work is still at an early stage, phase I studies in lung, and head and neck cancers have demonstrated that local injection of an adenoviral vector carrying the p53 gene leads to effective transfection, stable high rates of transgene expression and (in at least a proportion of patients) regression of tumor in target lesions.[16,17] However, exciting though these results are, it is important to note both that conventional chemotherapy will still be needed to combat distant disease, and that, even when attention is confined to the sites of intratumoral injection, there appeared to be interesting synergy between gene therapy and the administration of cisplatin.

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