Medical oncology in the 1990s

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The time has come to cut back on the clinical investigation of new chemotherapeutic regimens for cancer and to cast a critical eye on the way chemotherapeutic treatment is now being administered. A brief survey of the history of cancer chemotherapy may help us to make sound decisions for the future.

Between the late 1940s and the mid 1960s several active drugs were discovered, but, except in the case of childhood acute leukaemia, they had little impact on the treatment of neoplastic disease. Then came great progress. Curative drug combinations were found for Hodgkin's disease and non-Hodgkin lymphomas, for metastatic germ cell tumours and choriocarcinoma, and for tumours of children such as Wilms' and embryonal rhabdomyosarcoma. Long remissions were obtained in a high proportion of patients with metastatic breast, ovarian, and small-cell bronchogenic carcinoma, and most patients with myeloma or myeloblastic leukaemia showed a response to treatment. In various carcinomas and sarcomas adjuvant chemotherapy seemed to offer a chance of increasing the cure rates, and large scale controlled studies were initiated.

These achievements were won against considerable opposition. Because of the limited scientific basis for chemotherapy and its obvious toxicity, the medical community had strong reservations about the method and its practitioners. Many of the innovators displayed great courage and energy in the face of their colleagues' doubts, and this may account for the sanguine character and missionary zeal of so many medical oncologists today.

In the late 1970s there were good reasons to expect that the curable neoplasms would soon include metastatic breast and small-cell lung carcinomas, and that chemotherapy would prove useful in tumours of head and neck and gastrointestinal tract and in non-small-cell tumours of lung. In 1986 two sharply contrasting evaluations of our progress were published.[1,2] How do matters stand today?

The efficacy of adjuvant therapy for certain groups of breast cancer patients and for osteogenic sarcoma has been demonstrated, and we know that some locally advanced colon carcinoma patients benefit from adjuvant treatment. Increases in the remission rates of metastatic transitional cell tumours and colon carcinoma have been reported, but survival advantages have not been shown. Platinum-based drugs have improved results in advanced ovarian carcinoma. Hepatic artery infusion chemotherapy improves the remission rate of colonic hepatic metastases, and systemic infusion increases the radiocurability of locally advanced anal and rectal carcinomas. Bone marrow transplantation cures some leukaemias and lymphomas. But this is all. No disseminated neoplasm incurable in 1975 is curable today.

Various dose-intensive and alternating non-cross-resistant regimens have been studied. Biochemically sophisticated techniques, such as methotrexate therapy with citrovorum rescue, have permitted almost unlimited dose continuous infusions, have alleviated the toxic side-effects of several chemotherapeutic agents. But the rate and duration of remissions obtained for the more responsive tumours, such as small-cell lung cancer or stage IV breast cancer, have not improved, and cures are rare. Metastatic melanoma and sarcoma remain neglibly responsive. The apparent chemosensitivity of head and neck tumours is not reflected in survival benefits. The role of third-generation chemotherapy regimens in non-Hodgkin lymphomas remains uncertain. The last important new drug was etoposide, approved in the early 1980s, and it is not clear that the addition of estramustine, ifosamide, and mitoxantrone to the formulary has added much to cancer treatment today. The past decade has produced very interesting data on the mechanism of neoplastic cell resistance to cytotoxic drugs. Although clinical studies to determine the effects of blocking of these mechanisms have not yet improved response rates, they should be pursued. But the many failures of chemotherapy are more likely to be due to the intrinsic lack of sensitivity of most human tumours to all classes of cytotoxic drugs than to specific resistance mechanisms.

Despite these disappointments, there has been no let-up in effort devoted to trials of clinical chemotherapy; and in many of them the lack of benefit could have been predicted at the outset (a glance at any issue of *Cancer* or the *Journal of Clinical Oncology* illustrates the point). Yet at meetings of specific disease committees of cooperative groups there is a make-work atmosphere, with chairmen appealing to the audience to propose ideas for new regimens or drugs to study. These groups' *raison d'être* was not to invent questions, but to answer those arising from promising small (phase-II) therapeutic trials. The phase II trials continue to appear, but, since virtually none are promising, the cooperative groups have become aimless.

As to clinical practice, many medical oncologists recommend chemotherapy for virtually any tumour, with a hopefulness undiscouraged by almost invariable failure. The skills of many professionals are squandered upon these costly treatments.

The oncology community should respond to the data of the past decade by scaling back the whole chemotherapeutic enterprise. Chemotherapy should be prescribed only when there is a reasonable prospect either of cure or of benefit in quantity and quality of life. Our oncology trainees should be taught that chemotherapy is not part of the management of every cancer patient; for many or most patients medical intervention should be confined to symptom management and enrolment in a hospice programme.

On the clinical research side, studies should be confined to agents with novel mechanisms of action, and to refinement of regimens already known to be effective. The principle that every cancer patient should, if possible, be entered on a therapeutic protocol, is obsolete. We must learn to accept the limited role of conventional cytotoxic therapies in the oncological scheme of things.

Is there any gleam of light in this gloomy picture? One group of agents that deserve further investigation are the biological response modifiers. As with chemotherapy in its

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