

Chemotherapy for lung cancer

Lung cancer is a dismal disease, especially the small cell variety, in which, if it is untreated, the median survival is one to three months—owing to its propensity for widespread early metastasis. Radiation was shown to be superior to surgery for such tumours back in the 1960s, but it succeeded in raising the median survival only from three to seven months. In theory, however, the large proportion of the tumour that is actively growing and its relatively fast dividing time should make it susceptible to drugs. Indeed, 10 years ago the small cell type of lung cancer was found to be temporarily responsive to cyclophosphamide, whereas other cell types were not affected.¹ More recently the addition of other drugs to cyclophosphamide has led to reports of survival for over two years.²⁻⁴ The patients who survive longest are those with limited disease—cancer in one hemithorax, including ipsilateral mediastinal or supraclavicular lymph nodes.

Nevertheless, the first results of transferring to lung cancer experience with multiple drug regimens used in other neoplasms were not encouraging. In 1975 Laing *et al*⁵ showed that a quadruple chemotherapy regimen used in Hodgkin's disease gave poor results in lung cancer because of increased toxicity. Others have since pointed out that among the drugs included in the cocktail mustine, procarbazine, and prednisolone were inappropriate in small cell lung cancer and inferior to cyclophosphamide, adriamycin, and methotrexate.⁶⁻⁷ These last three, along with vincristine and lomustine (CCNU), have given better results in studies such as the Medical Research Council's recent trial showing improved survival to a year or so gained by adding chemotherapy to mediastinal radiation.⁸ Krauss and Perez have shown that when chemotherapy was given immediately after radiotherapy the complete remission rate was 52%, compared with 33% in patients given radiotherapy followed by drugs on relapse.⁹ The median survival for radiation with immediate chemotherapy was 330 days compared with 167 days for delayed chemotherapy. Greco's recent review of long-term survivors of combined treatment⁴ showed that a consistent 15% to 20% of patients with limited disease achieved impressive remissions (over two years) despite variations in the detail of chemotherapy protocols.

Much research is concerned with the relative merits of radiotherapy or chemotherapy as primary treatment. Three recent studies have indicated that chemotherapy alone is equal to, or better than, chemotherapy with radiation.¹⁰⁻¹² Hansen¹¹

found that chemotherapy produced a median survival of 14 months in 69 patients compared with 11 months for 65 patients given combined treatment. The numbers achieving complete remission were similar for each group, and the median duration of response has not yet been reached for the chemotherapy group. Clearly the place of radiotherapy in the control of intrathoracic disease will need re-examination.

Equally clearly, prophylactic radiation to the brain is an important development.¹³ The brain is a prominent site of relapse in patients otherwise free of disease—as was found in the early years of treatment of acute leukaemia in children. Drugs such as lomustine and procarbazine have been included in chemotherapy protocols in the hope that their penetration to the cerebrospinal fluid might be sufficient to cope with micrometastases, but this approach has proved ineffective. Indeed, some relapses have occurred in patients who have undergone prophylactic irradiation to the brain, though such exceptions seem to be rare and are probably the result of inadequate total dosage.¹⁴ Several American co-operative groups have recently reported the results of combining chemotherapy with radiation to the mediastinum and brain. This barrage of treatment was remarkably well tolerated, and indeed seems to have benefited almost every patient.¹⁵⁻¹⁷ Complete remission rates of 60% to 80% have been substantiated in these independent studies—and by complete response is meant disappearance of all disease as assessed by fiberoptic bronchoscopy, radiology, and radionuclide scans; relief of associated symptoms (including those related to inappropriate hormone secretion); and an improved quality of life. Twenty-six of 27 patients described by Greco *et al* fulfilled those criteria, and a median survival of over 19 months had been reached at the time of publication.¹⁸ So far, however, alternating chemotherapy regimens have not increased the rate of remission, though the duration of response may have been lengthened by the manoeuvre.¹⁹

What about patients with widespread small cell disease, who untreated have a median survival of one month? Radiation is inappropriate except in the treatment of painful bony metastases or nerve compression.²⁰ Combination chemotherapy is as good as radiotherapy for superior vena caval obstruction,²¹ and better for achieving complete remission and consequent improved survival.²² Complete remission rates may be pushed up as far as 40% by the use of four or more cytotoxic

drugs used in high dose, and Cohen has reported an impressive median survival of one year in this very poor-risk group.²³

Yet, while combinations of cytotoxic drugs and radiation have given most patients with small cell carcinoma of the lung longer survival, these treatments are not without problems. The radiosensitising effects of bleomycin and adriamycin have caused serious side effects, though these have been reduced in severity by modifications to the dose and appropriate scheduling. The extension of prophylactic brain radiation to include the spinal cord is under study, as is the use of intrathecal and high-dose intravenous methotrexate to lessen even further treatment failures due to disease in the central nervous system.

There are two challenges for the oncologist: firstly, to develop optimal induction regimens, perhaps incorporating the promising new drugs such as platinum diamminodichloride, ifosfamide, VP 16213, and hexamethylmelamine^{10 20 24}; and, secondly, to establish the form and duration of maintenance treatment. Both chemotherapy and irradiation need to be limited as much as possible, since the risks include not only the immediate side effects but also such possible late complications as second malignancy, already reported in one long-term survivor.¹⁰ Nevertheless, these successful early inroads into the treatment of lung cancer have justified other developments. Subsets of small cell cancers which will or will not respond might be identifiable, and we now require reproducible assays for tumour markers such as hormones or fractions of hormones. Techniques for improving and maintaining the nutritional and immune state during treatment might also lead to an improved outlook for a group of patients whose

numbers are not likely to diminish over the next decade, even if cigarette smoking were to be totally abolished.

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Penile prostheses in erectile impotence

Until recently, erectile impotence has been managed by a combination of urological and endocrine assessment, psychiatric evaluation, sex counselling, and, where indicated, hormone treatment, usually with disappointing results.^{1 2} Not surprisingly, attention has turned to surgical means of treatment.

Early penile prostheses were made of materials such as cartilage and bone,³ acrylic,⁴ silicone rubber,⁵ and polyethylene rods⁶; but these were superseded in 1973, when Small and Carrion implanted two semi-rigid, moulded, silicone shells with sponge-filled interiors via the perineum in the corpora cavernosa.⁷ After three years a satisfactory result had been achieved in 69 of 75 patients, with complications (wound infection, urinary retention, malposition) in only six.⁸ None of the men had any serious problems from pain, slippage, or extrusion. The prosthesis is flexible and has no mechanical or hydraulic components, but it is permanently semi-erect. A similar device implanted through a dorsal penile incision incorporating a flexible hinge at the perineal end to overcome this disadvantage has recently been introduced, and early reports show equally satisfactory results.⁹

An alternative approach has been developed at the Baylor Medical Center, Houston.¹⁰ Two inflatable silastic cylinders are placed in the corpora cavernosa through a midline incision and connected by silastic tubing to a pumping mechanism implanted in the scrotum. When the scrotal bulbs are pumped, inflation fluid stored in a reservoir behind the anterior rectus sheath enters the prosthesis, producing an erection; a release valve allows the fluid to return to the reservoir when desired. During five years, 235 patients with organic impotence and 10 with psychogenic impotence had surgery, and 234 have found

the device entirely satisfactory.¹⁰ These mechanisms may be prone to leakage, or kinking and rupture of the tubing, and indeed the first 102 patients required a second operation of some sort; none of the patients operated on in 1976-7, however, experienced any failures. This system has the advantage of being more "physiological" than the others, in that an erection can be produced at will without the problem of permanent semi-rigidity. Naturally, none of these prostheses produces climax or ejaculation, but if these are possible before operation they will be achieved with the implant, whichever type is used.

From the technical viewpoint, then, implantation surgery appears to give impressive results. Such techniques cannot, however, be judged in isolation from several other factors. The careful selection of cases is crucial to a successful outcome, and, while the final decision to operate rests with the urologist, the psychiatrist and sex counsellor should also make an assessment—emotional instability and psychiatric disease may preclude the operation. Coincidental physical disease must also be evaluated. For example, some of these patients will have neurogenic bladders and implantation may result in urinary retention. Diabetes, too, requires careful control if infection is to be avoided, and antibiotic cover for the operative period is advisable.

Another important conclusion that has emerged from the American experience is that counselling of the sexual partner is essential. A recent study in which the wives of recipients of a Small-Carrion prosthesis were interviewed showed that several men had not used their implants months after receiving them; some wives were even unaware that their husbands had them.¹¹ If a wife has adjusted to her husband's impotence over