Survival rates in undifferentiated small-cell carcinoma of the bronchus

A review and 2 case reports

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Summary

Patients with inoperable undifferentiated small-cell ( oat cell ) carcinoma of the bronchus rarely survive for long. The number of long-term survivors has always been variable and treatments given to them have differed markedly.

In this article we present 2 patients who have survived for 6½ years and 10 years respectively. These are the only patients surviving beyond 5 years out of 311 patients treated over a 30-year period.

The literature on survival of patients with this type of carcinoma is reviewed.

Case reports

Case 1

A Coloured man aged 41 years was admitted to Groote Schuur Hospital in July 1976 with a history of weakness of the right arm and right leg, a dry cough, lassitude and undetermined loss of weight over the previous few weeks. He had been a heavy smoker from his early teens and was a heavy drinker. He worked in a shoe polish factory.

On examination the patient appeared thin, but there were no positive findings other than some weakness of the right arm and right leg. No adenopathy, jaundice or visceromegaly was present.

Laboratory investigations showed a haemoglobin value of 20,8 g/dl, a leucocyte count of 6,8 x 10⁹/l and a platelet count of 293 x 10⁹/l. Blood biochemical values were normal except for a raised alkaline phosphatase level and an inverted albumin/ globulin ratio. A liver scan was normal.

A chest radiograph revealed that the heart was not enlarged. There was some consolidation and loss of volume in the right upper lobe, indicating an underlying mass in the anterior segment. The remaining lung fields were hyperinflated (Fig. 1).

Bronchoscopy showed fixity and narrowing from the origin of the right main bronchus with fixity of the carina. The lesion was inoperable and a specimen was taken. Histological examination showed a carcinoma consisting of sheets of dark cells with mitoses present. A diagnosis of undifferentiated small-cell carcinoma of the intermediate type was made. A bone marrow aspirate showed no evidence of malignant infiltration.

The patient received cobalt-60 irradiation to the right hilum and tumour mass, to a dose of 3000 rad in 15 fractions over 19 days. Cyclical cytotoxic therapy commenced 1 week before and again 1 week after completion of radiotherapy. Cytotoxic agents were given in the form of a 4'-demethyllepipodophyllotoxin ethylidene glucoside (etoposide, VP16-213) at a dose of 80 mg/m² (130 mg intravenously) with vincristine 2 mg intravenously and adriamycin 60 mg every 3rd week for 3 months, followed by intravenous cyclophosphamide 600 mg/m² every 3 weeks and oral methotrexate 30 mg/m² twice weekly for the next 3 months. Cytotoxic therapy was continued in 3-monthly cycles until November 1977, i.e. for a total of 16 months. The patient tolerated this form of treatment without severe side-effects and improved steadily. After 6 months the weakness of his right arm and right leg had resolved.

During March 1977 he developed an acute abdomen. Special investigations revealed calcified gallbladder calculi and a cholecystectomy was performed. By April 1978 he was well and back at work.

A chest radiograph taken in March 1980 revealed clear lung fields except for radiation fibrosis in the right upper lobe. There was no evidence of any local recurrence, secondary infiltration or adenopathy (Fig. 2). The patient is still well and working 6½ years after the initial diagnosis.

Case 2

A White man aged 61 years was admitted to hospital in February 1973 with a history of 6 months' progressive dry coughing, 3 months of pain and tightness in the chest, and progressive dyspnoea on effort. He was a moderate drinker and had smoked 20 cigarettes a day but had stopped smoking 1 year previously. He worked in an office as a bookkeeper.

The patient appeared well nourished, with no obvious weight loss. Clinical examination was entirely negative. The blood biochemistry values were normal. Skeletal survey showed no abnormality. On a chest radiograph it was seen that the heart was not enlarged and the aorta was unfolded, but there was some consolidation in the anterior and posterior segments of the right upper lobe (Fig. 3).

Mediastinotomy revealed a large tumour in the right hilum extending into the mediastinum and pericardium. This mass was biopsied and found to be composed largely of necrotic lymphoid tissue with atypical cells along the border. These cells could not be classified as a lymphoma and the likeliest diagnosis was that of an undifferentiated small-cell carcinoma of the bronchus. (Subsequent reviews of the slides in South Africa and abroad confirmed a diagnosis of fusiform undifferentiated small-cell carcinoma of the bronchus.)

The patient received no irradiation and was treated with a combination of cytotoxic agents which included a cell-cycle-stage sensitive and a cell-cycle-stage non-sensitive agent. The patient received cyclophosphamide 1 100 mg/m² intravenously...
every 3 weeks plus methotrexate 20 mg/m² orally twice weekly. All drugs were adjusted to the patient's tolerance and regularly monitored by blood count. After 3 doses of cyclophosphamide the patient developed haematuria and refused further cyclophosphamide therapy. He was then treated with 2-chloroethyl-3-cyclohexyl-1-nitroso-urea (CCNU, lomustine, NSC-79037) 50 mg/m² given orally every 6 weeks and hydroxyurea 700 mg 3 times a day twice weekly. The patient improved dramatically after the second dose of cyclophosphamide. Five months later the chest was radiographically free of disease (Fig. 4). He was then maintained on small doses of hydroxyurea for 1 year.

Two years after the first admission to hospital he became icteric and was found to have a 4 cm hepatomegaly; liver enzyme levels were grossly elevated. The bilirubin value was 27.4 µmol/l, with a conjugated fraction of 1.2%.
Fig. 3. Chest radiograph on admission showing consolidation in the anterior and posterior segments of the right upper lobe.

Fig. 4. Chest radiograph taken 5 months later, showing no evidence of disease.

As the liver scan was normal a diagnosis of viral hepatitis was made. The patient recovered within a month, but shortly afterwards (1975) developed transient episodes of blurred vision. A brain scan was normal. Four years later the patient became ataxic and experienced transient episodes of cerebrovascular paresis. Computed tomography of the brain revealed shadows in the right parietal and left occipital areas reported as possible metastases. Eventually these shadows were accepted as infarcts.

During 1980 the patient developed symptoms and signs compatible with the diagnosis of a cerebrovascular accident. A brain scan revealed insufficiency of the right internal carotid artery. No active treatment was thought necessary and he recovered partially.

Ten years after diagnosis the patient is still clear of his bronchial carcinoma and regularly attends hospital for therapy to several lesions of hyperkeratosis, squamous carcinomas and basal cell carcinomas of the skin of the hands and face.

Discussion

The natural history of small-cell carcinoma of the bronchus is significantly worse than that of the other common histological forms of bronchial cancer. In a large-scale study in which patients were randomized to receive radiation therapy or placebo, it was shown to be a rapidly fatal condition which if untreated has a median survival of 3 months from diagnosis to death. In this study radiation therapy was shown to prolong survival.

Surgery is only feasible in a minority of patients as it only occasionally results in long-term survival or even cure. This is due to the fact that small-cell anaplastic lung tumours are rarely localized at diagnosis. Clinical determination of the extent of the disease might become possible with improved, more sophisticated technology; as yet it can be determined accurately only at thoracotomy. Only a small percentage of patients are eligible for resection but in recent studies cures have been reported in early disease after resection. The group of patients selected for resection is so small that surgery would remain a rare feasible option in the treatment offered.

Radiotherapy surpasses surgery as a single modality in treating probably very early lesions, with 5-year survival in 4 patients. The results of treatment of early operable oat cell or small-cell undifferentiated carcinoma of the bronchus are so poor that radiotherapy was the mainstay of treatment for many years until the advent of chemotherapy.

Subsequently a clinical trial by Tucker et al. on oat cell carcinoma of the lung suggested that large doses of cyclophosphamide produced a longer survival time than irradiation of the chest. The longest survival in this study was 21 months. A median survival of 267 days was recorded in a further Cape Town study on a group of patients also treated with single-drug cytotoxic therapy in the form of VP16-213. A large international trial by Hansen et al. indicated a rather high degree of sensitivity for small-cell carcinoma and a definite role for combination chemotherapy. Various studies during the last decade have emphasized the sensitivity of small-cell carcinoma of the lung to chemotherapy and major advances in medical oncology have led to the study of various combined chemotherapy regimens. Treatment with various regimens is both rewarding and frustrating, since long-term disease-free survival remains unusual.

Recent trends in combination chemotherapy have included the use of conventional agents at maximally tolerated doses and alternating cycles of non-cross-resistant combinations. Improved response rates have been gratifying; however, the improvement in median survival times has been less impressive.

A recent study randomizing six cyclical treatment schedules resulted in a median survival exceeding 1 year; intensive combination chemotherapy with or without radiation failed to increase median survival for patients with limited disease beyond 16 months.
At a workshop held by members of the International Association for the Study of Lung Cancer (IASLC) in 1981 it was stated that there was a likelihood of cure in 5 - 10% of patients treated with aggressive chemotherapy producing considerable toxicity.15

Studies presented at the Third World Conference on Lung Cancer in Tokyo in 1982 and organized by the IASLC revealed varied improvements in survival rates. Akbıyık et al.,16 reviewed 560 cases between 1967 and 1977 and reported that with the advent of combination chemotherapy survival is the same for early disease as in cases of resectable non-small-cell carcinoma. A median 2-year survival rate of 38% was reported from China.17

The use of parenteral feeding as supportive therapy does not seem to alter the course of the disease significantly, as shown in an incomplete study by Serrou et al.18

In a review by Hansen19 of the management of small-cell anaplastic carcinoma from 1980 to 1982, he concluded that some response could be obtained in 80 - 90% of all patients but that a complete response was limited to 15 - 20%. However, the median survival for patients with limited disease remained 14 - 16 months despite intensive combination chemotherapy with or without radiotherapy. Other modalities of treatment studied were hyperthermia, interferon administration, bone marrow transplantation, total body irradiation and therapy in combination with anticoagulants.

The main form of treatment remains a combination including adriamycin, vincristine, cyclophosphamide, VP16-213, CCNU and methotrexate combined with radiotherapy. New studies are continuing with vindesine and cisplatin.

According to recent literature only an occasional patient survives for a long term, regardless of the form of cytotoxic or other therapy administered. The optimal mode of therapy has not been defined but the development of aggressive combination chemotherapy has led to an increase in disease-free survival. A significant minority of patients with early disease can now be expected to be alive and disease-free at 2 years.20 Continued research remains mandatory and should be directed towards using the most active drugs in the most effective manner with systematic inclusion of new agents.

The 2 patients described in this article are the only long-term survivors among the 311 patients with undifferentiated small-cell carcinoma of the bronchus seen at the Department of Radiotherapy, Groote Schuur Hospital, over the last 30 years. Both were treated with some form of combination chemotherapy adjusted to their individual tolerance. The authors feel that cyclical combination chemotherapy is undoubtedly the best form of treatment and it should be pursued in future studies. Whether it needs to be aggressive to be effective remains questionable, since the quality of survival remains of utmost importance.

REFERENCES