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Treatment of oesophageal small cell carcinoma by combined chemotherapy and surgical resection: report of two cases and review of published cases

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ABSTRACT Two patients with primary small cell carcinoma of the oesophagus were treated by multidrug chemotherapy followed by surgical resection. A partial response to chemotherapy was observed in both patients.

The optimum management of small cell carcinoma of the oesophagus is undefined, most cases of this rare and aggressive tumour being treated conventionally by surgery[1] or radiotherapy.[2] Kelsen *et al* in 1980[3] were the first to report a response to multidrug chemotherapy and since then there have been isolated case reports to support this treatment alone or in combination with surgery.[1 4–7] We describe our experience of treating two patients with small cell carcinoma of the oesophagus by multidrug chemotherapy followed by subtotal oesophagectomy.

Case reports

PATIENT 1

A 61 year old man presented with a six week history of dysphagia and weight loss. Investigation by barium meal, endoscopy and computed tomography showed an oesophageal tumour starting 38 cm from his incisors and extending into the cardia of the stomach; the maximal diameter was 3 cm and there was evidence of attachment to the pericardium. Biopsy showed a small cell carcinoma. There was no evidence of metastases on clinical examination, abdominal ultrasound or computed tomography and a biochemical screen showed nothing abnormal. His initial serum carcinoembryonic antigen concentration was marginally raised at 5·2 (normal $< 5{\cdot}0$) μg/l and varied over the next eight weeks from 2·6 to 6·0 μg/l. Two four week cycles of multidrug chemotherapy were administered (table 1). Treatment had to be delayed for one week during the first cycle because of neutropenia but was otherwise well tolerated. Computed tomography after treatment showed a 50% reduction in tumour size. Three months after presentation he underwent a subtotal oesophagectomy with oesophagogastric anastomosis in the neck. Histological examination showed the tumour to have infiltrated the full thickness of the distal oesophagus and cardia with spread to local vessels but without invasion of lymph nodes. There were areas of moderately differentiated adenocarcinoma as well as small cell carcinoma. The former was positive for carcinoembryonic antigen and the latter focally argyrophil positive. The patient made a good postoperative recovery but required two dilatations for an anastomotic stricture. He died 12 months after the original diagnosis was made with clinical evidence of liver metastases and obstruction of the inferior vena cava.

PATIENT 2

A 66 year old woman was referred with a six month history of epigastric pain and weight loss. She had previously undergone a barium meal and otolaryngeal examination 15 months earlier for mild dysphagia but no abnormality was found. Investigations performed at this time (oesophagoscopy, barium meal, abdominal ultrasound, and computed tomography) showed an 8 cm long, friable tumour starting 30 cm from the incisors with a maximum diameter of 4 cm. Biopsy showed a small cell carcinoma. There was no evidence of metastases. All blood tests, including a carcinoembryonic antigen test, gave normal results. She underwent two four week cycles of chemotherapy (table 1). This had to be delayed on two occasions because of neutropenia. She continued to eat normally and gained weight during the treatment period. A repeat barium meal and computed tomography after the chemotherapy showed no evidence of tumour.

Three months after presentation she underwent a subtotal oesophagectomy with oesophagogastric anastomosis in the neck. At operation there was mild thickening of the oeso-

Table 1 *The chemotherapy regimens used for the two patients*

Day	*Drugs*	*Dose*	*Route*
1	Cyclophosphamide,	400 mg/m^2	Intravenous
	doxorubicin	50 mg/m^2	Intravenous
8	Vincristine	1 mg/m^2	Intravenous
15	Methotrexate,	30 mg/m^2	Intravenous
	etoposide	100 mg/m^2	Intravenous
16	Etoposide	50 mg × 3/day	Oral
17	Etoposide	50 mg × 3/day	Oral
22	Vincristine	1 mg/m^2	Intravenous
29	Repeat		

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Table 2 *Summary of published reports on the use of chemotherapy for small cell carcinoma of the oesopahgus*

First author	Patients age (y), sex	Tumour location in oesophagus	Size (cm)	Metastasis	Chemotherapy	Outcome
Kelsen (1980)	76, F	Middle	5?	Bone	CP, ETS, CPA, DXR, VCR	PR 9 mo, died
Levenson (1981)	56, M	?	?	Lymph nodes	CPA, MTX, CCNU, VCR, DXR, PCB, IPM, ETS	CR
Rosenthal (1983)	74, F	Upper, lower	5–1 multiple	—	CPA, DXR, VCR	PR → RT outcome?
Karnard (1984)	46, M	Middle	7	brain, liver, lymph nodes	CPA, DXR, VCR (brain RT)	PR 6 mo, died
Iishi (1987)	76, M	Middle, upper	7, 4	liver, lymph nodes	CPA, VCR	PR 5 mo, died
Tanabe (1987)	68, M	Middle	9, 5	liver, lymph nodes, brain	CP, ETS, CPA, DXR, VCR	PR 9 mo, died

PR—partial response; CR—complete response; RT—radiotherapy; CP—cisplatin; ETS—etoposide; CPA—cyclophosphamide; DXR—doxorubicin; VCR—vincristine; MTX—methotrexate; PCB—procarbazine; IPM—ifosphamide; CCNU—[1-(2-chloroethyl)-3-cyclohexyl-1-nitrosoureal.

phageal wall but no definite evidence of tumour or gross metastatic spread. Gross examination showed a small area of ill defined induration 5 cm above the cardia; histological examination showed evidence of invasive carcinoma lying under an area of surface dysplasia. The carcinoma displayed small cell, glandular, and squamous patterns and was associated with much fibrosis. All lymph nodes and resection lines were clear.

The patient made an uneventful recovery. Twelve months after surgery she remains well but has developed a right sided pleural effusion; aspiration has shown small cell carcinoma cells to be present.

Discussion

Small cell carcinoma is most commonly found in the lung but has been reported infrequently in sites as diverse as the gastrointestinal tract, cervix, prostate, salivary glands, trachea, and skin.[4] Oesophageal small cell carcinoma was first described by McKeown in 1952 and since then over 80 reports have been published. The tumour is believed to arise from APUD cells of neuroectodermal origin.[2] The typical histological features are of small oval cells with scanty cytoplasm and a round or elongated hyperchromatic nucleus. They may be argyrophil positive, with neurosecretary granules seen on electron micrographs.[1] At least 60% of tumours have been made up of "pure" small cells, the remainder having a variable mixture of squamous, glandular, and carcinoid elements.[2]

Both squamous and adenocarcinomas of the oesophagus are conventionally managed by surgical resection. Recent reports suggest that survival and the resectability of squamous carcinomas may be improved by either chemotherapy or radiotherapy alone or a combination of the two.[9] Little is known about the optimum management of small cell tumours of the oesophagus. The small number of cases so far reported and the often advanced nature of the lesion at presentation make comparisons of different treatments difficult. Surgical resection has been performed in over 80% of reported cases with a median survival time of nearly eight months, the longest survival being 24 months after diagnosis.[1] Doherty *et al*[2] treated six patients by radiotherapy alone, with a median survival time of three months.

It is well recognised that 60–80% of small cell carcinomas of the lung respond to chemotherapy.[10] Recently there have been six isolated reports of similar regimens used alone or in combination with surgery to treat primary small cell tumours in the oesophagus (table 2). Five patients showed a partial response to treatment and in a further patient complete response to treatment was confirmed at necropsy after a death unrelated to cancer.[4]

The two patients described in this report responded to chemotherapy. In the first patient there was at least a 50% reduction in tumour size as judged by computed tomography. In the second patient the response was dramatic, no evidence of tumour being found by computed tomography or macroscopic examination of the resected organ. Histological examination of the latter specimen showed a mixed tumour containing small cell elements under a relatively normal epithelial surface. An interesting feature was the presence of large amounts of fibrosis.

The histological diagnosis of a small cell carcinoma of the oesophagus has important clinical implications, and with greater awareness this tumour is likely to be recognised more frequently. Our two cases and the others reviewed in this paper suggest that even if it is combined with other cell types this tumour may respond to chemotherapy like the more common lung small cell carcinoma. As yet, however, no long term survivors have been reported after any form of treatment.

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