Concomitant chemo-radiotherapy as standard therapy in limited-stage small-cell oesophageal cancer : A summary of 3 clinical cases and review of the literature

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Abstract

Small-cell carcinoma of the oesophagus (SCCO) is a rare and aggressive malignant tumour associated with a poor prognosis. Between 1994 and 2002, three patients with SCCO were treated in our institution, representing 1.96% (3 out of 153) of all oesophageal malignancies seen during this period. All of these patients had limited-stage SCCO at initial diagnosis and were treated by chemotherapy (cisplatin and etoposide) with concomitant radiotherapy. An initial complete response of the primary lesion was observed in all cases and a persistent complete remission in two of the cases. Chemo-radiotherapy should be considered as a valuable treatment alternative to surgery for limited-stage small-cell carcinoma of the oesophagus. (Acta gastroenterol. belg., **2008**, 71, **325-329**).

Key words : chemotherapy, oesophagus, radiotherapy, small-cell carcinoma.

Introduction

Small-cell carcinoma (SCC) is an aggressive tumour most frequently described in bronchial tree, representing about 15% of all lung cancers. Extrapulmonary SCC is extremely rare. These tumours have been described mainly in the urinary bladder, prostate, salivary glands, pharynx, larynx, oesophagus, stomach, pancreas, colon, rectum, skin and cervix (1-3).

The incidence of small-cell carcinoma of the oesophagus (SCCO) is usually reported between 0.4 and 2.8% of all oesophageal tumours (4-7) but an incidence of up to 15% is described by Japanese authors (8).

Since the first description of SCCO, more than 200 cases have been reported in the literature (9).

Similarly to small-cell lung carcinoma (SCLC), SCCO is an aggressive tumour associated with poor prognosis (5,10). SCCO is associated with metastatic dissemination at initial diagnosis in 31 to 90% of cases (5,9-12).

Consequently, the management of so-called limited-stage SCCO (stage I-III) is still controversial and the role of surgery is ill-defined.

We report here three patients with limited-stage SCCO treated in Institut Jules Bordet by concomitant chemo-radiotherapy.

Cases report

Case 1

A 71-year-old woman diagnosed in April 1994 with a 2-months history of dysphagia and loss of appetite. She was a social drinker of alcohol and had a history of smoking (ten pack-years). Performance status was 0 and physical examination was normal. Complete blood count and serum biochemical analysis showed no abnormalities. Serum concentration of carcinoembrionic antigen (CEA) and neuron-specific enolase (NSE) were within normal limits. Chest X-ray was normal. Oesogastroscopy revealed a 2 centimetres (cm) necrotic ulcer at the medium/lower third transition (30 cm from the incisors). Histological findings on the biopsy specimens showed spindle-shaped cells with scanty cytoplasm and hyperchromatic nuclei, consistent with small-cell undifferentiated carcinoma (Fig. 1). Immunohistochemistry confirmed the diagnosis of SCCO with positive staining for CD 56 and chromogranin (Fig. 2). A barium study of oesophagus showed a tumoural infiltration of 6 cm in length with a small central ulceration in the right posterior wall the union of the middle and lower thirds. Endoscopic ultrasonography defined an ulcerated lesion of the mucosa and sub-mucosa. A thoracic computed tomography (CT) scan demonstrated a thickened oesophageal wall. Bronchoscopy and cytology were normal. Bone scintigraphy, brain and abdominal CT scan did not reveal metastasis. The patient was therefore staged as having uT1N1M0 (stage IIb) SCCO, according to the TNM classification.

The patient was treated with concomitant chemo-radiotherapy : cisplatin 90 mg/m² day 1 and etoposide 100 mg/m² from day 1 to 3, every three weeks associated

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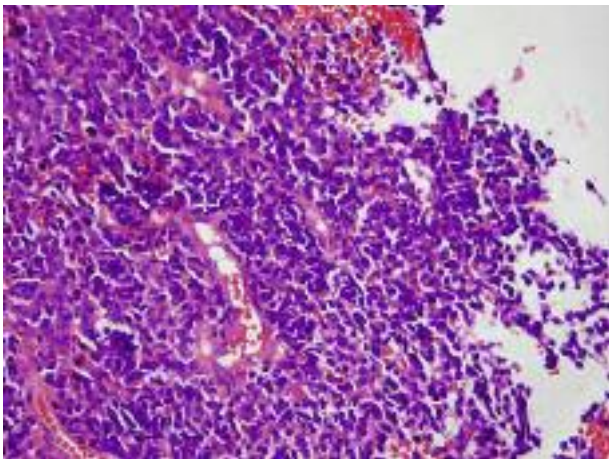

Fig. 1. — Proliferation of small cells with scanty cytoplasm, granular nuclei and inconspicuous nucleoli (H&E, × 520).

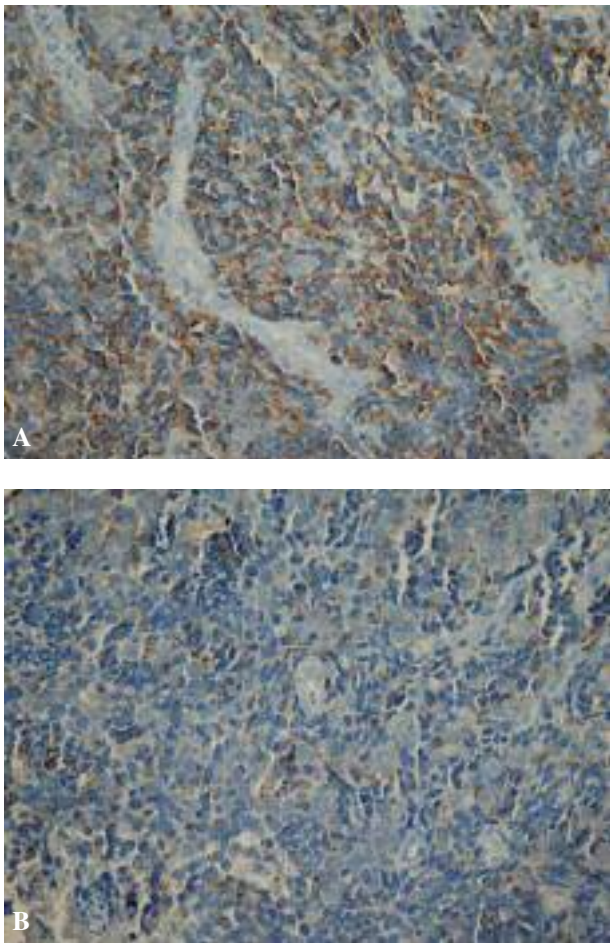

Fig. 2. — Immunohistochemical staining in small-cell oesophageal carcinoma (LSAB × 400). A. CD 56 staining ; B. Chromogranin staining.

with a total dose of 45 Gy radiation therapy (1.8 Gy/day, 5 days a week).

After three courses, concomitant to radiotherapy, clinical improvement was observed. Biologic analysis with serum tumour markers remained normal and endoscopic study demonstrated complete regression of the primary tumour. However, abdominal CT scan in August 1994 indicated a suspect retro-hepatic lymph node. After a total of six courses, oesogastroscopy, thoracic CT scan and abdominal CT scan did not show any suspect lesions, and patient was considered in complete remission.

In February 1995, serum concentration of CEA and NSE increased. Celiac and retroperitoneal lymph nodes, hepatic and bone metastases were identified. The general status deteriorated quickly and the patient was admitted for confusion. Multiple brain and cerebellar metastases were detected by CT scan and treated by palliative radiation therapy. The patient died within 1 month, 11 months after diagnosis and 8 months after the documentation of complete response.

Case 2

A 50-year-old man presented in June 1997 with a one month history of dysphagia. He was alcoholic and smoker (35 pack-years). Performance status was 0 and physical examination revealed smooth hepatomegaly palpable 2 cm below the right costal grill. Results of routine complete blood count were normal, blood chemistry revealed perturbation of liver tests (SGOT 54 U/L ; γGT 209 U/L ; Bilirubin 1,3 mg/dl). Serum levels of CEA and NSE were within normal range. Chest X-ray was normal. At endoscopy, an infiltrative lesion in the middle third of the oesophagus was visible. The histology of the biopsy specimens showed a diffuse growth of small's cells with scanty cytoplasm, hyperchromatic and anisonucleosic nuclei. Immunohistochemically, the tumour cells were negative for NSE, excluding a SCLC. Chromogranin and synaptophysin were also negative but stained positively for AE3 (an epithelial marker). The tumour was therefore diagnosed to be SCCO. Barium series showed an irregular ulcerated stenosis of 6 cm in length at the middle part of the oesophagus. Endoscopic ultrasonography revealed a constrictive tumour at 27 cm from the incisors with infiltration to the muscularis propria without extension to the bordering organs and two suspect lymph nodes of 1 cm diameter. The patient was staged uT2N1M0 (stage IIb). Thoracic CT scan revealed lymph node metastasis of the upper mediastinum. Abdominal CT scan and bronchoscopy were normal.

A concomitant chemo-radiotherapy was initiated. The patient received a total of 5 courses of cisplatine 90 mg/m² from day 1 and etoposide 100 mg/m² from day 1 to 3, every three weeks. A total dose of 45 Gy radiation therapy (1.8 Gy/day, 5 times a week) was performed. The sixth course has not been administrated because of significant haematological toxicity (pancytopenia) and progressive renal insufficiency with a creatinin up to 1.5 mg/dl.

A complete response was achieved on January 1998. Follow-up was performed every 3 months with serum tumour markers, oesogastroscopy and thoracic CT scan. Examinations remained normal till may 2001. In May 2001, oesogastroscopy with Lugol's staining showed an erosive infiltration at 29 cm from the incisors. Histological analysis of the biopsy specimen showed in situ epithelioma and considered as a second cancer. In June 2001 the tumour was removed by endoscopic mucosectomy. The resection margins were clear of tumour involvement. Endoscopic follow-up with Lugol's staining was normal. Till February 2007, this patient is considered in complete remission for the SCCO and for the second tumour, more than nine years after the initial diagnosis.

Case 3

A 59-year-old woman consulted in December 2002 with a two month history of fatigue, loss of 7 kg associated with dysphagia, retrosternal pain and melena. She was a social drinker of alcohol, and an active smoker (50 pack-years). Performance status was 0 and physical examination was normal. Complete blood count, NSE and CEA were normal. Chest X-ray revealed no abnormalities. Oesogastroscopy showed a large tumour of the lower third of the oesophagus. The histology showed a typical aspect of small-cell carcinoma and immunohistochemistry were positive for chromogranin. An endoscopic US was performed showing tumour involvement of the muscularis propria with retrocardiac lymph node enlargement. A thoracic CT scan showed a thickened left bronchia tube but bronchoscopy and cytology were negative. Abdominal US did not reveal any metastasis. Pet-scan did not show any spot except for the fixation on lower third of the oesophagus corresponding to local tumour. The patient was staged uT4N1M0 (stage III).

She underwent chemotherapy (cisplatin 90 mg/m² from day 1 and etoposide 100 mg/m² from day 1 to 3, every three weeks) associated with concurrent radiotherapy (45 Gy, 1.8 Gy/day, 5 times a week).

After a total of 6 curses of chemotherapy, endoscopic and radiological exams did not reveal any residual disease. Follow-up was performed every 3 months with serum tumour markers, oesogastroscopy with Lugol's staining and thoracic CT scan. Till February 2007, the patient is still considered in complete remission, more than four years after the initial diagnosis.

Discussion

SCCO is the most frequently reported site of extrapulmonary SCC. The incidence ranged from 0.4 to 2.8% of all oesophageal malignancies (4-7). In our experience, SCCO represent 1.96% (3/153) of all oesophageal cancer. The majority of literature cases have been reported in men with a male to female ratio of 1.57. The tumour occurs in the sixth to eighth decade. The most common complaining symptoms were rapidly progressive dysphagia and weight loss, as seen in the more classical types of oesophageal cancers. In most cases, the tumours are located in the middle and the lower third. Although the risk factors are not well-defined, they seem to be similar to squamous cell oesophageal cancer (history of alcohol consumption and smoking) (6,7,9,13). Similar clinical characteristics were observed in our patients.

Metastases are often reported at the initial diagnosis of SCCO (5,9-12) but our three cases had only locally advanced disease at the time of initial diagnosis.

The histology of SCCO is similar to SCLC, consisting of round of spindle-shaped cells with scanty cytoplasm, hyperchromatic nuclei, inconspicuous nucleoli, and structural and immunohistochemical evidence of neuroendocrine differentiation (14). The diagnosis of SCC is primarily made on light microscopy. Although electron-microscopical, immunohistochemical, and molecular-biological findings have considerably increased the understanding of the pathogenesis and progression of malignant tumours, routine pathological-anatomical diagnostics are still decisively based on light-microscopical evaluation of tissue samples (15). In immunohistochemistry, virtually all SCC are immunoreactive for keratin, epithelial membrane antigen or other epithelial markers as AE3 in our second case because of their epithelial cellular origin. Because of their neuroendocrine differentiation, SCC can be immunoreactive to NSE, chromogranin A, CD 56, gastrin releasing peptide or IGF-1. One or more markers of neuroendocrine differentiation can be found in approximately 75 percent of SCC and a complete negative neuroendocrine staining doesn't exclude the diagnosis (16). Our second case is therefore considered as a SCCO although the neuroendocrine markers are absent on biopsy.

Chemotherapy is now recognised as the cornerstone of treatment for extrapulmonary small cells tumours (17), for limited-stage SCCO (9,18) as well extensive stage SCCO (6,7).There is no consensus about the combination chemotherapy to be used. Cisplatin, etoposide and 5-fluorouracil have been reported to be active agents against SCCO (19) and the combination of cisplatin/etoposide seems to be the most frequently prescribed, probably by analogy with SCLC.

For limited-stage SCCO, the question of local therapy remains controversial. Law *et al.* (20) recommended chemotherapy associated to surgery as local therapy based on retrospective data of 5 patients with limited-stage SCCO. More recent retrospective study included 20 patients with limited-stage SCCO compared chemotherapy associated with oesophagectomy (8 cases) vs. concomitant chemo-radiotherapy (12 cases) and reported no survival difference between the two groups with median survival of 24 months (18). The same results are found in a data review of 199 SCCO published in 1997 (9) with no significant difference for limited-stage patients regarding local control (chemotherapy associated to surgery vs. radiation therapy) with a median survival of 24 months

Table 1. — **Studies included limited-stage small-cell oesophageal carcinoma**

Studies	SCCO (n)	LS	Treatment	Best R	Survival (months) and disease status	Rem
Bennouna (7)	10	4	CT-RT (3) CT alone (1)	CR (3) PD	18-19-alive at 36 2	
Casas (9)	199	93			8	No statistic difference with regard of local treatment (radiation therapy vs surgery)
Hosokawa (6)	14	3	CT alone (1) CT-surg. (1) Surg. alone (1)	NE PR	0.6 alive at 13.4 2.4	
Law (20)	11	5	CT-surg. (1) Surg. alone (3) Surg.-RT		72 3.4-22.3-lost FU 9.1	
Nemoto (18)	20	20	CT-esophagectomy (8) CT-RT (12)		24	No statistic difference with regard of local treatment (radiation therapy vs surgery)
Medgyesy (21)	8	6	CT-surg. (1) CT-surg.-RT (3) RT alone (1)		15 16-alive at 16-alive at 57 5-alive at 33	
Van der Gaast (17)	2	2	CT-RT (2)	CR (2)	14-22	
Nichols (5)	11	3	CT-RT (1) CT-surg. (2)	CR CR (2)	21 8 -NA	

Best R : Best response ; CT : chemotherapy ; CR : complete response ; FU : follow-up ; LS : limited-stage ; NA : no available ; NE : not evaluable ; PD : progressive disease ; PR : partial response ; RT : radiotherapy ; SCCO : small-cell carcinoma of the oesophagus ; Surg. : surgery.

(Table 1). Although concomitant chemo-radiotherapy is recognised in the literature as a standard approach for the treatment of limited-stage SCCO, some authors still consider that surgery performed with a curative intent should be the main treatment or a part of a multimodal management in limited-stage disease (11,18,21). In reality, there is a complete lack of valuable and prospective data in the literature to approve the surgery attitude. Furthermore, the indications of emerging techniques as endoscopic mucosal resection used in superficial squamous cell oesophageal cancer have to be defined in SCCO (22-24).

There is no available data regarding the optimal radiation schema for SCCO. Current treatment is adapted from the SCLC management. In SCLC, local recurrence is observed in approximately half of the patients receiving a total dose of 40 to 50 Gy irradiation (25) but seems to be reduced by higher radiation doses (26). In limited-stage SCCO, 40 to 50 Gy seems to be an adequate dose in patients who were postoperatively irradiated but higher doses are recommended for definitive radiation therapy (18). The higher series of limited-stage SCCO treated by concurrent radio-chemotherapy reported in the literature (12 cases) suggested that a radiation dose of 60 to 70 Gy is adequate as definitive radiation therapy with a local control rate of 92% at 5 years (18).

In our three cases, limited-stage SCCO were treated by concomitant chemo-radiotherapy with a combination of cisplatin/etoposide associated with definitive radiation therapy of 45Gy. An initial complete response was observed in all cases and a persistent complete response in two of the three cases. The only recurrence appeared quickly outside the radiation field, illustrating the metastatic potential of this tumour.

Our experience reinforce the opinion that concomitant chemo-radiotherapy should be considered as an important treatment option for limited-stage SCCO.

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