Chapter 4:

Small Cell Carcinoma of the Bladder: A Single Centre Study of 25 Cases Treated in Analogy to Small Cell Lung Cancer

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Abstract

Purpose: To evaluate the feasibility and efficacy of a therapeutic algorithm for the management of small cell carcinoma (SCC) of the bladder derived from the treatment of small cell lung cancer (SCLC).

Materials and Methods: Over a period of 10 years, 25 consecutive patients with SCC of the bladder were defined as having limited disease or extensive disease in analogy to SCLC. Patients with limited disease were eligible to systemic chemotherapy and sequential radiotherapy with curative intent. Patients unfit for chemotherapy were offered salvage cystectomy for large symptomatic tumours or radiotherapy in the absence of local symptoms. Patients with extensive disease were offered palliative chemotherapy.

Results: Twenty-three patients were male, 2 were female. Median age was 64 years (range 40 to 90 years) with 8 patients (32%) older than 75 years. Seventeen patients (68%) had limited disease and 8 (32%) extensive disease. Without regard to stage, surgery or radiotherapy, median survival of those receiving chemotherapy was 15 months versus 4 months for those who did not. Median survival for limited disease was 12 months versus 5 months for extensive disease. Nine patients (52.9%) with limited disease could not undergo chemoradiation because of comorbidity and reduced performance (n=7), progression (n=1) and drug-related death (n=1). Two underwent a salvage cystectomy and 5 received radiotherapy only.

Conclusions: SCC of the bladder has a poor prognosis and this treatment algorithm offers bladder sparing in the majority of patients. Long-term remission and cure can be achieved in some, especially in patients with small confined tumours. None of the patients who died of disease, died of locoregional tumour progression which supports that cystectomy should be reserved for limited-disease patients with contraindications for systemic chemotherapy and radiotherapy. With a significant proportion of elderly, comorbid patients, the concept of chemoradiation was not feasible in more than half of the patients with limited disease.

Introduction

Small cell carcinoma accounts for a fifth of lung cancer cases but is rarely observed in extra pulmonary primaries.[1] The first case of primary small cell bladder cancer (SCCB) was reported in 1981.[2] Since then some 150 cases diagnosed according to World Health Organization (WHO) criteria[3,4] have been published in small series and case reports.[5-15] The prognosis of SCCB is poor and only Cisplatin-based chemotherapy has been predictive to influence survival.[11] Local therapy often fails due to micrometastases at diagnosis, but cases have been reported in which locally confined disease was curable.[10] The paucity of SCCB precludes prospective randomized trials and the optimal therapeutic strategy is still unknown. Cystectomy with adjuvant chemotherapy has been propagated[9] as well as combinations of chemotherapy with transurethral resection (TUR), partial cystectomy and radiotherapy.[10-12] In contrast, SCLC, which shares many clinicopathological features with SCCB, is far more common. A clinically relevant two-stage system of limited and extensive disease is widely used to determine prognosis and treatment and a consensus of combination chemotherapy and radiotherapy emerged, depending on the extent of the disease.[16-18] Due to the dismal prognosis of SCCB an organ sparing treatment strategy of chemotherapy and radiotherapy in analogy to its pulmonary counterpart depending on a simple two stage system is an attractive concept. To evaluate a therapeutic algorithm for SCCB we defined a two-stage system of limited and extensive disease in analogy to the practised staging and treatment for SCLC. We investigated the feasibility of a bladder sparing approach and its impact on clinical outcome and survival. The results are discussed with regard to treatment of SCCB in the literature.

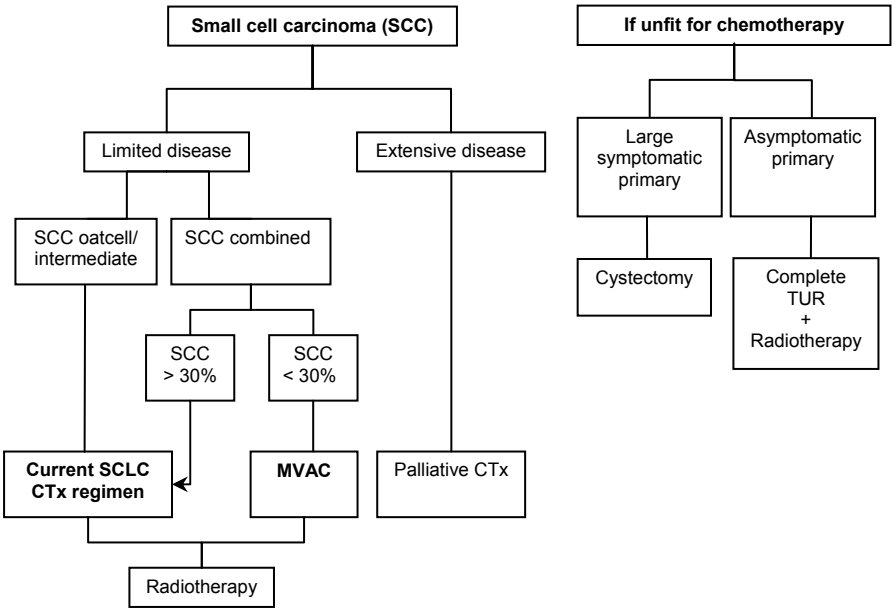
Material and Methods

From 1993 patients with a histopathological diagnosis of primary SCCB at TUR based on the WHO criteria[3] were included to investigate feasibility of a bladder sparing approach in analogy to chemoradiation of SCLC (figure 1).

The tumours were staged according to the TNM classification. In analogy to SCLC, patients with any local stage, no distant metastases and involvement of maximally one locoregional lymph node less than 2 cm (Tx N0-1 M0) were defined as having limited disease, all others (Tx Nx M1/ Tx N2-3 M0) as extensive disease. Patients with limited disease were eligible to systemic chemotherapy followed by external beam radiotherapy with a curative intent. Patients with a performance status (PS) WHO > 2 were offered a macroscopically complete TUR followed by radiotherapy. Only in exceptional cases of large symptomatic tumours a cystectomy was considered. Patients with extensive disease were offered palliative chemotherapy. Chemotherapy would follow the accepted protocols for SCLC, with the exception that patients with < 50% SCCB in combination with TCC in tumour tissue obtained at TUR received 4 courses methotrexate 30 mg/m^2, vinblastine 3 mg/m^2, doxorubicine 30 mg/m^2 and cisplatin 70 mg/m^2 (MVAC). Over the course of

10 years the cisplatin-based SCLC-regimen changed. Four courses ifosfamide 1.2 g/m^2 (maximum 1.75 g), VP-16 (etoposide) 75 mg/m^2 and cisplatin 20 mg/m^2 (VIP) day 1-4, repeated after 21 days were later replaced by 4 courses cisplatin 75 mg/m^2 day 1 with etoposide 100mg/m^2 i.v. (CE) day 1-3, repeated after 21 days. Patients with contraindications for cisplatin but a PS WHO ≤ 2, received 5 courses cyclophosphamide 1.0 g/m^2 (day 1), doxorubicine 45 mg/m^2 (day 1) and etoposide 100 mg/m^2 (day 1-3) (CDE) repeated after 21 days. Radiotherapy was applied using 8-18 MV photons with a three or four-field technique. The mean dose was 60 Gy varying from 56 to 70 Gy. The target area consisted of the bladder and the tumour. In case the total dose was 70 Gy (n=3), 50 Gy was given to bladder and tumour with a 20 Gy boost to the bladder tumour area only.

Figure 1: *Patients presenting with small cell carcinoma and eligible for chemotherapy (CTx) are treated according to the left algorithm, those ineligible for CTx according to the right.*



Limited disease: Tx N0-1 M0. Extensive disease: Tx N2-3 M0 or Tx Nx M1. SCLC: small cell lung carcinoma. CTx: chemotherapy. MVAC: Methotrexate, Vinblastine, Adriamycin and Cisplatin.

All patients were staged with CT scan of abdomen and chest, bone scan, laboratory evaluation, cystoscopy and cytology at baseline, repeated in three-monthly intervals during follow-up. WHO criteria were used to assess response to chemotherapy. In patients with limited disease evaluation of response of the primary tumour following chemotherapy included cystoscopy, cytology and CT scan and was repeated at three-monthly intervals following radiotherapy. A TUR was repeated in case of any macroscopical residual disease or suspicious cytology following chemotherapy and radiotherapy or during follow up.

Study design and statistical considerations

This feasibility study was designed to investigate efficacy and safety of bladder preservation in limited SCCB after staging patients into limited and extensive disease in analogy to SCLC. Primary endpoints were proportion of clinical complete remissions (CR) achieved in limited disease following chemoradiation or - if ineligible for chemotherapy - TUR and radiotherapy, as well as number of cystectomies performed. Secondary endpoints were overall survival for limited and extensive SCCB, overall survival for patients receiving chemotherapy versus those who did not and duration of clinical CR in limited disease. The hypothesis was that a bladder sparing approach should result in a clinical CR proportion of 80% with an acceptable lowest CR of 50%. Bladder sparing would be considered not feasible if more than 50% would fail to reach a clinical CR requiring additional salvage cystectomy. A sample size of 20 patients with limited disease would be needed to allow the exclusion of a clinical CR rate of 50% or less with an alpha of 0.05 and to detect an expected proportion of 80% clinical CR with a power of 80%. Regarding the low incidence time of accrual was unknown. Due to small sample sizes a univariate analysis of survival was performed.

Results

Patient characteristics

From August 1993 until September 2003, 25 consecutive patients with SCCB were included. Twenty-three patients were male, 2 were female. Median age was 64 years (range 40 to 90 years) with 8 patients older than 75 years (32%). Seventeen patients (68%) had limited disease and 8 (32%) extensive disease.

Light microscopy and immunohistochemistry

Eleven of 25 patients (44%) had combined tumours of which 4 with more than 70% component of TCC. Eight of 11 combined tumours (72.7%) contained TCC, of which 4 with additional adenocarcinoma, squamous cell and sarcoma. Other combinations contained large cell and squamous cell tumours. None of the patients had a significant adeno- , squamous cell- or large cell carcinoma component. Immunohistochemistry (CAM 5.2, neuronal-specific enolase, chromogranine A, synaptophysine) was performed in 17 specimens, but no pattern emerged with regard to prognosis or treatment outcome.

Treatment of all stages

Overall median survival was 8 months (range 2-84 months). Overall median survival of patients with limited disease (n=17) was 12 months (range 4-84 months) versus 5 months (range 2-17 months) for extensive disease (n=8) (p 0.09). Regardless of tumour stage, overall survival of patients receiving chemotherapy (n=13: 10 limited and 3 extensive disease) was 15 months (range 4-52 months) versus 4 months (range 2-84 months) for patients who did not receive chemotherapy (n=12: 7 limited and 5 extensive disease) (p 0.003).

Treatment of limited disease

Of 17 patients with limited disease 10 underwent upfront chemotherapy (n=2 CDE, n=3 VIP, n=2 CE and n=3 MVAC). One patient died due to neutropenic sepsis following the 3rd course of MVAC; another progressed during the 2nd course VIP. Ultimately, 8 of 17 patients (47%) had a clinical CR after chemotherapy and received sequential radiotherapy according to plan. However, 5 of those patients had a complete TUR before chemoradiation. One patient developed a local recurrence after 2 years, underwent salvage cystectomy with a surgical CR for 11 months and died disease related 52 months after diagnosis.

The other 7 patients (41%) were not eligible for chemotherapy (PS WHO 3): five were treated with radiotherapy alone after complete TUR: in 2 patients radiotherapy failed and 3 developed a clinical CR. Two patients underwent a cystoprostatectomy: in a patient with end-stage renal failure tumour extent precluded radiotherapy, the other had a history of radiotherapy for prostate cancer.

Eleven of 17 patients (64.7%) developed a clinical CR with a bladder sparing approach, including all (n=8) treated with chemoradiation and 3 with TUR and radiotherapy. Median duration of CR was 15 months (range 3 to 84 months) with 5 ongoing at 14-42 months. None has survived 5 years yet. Median survival of those treated with chemoradiation (n=8) was 15 months (range 11-52 months), and 14 months (range 4-52 months) for all receiving chemotherapy (n=10). Those ineligible for chemotherapy (n=7) had a median survival of 6 months (range 4-84 months), except one patient, who died of pancreatic carcinoma 84 months after TUR and radiotherapy .

Treatment of extensive disease

Six of 8 patients were eligible for chemotherapy, but 3 refused after counselling. Those who received chemotherapy survived 6, 16 and 17 months. One patient with N2 disease was ineligible for chemotherapy because of PS WHO 3 and underwent palliative cystoprostatectomy and extensive lymphadenectomy due to a symptomatic tumour too large for radiotherapy. He is alive with progressive disease after 8 months. One patient could not undergo chemotherapy due to extensive comorbidity and progressed rapidly. All but one patient died disease related.

Discussion

SCCB is a rare disease and it took 10 years to include 25 patients in this single-centre study. When accrual was halted 3 patients would still be needed to reach the full sample size of 20 patients with limited disease. Statistical analysis is therefore influenced by inherent biases, low numbers and consequently low power. In 64.7% of the patients with limited disease the bladder preserving strategy resulted in a clinical CR. The difference in survival between limited and extensive disease is not statistically significant, though the statistical power to detect a difference is limited by the small number of patients in each group. Due to the small sample size of patients with limited

disease downstaged by TUR and chemotherapy prior to radiotherapy no relation could be established with regard to predicting response to radiotherapy or systemic progression. Interestingly, the difference in survival of patients who received chemotherapy versus those who did not was significant regardless of tumour stage ($p = 0.028$). In a Cox-regression analysis chemotherapy was an independent prognosticator for survival when corrected for stage, though it is conceivable that selection criteria for chemotherapy were a major source of bias. These results are in line with a retrospective literature search involving 106 reported cases of SCCB: Metastatic disease predicted poor outcome while only cisplatin therapy, not primary surgery, improved survival.[11]

Sufficient data were accumulated in the past to demonstrate a similarity of the clinical course of SCCB and SCLC.[7] In SCLC survival increased only after the introduction of multi-agent chemotherapy regimens. Most of the benefit occurred in patients less than 65 years of age.[19] The definition of limited-SCLC takes early metastasis into account with tumour confined to the hemithorax of origin, the mediastinum or the supraclavicular lymph nodes. All patients with tumour beyond these confinements have extensive disease. The current treatment of limited-SCLC comprises a combination of cisplatin and etoposide plus chest irradiation preferably during the first or second cycle of chemotherapy.[20-22] A prophylactic cranial radiation follows in patients with a complete response. This strategy may result in median survival of 18 to 24 months and 50% 2-year survival.[17,20,23] Extensive-stage disease is treated primarily with chemotherapy resulting in response rates of 70% with a CR in 20% to 30% but with a poor median survival of 9 months.[24,25] Due to early micrometastasis the overall survival of SCLC remains poor with 5% to 10% after 5 years.[26]

While the clinical utility of the two-stage system in SCLC has been supported by multiple studies, SCCB is staged according to the TNM classification which fails with regard to micrometastases. In the largest retrospective analysis of SCCB[11], tumour stage was not independently associated with survival suggesting that micrometastases are often present in clinically localized disease. Because of the clinicopathological similarities between both tumour sites, the simplicity of the two-stage system and its clinical relevance for treatment decisions, we decided to define limited- and extensive-SCCB in analogy to SCLC. To account for the presence of micrometastasis, limited-SCCB, as limited-SCLC, would not differentiate between locoregional N0 and N1 disease. Extensive-SCCB would require larger lymph nodes or distant metastasis.

The benefit of cisplatin-based chemotherapy for SCCB has been observed in earlier studies.[7-9,12] Combinations without cisplatin were not associated with prolonged survival[11], though this should be interpreted with caution. Good performance status required for cisplatin-based chemotherapy may explain the observed association of this drug with improved survival in retrospect. In this study, 3 patients received a combination containing no cisplatin. In SCLC 2 or more drugs are needed for maximal effect but most regimens produced similar survival outcomes regardless of

cisplatin[16,17]. Combined SCCB is observed between 23% and 75% and the TCC, adenocarcinoma or squamous cell components have no apparent prognostic influence.[7,9,12,13] The proportion of the non-SCCB component may be 50 to 60% of the resected volume.[7,9,13] There is ample evidence from the literature that the presence of SCCB in combined bladder tumours is the leading prognosticator[6,9-11] and that it should be managed like pure SCCB with cisplatin-based chemotherapy. If the TCC component obtained at TUR was significantly present (> 50%) we applied MVAC as suggested in the literature.[9]

Concurrent radiotherapy for SCLC has been introduced between 1999 and 2002 and the decision was made to continue with sequential radiotherapy. We did not perform prophylactic cranial irradiation and none of the patients in our series died of a brain metastasis. Another difference between SCLC and SCCB is observed in the percentage of patients with extensive disease. Sixty to 70% have extensive-SCLC at presentation, whereas we observed 30% in SCCB. This may be due to a difference in definition or clinical signs such as haematuria leading to early diagnosis, but it is known that extent of disease and prognosis is partially depending on the primary disease site.[11] Whether this is due to distinct anatomical features of a particular site or underlying differences in genetic patterns remains to be established.[27]

Patients with SCCB are typically elderly men and in some series more than half of the patients were over 70 years of age.[12,13] Though there have been reports that chemotherapy for SCLC is feasible in elderly patients[19], we observed a high rate of age-related comorbidity among patients older than 70 years. Forty-eight percent of our patients were older than 70 years (12/25). In patients with limited disease unfit for chemotherapy we offered radiotherapy subsequent to a macroscopically complete TUR. Long-term survivors have been reported in a retrospective series with this strategy.[10] Exceptionally, cystectomy was performed if severe locoregional symptoms and/or contraindications for radiotherapy were present. Ultimately 9 of 17 patients (52.9%) with limited disease could not be treated with chemotherapy and sequential radiotherapy, mostly because of PS WHO 3 (n=7). Disease related survival and time to progression do not differ from the literature, in which a median survival of 13 months for all stages is reported in the larger series.

Conclusion

SCCB has a poor prognosis which may only be influenced by extent of the disease at diagnosis and combination chemotherapy. Therefore, a bladder-preserving strategy is an attractive concept. The treatment algorithm based on a two-stage system of limited and extensive disease is feasible. With a strategy of chemoradiation cystectomy can be avoided in the majority of patients. Long-term remission and potentially cure can be achieved in some, especially in patients with small confined tumours. The fact that none of the patients died of locoregional tumour progression supports our view that cystectomy is not the preferred treatment for limited-SCCB. However, the significant proportion of elderly, comorbid patients with a reduced perform-

ance status, precluded chemoradiation in more than half of the patients with limited disease.

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