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Small Cell Prostate Cancer: What about the Management? A Case Report

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Abstract

Small cell prostate cancer (SCPC) is a very uncommon histological type of prostate cancer and one of the least common sites of extrapulmonary small cell cancer (EPSCC). Because this rarity, there is an absence of either randomized trials or specific guidelines for the management of the SCPC. We reported, here, the case of patient diagnosed with metastatic mixed form of SCPC (conventional adenocarcinoma prostate plus variable neuroendocrine cells), we discussed the prognosis and the treatment of this rare entity and we briefly reviewed the literature

Introduction

Prostate cancer (PC) accounting for 1/4 of all diagnosed cancer cases in men, and is the second most common cause of cancer-related mortality among men (1, 2). The 2004 World Health Organization (WHO) classification has defined two groups of histological variants of PC. The first group comprises histological variants of acinar adenocarcinoma, which is the most frequent histological type of PC. The second group non-acinar adenocarcinoma accounts for about 5-10% of carcinomas that originate in the prostate and include neuroendocrine and others (2). Neuroendocrine cancer includes well-differentiated, low-grade (carcinoid tumor), moderate differentiated, intermediate-grade (atypical carcinoid) and poorly differentiated tumor, high-grade (Small cell cancer and large neuroendocrine cancer).

Small cell prostate cancer (SCPC) is a very uncommon type of PC, rarely arises De novo.

SCPC comprises two main forms, a pure form, exclusively small cells, rarest, represents between 0.2 and 1% (3,4), and a mixed form less 10%, contains conventional adenocarcinoma prostate often poorly differentiated and variable neuroendocrine (NE) cells (4, 5). In this entity, recent evidence indicated a possible role of component NE cells in tumor proliferation, progression and development of androgen refractory state.

Thus, NE differentiation generally involves more aggressive PC clinical behavior and an unfavorable prognosis. Makey and al. showed in their studies a worse prognostic for SCPC with median survival of 7 months. Primary surgical therapy was associated with prolonged survival while metastatic disease at presentation predicted poor survival (6). SCPC has received increasing attention in recent years due to prognostic and therapeutic implication.

In this case, we presented the case of a patient who was initially diagnosed with metastatic mixed-SCPC.

Case report

In October 2012, a 54 year-old man consulted for dysuria, acute urine retention and diffuses bone pain. The serum prostate-specific antigen (PSA) was 5.24 ng/ml. He had transurethral resection of the prostate. Pathology review revealed poorly differentiated glandular carcinoma for prostatic origin with a large proportion of chromogranin A- and synaptophisyn -positive small cells in immunohistochemistry, indicating the presence of component NE cells and diagnostic of mixed-SCPC. Chest-Abdominal-pelvis (CAP) Computed Tomography (CT) showed bilateral pulmonary metastases and bone scan also revealed axial and peripheral skeletal metastases.

His Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was 1 and laboratory tests were normal with creatinine clearance 94.4 ml/minutes according to Cockroft and Gault formula.

Patient was treated with combination of cisplatin 80 mg/ m^2/Day (D) D1 and etoposide 100 mg/ m^2/D, D1-D3 every three weeks. After three cycles, we obtained clinical and biological response with bone pain control and decrease of PSA 2.46 versus 5.24 ng/ml. CAP CT revealed persistent pulmonary micronodules and bone metastasis. This response was maintained after nine cycles and chemotherapy was stopped in April 2014 because patient developed ototoxicity and renal failure to cisplatin. He continued monthly bisphosphonate (Acid Zoledronic) with adjusted dose to renal function.

January 2015 (8 months after end of chemotherapy), there was an appearance of bone and pelvic pain but CAP CT and bone scan revealed a status quo of metastases. The patient

received 4 cycles of second line of chemotherapy with docetaxel 75 mg/m²/D every three weeks associated to acid zoledronic and morphine for pain. The pain was partially controlled but patient died in May 2015. Its overall survival was 32 months.

Discussion

Small cell prostate cancer (SCPC) is a rare and aggressive form of the prostate cancer that is almost unfirmly fatal. The onset is usually between of ages 40 and 60. SCPC is the least common type of extrapulmonary small cell cancer (EPSCC) and comprises two mains form. The pure form may arise de novo as in small cell lung carcinoma. While the mixed SCPC (prostate adenocarcinoma with foci of neuroendocrine differentiation) occurs usually in conventional prostate adenocarcinoma during resistance castration phase after long-term androgen deprivation therapy (7).

Neuroendocrine cells component are androgen receptor- and prostate-specific antigen (PSA)-negative, and secrete many neuropeptides, such as chromogranin-A, adrenocorticotropic hormone (ACTH). Thereby SCPC can be associated with paraneoplastic syndromes such as Cushing's syndrome (8), peripheral neuropathy, and hypercalcemia without bone metastases (9).

In contrast to prostate adenocarcinoma, serum level of PSA is relatively low, do not correlate with disease activity and are not useful for posttreatment surveillance or as a marker of treatment benefit in the setting of advanced disease. Furthermore, elevated serum chromogranin A, neuron-specific enolase (NSE) and carcinoembrionic antigen (CEA) levels are frequently observed in SCPC and correlated to tumor activity (7, 10, 11). Our patient are not evaluated for serum chromogranin A and NSE because its unavailability in our laboratory at diagnostic.

In pathologic review SCPC like other small cell carcinomas is a poorly differentiated tumor positive for markers of neuroendocrine differentiation including chromogranin A, NSE (7), synaptophysin and neural cell adhesion molecule (NCAM, CD56).

SCPC is characterized by frequent visceral metastases, lytic bone involvement, relative low PSA concentration, resistance to androgen ablation, and a high response rate to etoposide/cisplatin chemotherapy (12, 13). Visceral metastases of SCPC include early symptomatic brain metastases but its incidence is unclear and prophylactic brain irradiation remains controversial (14).

Symptoms due to the primary SCPC are the same as those seem in others prostate cancer and can be due to metastatic disease.

Management of metastatic SCPC requires a combined multimodality treatment. According to National Comprehensive Cancer Network (NCCN) guidelines, SCPC like EPSCC is treated as small cell lung cancer (SCLC) with regimens such platinum associated to etoposide. Due the lack studies in these tumors, many others authors refer to the large literature on high-grade SCLC to establish treatment strategies (15). Therefore, standard regiment includes 4 to 6 cycles of cisplatin plus etoposide. The rationale of such strategies is unclear and several series pointed out many differences between pulmonary and EPSCC(16-18). Palliative radiotherapy and other supportive care can be considered in some cases.

Given the high frequency of mixed form -neuroendocrine and prostate adenocarcinoma within tumors-, hormonal therapies should be considered either first or in combination with platinum-based chemotherapies, depending on the clinical scenario, with a rationale of treating both adenocarcinoma and NE components. Pure SCPC would not be expected to respond to hormones or taxanes, and a small-cell lung regimen such as cisplatin-etoposide should be considered (12).

Thus, due to presence of large NE cells component and low serum level PSA, our patient was treated by cisplatin-etoposide regimen only. He benefited this regimen because we observed decreased bone pain and partial response of pulmonary metastases.

Culine et al used docetaxel plus cisplatin in their series of 41 patients with androgen-independent prostate cancer and elevated serum neuroendocrine markers (NSE and chromogranine A) and showed 41% response rate and 12 months of median survival (19).

In a phase II study, Papandreou and al. treated 38 patients with SCPC (pure and mixed) with doxorubicin, etoposide and cisplatin. This regimen caused higher toxicity in this patient population and failed to improve outcome (13).

Other cases reports were attempted the three drugs such gemcitabine, docetaxel and carboplatine or cyclophosphamide, doxorubicin and vincristine and showed objective response (20, 21).

Another viable treatment option of neuroendocrine prostate cancer may be the therapeutic targeting of the somatostatin receptors in the surface of the neuroendocrine tumor cells with a somatostatin analogue (1). Before initiating this treatment, it is mandatory to perform somatostatin receptor scintigraphy (Octreoscan) to establish the adequate presence of somatostatin receptors in the metastatic lesions (1, 23-25). The combination of somatostatin analogues with various chemotherapeutic and other agents has been also investigated in clinical studies, especially in hormone- refractory metastatic prostate cancer patients with favorable results in terms of progression-free survival (25), decreasing bone pain and in increasing Karnofsky performance status. But in these studies, it is unexplained whether somatostatin analog is effective on small cell components but it failed to induce objective response in SCLC (25). Therefore, somatostatin analog used in treating paraneoplasic syndrome in patients with SCLC or EPSCC (25).

However, SCPC relapses are common, and most patients with SCPC survive less than one year (12, 22), the PFS of our patient was 16 months and progression was clinic without radiological and biological confirmation. Our patient has been

a long survivor with an overall survival of 32 months.

In conclusion, since the 20th century, the management and prognosis of SCPC were not improved. The results presented above, show the lack of standardization and evidence based medicine in SCPC management. Further randomized studies, including a higher number of patients, are required to understand biology and histological behavior of SCPC, to identify specific prognostic markers and to establish standard multimodal treatment.

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