This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 License (www.karger.com/OA-license), applicable to the online version of the article only. Distribution for non-commercial purposes only.

Carcinomatous Meningitis: The Natural History of Successfully Treated Metastatic Bladder Cancer

S. Tadepalli^a T. Coleman^a L.A. Hackett^a G.B. Liles^b

^a Department of Hematology and Oncology and ^b Department of Pathology, Georgia Health Sciences University, Augusta, Ga., USA

Key Words

Carcinomatous meningitis · Central nervous system · Complete response · Intrathecal methotrexate · Methotrexate, vinblastine, Adriamycin, and cisplatin combination treatment · Transitional cell carcinoma

Abstract

Carcinomatous meningitis due to bladder cancer is a rare entity reported only in case reports. Optimal therapy is thus poorly defined with earlier cases reporting an unsuccessful outcome. Here we report a case of late carcinomatous meningitis secondary to transitional cell carcinoma (TCC) of the bladder occurring in a patient in complete remission. He was successfully treated with intrathecal methotrexate and whole brain irradiation and experienced prolonged survival after treatment. With modern chemotherapy increasing complete remissions and survival rates in patients with TCC, more and more patients are being reported with carcinomatous meningitis. We raise the question of whether central nervous system prophylaxis should be considered in patients with TCC achieving a complete remission to chemotherapy in the metastatic setting.

Introduction

Carcinomatous meningitis due to bladder cancer is a rare entity reported only in case reports. Optimal therapy is thus poorly defined, with most cases reporting an unsuccessful outcome. Here, we report a case of carcinomatous meningitis secondary to transitional cell carcinoma (TCC) of the bladder successfully treated with intrathecal methotrexate (MTX) and whole brain irradiation.

Case Report

A 47-year-old white male presented with TCC of the bladder which had metastasized to bone as revealed by PET-CT. Chemotherapy with cisplatin and gemcitabine resulted in a radiographic complete remission after 7 cycles. Three months after completing chemotherapy, the patient presented with headache. A brain MRI suggested carcinomatous meningitis (see [fig. 1](#), [fig. 2](#)). He then developed a right CN III palsy. A lumbar puncture confirmed the diagnosis (see [fig. 3](#)). The patient was treated with biweekly intrathecal MTX via an Ommaya reservoir for 6 weeks, resulting in the clearance of his cerebrospinal fluid; however, his cranial nerve palsy persisted. He then underwent whole brain irradiation (3,960 cGy at 180 cGy per day over 22 days by the ‘German Helmet’ technique) with resolution of his cranial nerve palsy. He is currently alive 9 months after his diagnosis of carcinomatous meningitis.

Discussion

Cancer of the urinary bladder is diagnosed in approximately 70,500 people each year in the United States, and about 14,000 individuals die [1]. Central nervous system (CNS) involvement is rarely reported. In a study by Anderson et al. [2] involving CNS complications occurring in bladder cancer, no patient developed carcinomatous meningitis and only 1% of patients developed brain metastasis in a series of 359 patients.

For carcinomatous meningitis associated with other solid tumors, a typical induction regimen consists of a fixed dose of 10 or 12 mg of intrathecal MTX twice weekly for 4 weeks. If clinical response occurs, the frequency of administration is decreased to once weekly for 4–8 weeks; a maintenance regimen is then continued with drug administration every 2 weeks for several months, and then monthly for 2–4 months. The optimal duration of therapy is unknown [3].

The route of delivery of intrathecal chemotherapy may impact outcome. Shapiro et al. [4] demonstrated that MTX administration using an Ommaya reservoir more reliably produced adequate cerebrospinal fluid distribution than administration by lumbar puncture. In another study, 100 patients with clinically and cytologically or radiographically documented neoplastic meningitis stemming from solid tumors received intracerebrospinal fluid liposomal cytarabine or MTX. Progression-free survival (the primary study endpoint) was identical between the sustained-release cytarabine and MTX treatment arms for all 100 patients (35 vs. 37.5 days, respectively, $p = 0.79$). When progression-free survival was examined as a function of the route of chemotherapy administration (lumbar vs. ventricular), there was no difference for patients treated with sustained-release cytarabine (29 vs. 43 days, respectively, $p = 0.35$). For patients treated with MTX, however, there was a statistically significant difference favoring patients receiving intraventricular therapy (19 vs. 43 days, respectively, $p = 0.048$) [5]. Hitchins et al. [6] also noted that responses were more frequent if therapy was administered via an Ommaya reservoir. We speculate that placing an Ommaya reservoir in our patient may have contributed to his relatively prolonged overall survival.

There are several cases of transitional cell carcinomatous meningitis reported in the literature – with our case bringing the total to 30. While some patients presented with grossly widespread disease including the CNS, our literature review suggests that many patients had the complication occur after successful treatment of their systemic disease (see [table 1](#)). For example, Bishop et al. [7] reported 2 patients developing disease after systemic treatment with MTX, vinblastine, Adriamycin, and cisplatin (MVAC).

Matsushita et al. [8] reported a case occurring 16 months after their patient had had a complete response following chemotherapy and surgery, and Boukriche et al. [9] reported a case occurring 4 years after adjuvant treatment for resected bladder cancer. Still, just as many cases present concurrently with widespread systemic disease, suggesting that TCC may have an affinity for the CNS and that carcinomatous meningitis may be more common than realized. The prognosis for most patients with carcinomatous meningitis secondary to TCC is dismal, with patients surviving a median of 38 days [31]. Our review confirms the poor prognosis with an average survival of 2.2 months for all patients in which survival has been reported. Interestingly, the average time to the development of carcinomatous meningitis is 14 months (see [table 1](#)).

With more cases appearing in the literature, it raises the question: does the successful treatment of systemic disease with modern chemotherapy change the natural history of the disease? Dhote et al. [33] reported on 50 patients with advanced TCC of the bladder treated with MVAC and noted that 8 patients experienced a CNS relapse (16%). In their series, brain metastasis occurred within a mean of 21 months. In the series by Bishop et al. [6], 2 of 17 patients treated with MVAC had carcinomatous meningitis (12%). Finally, in a series reported by Sternberg et al. [34], 2 out of 12 patients achieving complete response on MVAC later developed CNS disease (17%). We can only surmise that in the series by Anderson et al. [2], in which data was collected on patients between 1962 and 2001, the majority of patients did not receive cisplatin-based chemotherapy. With the rising incidence of TCC of the bladder, more and more patients are now dying of complications seen only in advanced stages of disease. With modern chemotherapy, median survival has increased from 3–6 months in the pre-MVAC era to its current figure of almost 1 year. This combination chemotherapy, in a multicenter phase III trial, was shown to increase median survival from 8.2 to 12.5 months [35]. As with any chemotherapy, MVAC is associated with complications like cardiac and renal toxicities, along with neutropenia and mucositis. The rate of death due to MVAC toxicity is around 3–4% and the disease-free survival rate is 3.7% at 6 years [34, 35]. A newer phase III study has shown the clear advantage of using the gemcitabine-cisplatin combination as it is as effective as MVAC, but with less systemic toxicity [36]. Reports of carcinomatous meningitis occurring when the gemcitabine-cisplatin combination is used are increasing, similar to the trend reported for MVAC. As more and more cases appear in the literature, it may be reasonable to consider CNS prophylaxis in patients who achieve complete remission on chemotherapy in a metastatic setting.

Table 1. Summary of reported cases on transitional cell carcinoma of bladder and its metastasis to CNS

Study first author	Stage at DX	Disease course and treatment summary	CR	Time to CNS disease months	TX CNS	OS after CNS disease months
Hust, 1980 [10]	nr	cobalt XRT	nr	5	none	5
Hust, 1980 [10]	IV	meningitis at presentation	na	0	none	0
Mandell, 1985 [11]	nr	radiation and cystectomy at diagnosis, cisplatin × 5 at relapse	yes	10	IT MTX/XRT	nr
Bishop, 1990 [7]	III	MVAC × 4, meningitis after cycle 4	no	32	IT MTX/XRT	5
Bishop, 1990 [7]	T4	cystectomy, MVAC × 3, meningitis after cycle 3	no	–	none	4
Hussien, 1989 [12]	IV	MVAC × 5, PR, progressed in 3 months, phase I piritrexim with PR	no	9	IT MTX/XRT	5
Raghavan, 1991 [13]	nr	cisplatin and radiation for localized disease relapsed in 16 months, MVAC × 2, IT therapy and MVAC × 4	yes	16	IT MTX-O	4
Eng, 1993 [14]	IV	MVAC × 5, pelvic XRT, PR	no	9	none	0
Eng, 1993 [14]	IV	cisplatin and MTX with CR, relapsed 2 years later	yes	24	IT MTX/XRT	3
Steg, 1993 [15]	nr	nr	nr	nr	none	1
Sugimori, 2005 [16]	IV	presented with meningitis, died of cardiac disease	na	0	none	3
Imamura, 1997 [17]	IV	presented with meningitis	na	0	none	3
Bloch, 1987 [18]	IV	surgery for presumed localized disease, brain metastasis 2 weeks after surgery, whole body XRT, meningitis 3 months later	na	3	–	5
Hasbini, 1997 [19]	T3N2	surgery, MVAC × 4 with CR, meningitis 1 month later	yes	7	–	1
Santarossa, 1997 [20]	T4N3	MVAC × 6, presented 8 months later with meningitis	yes	14	IT MTX/XRT	9
Loizaga, 1998 [21]	I	BCG vaccine, mitomycin B, then developed meningitis	na	15	CMV	0
Cozzarini, 1999 [22]	III	MVAC × 2 with no improvement, surgery, MVAC × 4, then developed meningitis	no	6	IT MTX	3
Cozzarini, 1999 [22]	III	MVAC × 3, PR, surgery, MVAC × 2	no	9	IT MTX	1
Vidal, 2000 [23]	IV	presented with carcinomatous meningitis, 4 doses IT MTX.	na	0	IT MTX	1
Vidal, 2000 [23]	IV	presented with panhypopituitarism, later diagnosed with meningitis	na	1	none	2
Bruna, 2001 [24]	IV	presented with meningitis, died of infection	na	0	IT MTX	2
Bodi, 2004 [25]	I	TURBT	na	9	none	1.5
Matsushita, 2004 [26]	III	MVAC × 3, surgery	yes	16	none	25
Kim, 2005 [27]	nr	surgery	na	108	none	1
Goodman, 2009 [28]	IV	taxol/carboplatin/gemcitabine/trastuzumab, surgery	yes	nr	IT MTX-O	1.5
Butchart, 2010 [29]	II	gemcitabine-cisplatin, XRT	yes	5	none	1
Bowen, 2010 [30]	nr	surgery, gemcitabine-cisplatin × 4	yes	31	XRT	nr
Uncu, 2010 [31]	IV	radiation, gemcitabine-cisplatin × 6, relapsed in lungs in 22 months, gemcitabine-cisplatin resumed, CNS disease 2 months later	yes	36	IT MTX/XRT	2
Zada, 2010 [32]	IV	nr	nr	nr	nr	nr
Tadepalli, 2010 [current report]	IV	MVAC × 7	yes	14	IT MTX/XRT	8

CR = Complete remission; Dx = diagnosis; IT = intrathecal; MTX = methotrexate; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; na = not applicable; nr = not reported; OS = overall survival; PR = partial remission; TURBT = transurethral resection of bladder tumor; Tx = treatment; XRT = radiation.

Fig. 1. T₁-weighted gadolinium-enhanced MRI showing abnormal leptomeningeal enhancement patterns of the infratentorial compartment and the supratentorial basal cisterns.

Fig. 2. T₁-weighted gadolinium-enhanced MRI showing left cerebellar encephalomalacia consistent with an old infarct of the left posterior inferior cerebellar artery.

Fig. 3. Cytopsin analysis of cerebrospinal fluid reveals numerous malignant cells with features consistent with metastatic high-grade TCC including large, atypical cells with increased nuclear size, prominent nucleoli, and irregular nuclear contours (**a–c**). Clusters of atypical cells with a papillary configuration are also identified (**d**). (HE $\times 400$).

References

- 1 Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277–300.
- 2 Anderson TS, Regine WF, Kryscio R, et al: Neurologic complications of bladder carcinoma: a review of 359 cases. *Cancer* 2003;97:2267–2272.
- 3 DeAngelis LM: Current diagnosis and treatment of leptomeningeal metastasis. *J Neurooncol* 1998;38:245.
- 4 Shapiro WR, Young DF, Mehta BM: Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. *N Engl J Med* 1975;293:161–166.
- 5 Glantz MJ, Van Horn A, Fisher R, et al: Route of intracerebrospinal fluid chemotherapy administration and efficacy of therapy in neoplastic meningitis. *Cancer* 2010;116:1947–1952.
- 6 Hitchins RN, Bell DR, Woods RL, et al: A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. *J Clin Oncol* 1987;5:1655.
- 7 Bishop JR Jr, Moul JW, Maldonado L, et al: Transitional cell carcinomatous meningitis after M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) chemotherapy. *Urology* 1990;36:373–377.
- 8 Matsushita M, Kawasaki Y, Okada Y: Carcinomatous meningitis from urothelial carcinoma of bladder and ureter: case report. *Nippon Hinyokika Gakkai Zasshi* 2004;95:817–819.
- 9 Boukriche Y, Bouccara D, Cyna-Gorse F, et al: Sudden bilateral hearing loss disclosing meningeal carcinomatosis. *Rev Neurol (Paris)* 2002;158:728–730.
- 10 Hust MH, Pfitzer P: Cerebrospinal fluid and metastasis of transitional cell carcinoma of the bladder. *Acta Cytol* 1980;26:217–223.
- 11 Mandell S, Wernz J, Morales P, et al: Carcinomatous meningitis from transitional cell carcinoma of bladder. *Urology* 1995;25:520–521.
- 12 Hussein AM, Savaraj N, Feun LG, et al: Carcinomatous meningitis from transitional cell carcinoma of the bladder: case report. *J Neurooncol* 1989;7:255–260.

- 13 Raghavan D, Chye RWM: Treatment of carcinomatous meningitis from transitional cell carcinoma of the bladder. *Br J Urology* 1991;67:438–440.
- 14 Eng C, Cunningham D, Quade BJ, et al: Meningeal carcinomatosis from transitional cell carcinoma of the bladder. *Cancer* 1993;72:553–557.
- 15 Steg R, Frank AR, Lefkowitz DM: Complex partial status epilepticus in a patient with dural metastases. *Neurology* 1993;43:2389–2392.
- 16 Sugimori K, Kobayashi K, Hayashi M, et al: Leptomeningeal carcinomatosis from urinary bladder adenocarcinoma: a clinicopathological case study. *Neuropathology* 2005;25:89–94.
- 17 Imamura M, Imamura S: Clinicopathologic study of leptomeningeal carcinomatosis involving the temporal bone. *Ann Otol Rhinol Laryngol* 1997;106:674–679.
- 18 Bloch JL, Nieh PT, Walzak MP: Brain metastases from transitional cell carcinoma. *J Urol* 1987;137:97–99.
- 19 Hasbini A, Himberlin C, Beguinot I, et al: La méningite carcinomateuse: une complication rare du cancer de la vessie. *Rev Méd Interne* 1997;18:402–406.
- 20 Santarossa S, Vaccher E, Balestreri L, et al: Solitary meningeal recurrence in a patient with transitional cell carcinoma of the bladder with locally bulky disease at presentation. *J Neurooncol* 1997;35:141–143.
- 21 Loizaga A, Arciniega J, Infante R, et al: Carcinomatosis meníngea en un tumor vesical. *Actas Urol Esp* 1999;23:873–875.
- 22 Cozzarini C, Reni M, Mangili F, et al: Meningeal carcinomatosis from transitional cell carcinoma of the bladder: report of two cases and review of the literature. *Cancer Invest* 1999;17:402–407.
- 23 Vidal OJ, De Paz L, Catalá J, et al: Carcinomatosis meníngea como primera manifestación del carcinoma de vejiga: a propósito de dos casos. *An Med Interna* 2000;17:425–428.
- 24 Bruna J, Rojas-Marcos I, Martínez-Yelamos S, et al: Meningeal carcinomatosis as the first manifestation of a transitional cell carcinoma of the bladder. *J Neurooncol* 2003;63:63–67.
- 25 Bodi I, Andrews TC, Howard RS, et al: Carcinomatous meningitis from primary signet ring cell carcinoma of bladder. *Histopathology* 2004;44:394–396.
- 26 Matsushita M, Kawasaki Y, Okada Y: Carcinomatous meningitis from urothelial carcinoma of bladder and ureter: case report. *Nippon Hinyokika Gakkai Zasshi* 2004;95:817–819.
- 27 Kim P, Ashton D, Pollard JD: Isolated hypoglycorrachia: leptomeningeal carcinomatosis causing subacute confusion. *J Clin Neurosci* 2005;12:841–843.
- 28 Goodman OB, Milowsky MI, Kaplan J, et al: Carcinomatous meningitis in a patient with Her2/neu expressing bladder cancer following trastuzumab and chemotherapy: a case report and review of the literature. *J Med Case Reports* 2009;3:9110.
- 29 Butchart C, Dahle-Smith A, Bissett D, et al: Isolated meningeal recurrence of transitional cell carcinoma of the bladder. *Case Rep Oncol* 2010;3:171–175.
- 30 Bowen CD, Von Burton G, Barga RC, et al: Carcinomatous meningitis secondary to transitional cell bladder cancer. *South Med J* 2010;103:809–812.
- 31 Uncu D, Arpacı F, Beyzadeoglu M, et al: Meningeal carcinomatosis: an extremely rare involvement of urinary bladder carcinoma. *Tumori* 2010;96:352–354.
- 32 Zada G, Chen T: A novel method for administering intrathecal chemotherapy in patients with leptomeningeal metastases and shunted hydrocephalus: case report. *Neurosurgery* 2010;67(3 Suppl Operative):onsE306–onsE307, discussion onsE307.
- 33 Dhote R, Beuzeboc P, Thiounn N, et al: High incidence of brain metastases in patients treated with an M-VAC regimen for advanced bladder cancer. *Eur Urol* 1998;33:392–395.
- 34 Sternberg C, Yagoda A, Scher H, et al: Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. *J Urol* 1985;133:403–407.
- 35 Loehrer PJ Sr, Einhorn LH, Elson PJ, et al: A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992;10:1066–1073.
- 36 von der Maase H, Hansen SW, Roberts JT, Dogliotti L, et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068.