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Clinical problems in advanced bladder cancer

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BLADDER CANCER LESSON

Bladder cancer is one of the most common malignancies in Western society and is associated with a history of cigarette smoking, previous bilharziasis, paraplegia, chronic renal tract infection, exposure to industrial toxins and dyes, and possibly low fluid intake [1]. Bladder cancer has quite a high incidence in the Balkan nations, due either to the above factors or additional exposure to plant carcinogens. Although the prognosis of superficial bladder cancer (stages Ta, T-i-s,T1), which represents about 80% of incident cases, is good, with 80% 5-year survival, the natural history and outcome of treatment for invasive and metastatic disease remain far less satisfactory, and more than half of the incident cases are dead within 5 years [2]. It is appropriate to focus this post-graduate lesson on strategies of treatment of this aggressive malignancy.

INVASIVE BLADDER CANCER

Clinical Case Study 1

A 65-year-old male with a history of ischemic heart disease but no recent angina pectoris presents with hematuria and right-sided pelvic discomfort. A CT scan of the abdomen and pelvis reveals a large right-sided bladder mass with lateral extension and minor right-sided hydronephrosis. Renal and liver function tests are normal. Cystoscopy and examination under anesthesia reveals an 8 cm right-sided sessile tumor adjacent to the right ureteric orifice, with an ill-defined, palpable right-sided mass. Biopsy reveals high grade invasive bladder cancer with muscle infiltration, clinical stage T3a.

Which of the following options of definitive treatment is not optimal therapy:

a. Neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy followed by cystectomy.

b. Radical cystectomy followed by consideration of adjuvant chemotherapy, depending on pathological staging information.

c. Gemcitabine plus cisplatin chemotherapy, six courses, followed by observation.

d. MVAC chemotherapy, six courses, followed by observation.

Invasive bladder tumors penetrate into (T2) and beyond (T3, T4) the muscularis propria. They are aggressive and tend to metastasize early. About 20% of patients have invasive cancer at presentation. The most important prognostic factor is the depth of tumor invasion (stage). Tumor grade is also an important factor. Low grade (I) tumors rarely progress, while most high grade (III) tumors progress and are often associated with a poor survival rate. Vascular or lymphatic invasion predicts an increased risk of

invasion and metastasis. The presence of T-i-s significantly increases the risk of invasion when identified in association with other foci of superficial disease. Other prognostic factors include the absence of expression of blood group antigens on the tumor cell surface, DNA ploidy, expression of epidermal growth factor receptor, and presence of mutations of the P53 suppressor gene. It has also been shown that expression of other genes, including P16, P21, and Rb, correlates with prognosis, predicated largely in terms of a functional cell regulatory complex that involves the function of these genes in concert with P53 [3,4]. More recently, studies have begun to address the use of molecular prognostication to predict the outcomes of specific treatments, such as chemotherapy, as reviewed elsewhere [5].

For patients with organ-confined invasive bladder cancer, cystectomy is viewed as the standard treatment in North America and Europe. Radical cystectomy involves the en bloc removal of the anterior pelvic organs, which includes the bladder, prostate, and seminal vesicles in men and the bladder, urethra, uterus, ovaries, and vaginal cuff in women [6-8]. Bilateral pelvic lymph node dissection is often performed. The ureters are reconnected to an intestinal conduit as a urinary diversion. In past conventional surgical practice, the ileal conduit drained into an external collecting bag attached to the abdominal wall. However, in most instances today, continent reservoirs such as the Koch pouch (ileal reservoir) and Indiana pouch (ileocecal segment) are applied, especially for the younger, healthier patient who desires to retain urinary continence. In most clinical practice settings, radical cystectomy results in 60-75% 5-year survival rate for stage T2 disease and 20-40% for T3 or T4 disease, but the overall survival for invasive bladder cancer is only around 50%. In some university and tertiary referral centers, 10-year survival of 85% has been reported for patients with high grade, invasive but organ-confined disease (Figure 1) [8].

For patients with localized invasive disease, who are not surgical candidates, radiation is another option. To date, there have not been any well-designed studies that have compared radiation to surgery among patients with similar characteristics. Toxicities of radiation may include cutaneous reaction, proctitis that is occasionally complicated by bleeding and obstruction, cystitis or bladder fibrosis, impotence, and development of secondary malignancies in the radiation field. Analogous to surgery, patient selection is very important – for example, the patient who has previously undergone multiple transurethral resections of the bladder, and who has a scarred and contracted bladder, is likely to suffer

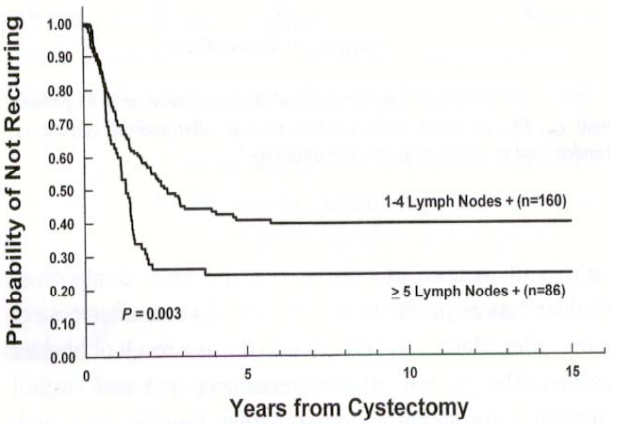

Figure 1. USC experience of radical cystectomy for lymph node positive bladder cancer.

[Reprinted from *Stein et al., J Clin Oncol 2001; 19: 666-675]*

a greater level of side effects than the patient treated for a first presentation. Of importance, Coppin et al [9] have shown that greater local control is achieved by the combination of cisplatin-chemotherapy plus radiotherapy, compared to radiotherapy alone. Although several phase II studies have shown quite impressive outcomes from chemoradiation with bladder preservation [10-12], comparable long-term survival (compared with cystectomy) has not been shown in any randomized trials.

Combined modality approaches, incorporating systemic chemotherapy with definitive local modalities, have been studied extensively in the past few years in the hope of sparing the bladder or to improve overall survival [2]. This has been based on the idea that intravenous chemotherapy may shrink the primary tumor and treat occult metastases at the same time.

The role of neoadjuvant (first-line) systemic chemotherapy, followed by definitive radiotherapy or cystectomy has been studied in detail, and many of the early randomized trials failed to improve survival from the combined modality approaches when compared to treatment by single modality radiation or cystectomy (Table 1). The largest randomized trial to date, conducted by the MRC-EORTC, revealed a 5-7% improvement in long-term survival from neoadjuvant cisplatin, methotrexate, vinblastine (CMV) chemotherapy followed by definitive local therapy, compared to local therapy alone [13]. This study was designed to identify a 10% difference in long-term survival and was accordingly reported as a negative trial. The Radiation Therapy Oncology Group, also testing the utility of neoadjuvant CMV chemotherapy followed by chemoradiation *versus* chemoradiation alone, showed identical 3-year survival, which may have been explained by

Table 1. Results of clinical trials of preemptive chemotherapy for invasive bladder cancer

Series	*Reference*	*Median survival Regimen*	*Actuarial long-term (mo)*	*survival*
Raghavan	[32]	C-RT/S	32	40% 5-yr 30% true 5-yr
Shipley	[14]	CMV/C-RT	36	48% 5 yr
Shipley	[14]	C-RT	36	49% 5 yr
Shearer	[33]	M-RT	23	39% 3-yr
Shearer	[33]	RT only	20	37% 3yr
Wallace	[34]	C	~24	39% 3-yr
Wallace	[34]	RT only	~22	39% 3-yr
MRC-EORTC	[13]	RT/S only	37.5	50% 3-yr
MRC-EORTC	[13]	CMV-RT/S	44	55% 3-yr
Intergroup	[15]	MVAC	72	?
Intergroup	[15]	Observation	45	?

RT: radiotherapy; C: cisplatin; M: methotrexate; A: doxorubicin; V: vinblastine; S: surgery (usually radical cystectomy)

the use of extensive transurethral tumor resection or systemic chemotherapy in both arms [14].

The North American Intergroup trial, in which neoadjuvant MVAC chemotherapy plus cystectomy was compared to cystectomy alone, showed a statistically significant survival benefit for the combined approach [15]. It required more than 10 years for this study to be completed, but an important proportion of the patients had been entered relatively recently at the time of reporting. Although the median survival values were 6 years and 3.8 years, respectively, and the 2-sided p value approached 0.05, and the curves appear to be separating with time. In addition, a recent meta-analysis of all known randomized trials has shown a similar increment of around 5-7% in long-term survival from the use of neo-adjuvant combination chemotherapy prior to radical cystectomy [16].

Adjuvant (postoperative) chemotherapy has also shown some promise in improving survival for patients with invasive bladder cancer. Randomized trials assessing the utility of combination chemotherapy (such as the combination of methotrexate, vinblastine, and cisplatin, with or without doxorubicin or epirubicin – the "CMV", "MVAC" or "MVEC" regimens), administered after radical cystectomy for patients with involved lymph nodes, have suggested improved *disease-free* survival may be achieved [17,18]. However, the published trials have been weakened by poor statistical design or execution, and thus the absolute proof of benefit is simply not available. Accordingly, the EORTC is attempting to address this issue in a well designed, randomized trial, in which standard local therapy is compared to standard local therapy plus the addition of adjuvant chemotherapy. In this trial, adjuvant chemotherapy has been defined as either the MVAC regimen (conventional or high dose) or a novel approach using gemcitabine plus cisplatin. This latter regimen has been tested for patients with metastatic disease, but has not yet been validated for use in the adjuvant or neoadjuvant setting. We have completed a preliminary assessment of our experience with 3-4 cycles of adjuvant gemcitabine plus cisplatin at USC. We have treated 25 patients with high grade, invasive bladder cancer demonstrated to be deeply invasive or with involved lymph nodes and have shown that the regimen is well tolerated and yields a 3-year disease free actuarial survival of 70% [19]. Of course, this approach will require further characterization, including long-term follow-up and validation in a randomized trial setting.

To date, there is little published experience with the use of systemic chemotherapy alone for patients with high grade, invasive, clinically non-metastatic bladder cancer. However, in many of the case experiences reported, small numbers of patients have declined to undergo local definitive treatment by radiotherapy or cystectomy after achieving complete clinical remission after chemotherapy alone. This is usually (but not always) associated with early local or systemic relapse. Accordingly, I do not view this as a safe option for most patients, and do not routinely offer it to patients in the clinical setting.

RECURRENT AND METASTATIC BLADDER CANCER

Clinical Case Study 2: Metastatic Bladder Cancer

A 70-year-old male presents with abdominal pain and cough 2 years after radical cystectomy for T4aN1M0 high grade bladder cancer. He has no weight loss, but has recently noted anorexia and general malaise. He has a previous history of maturity onset diabetes mellitus, and has been a heavy cigarette smoker for 30 years. Investigations show that he has normal renal and liver function tests, normal serum alkaline phosphatase, but a chest x-ray reveals three 2 cm pulmonary lesions in the right lung and a CT scan reveals two areas of matted para-aortic lymph node enlargement, each measuring approximately 4 cm in longest diameter. Fine needle biopsy of one of the pulmonary lesions reveals poorly differentiated transitional cell carcinoma, identical to the primary tumor.

Which of the following statements is true:

a. The patient's likely life expectancy with cisplatin-based chemotherapy is 6 months.

b. The combination of gemcitabine plus cisplatin will be expected to produce objective tumor response in 85% of cases.

c. The MVAC regimen has approximately equal likelihood of producing remission, but at the cost of more toxicity.

d. The paclitaxel-carboplatin regimen produces equal survival to the MVAC and gemcitabine-cisplatin regimens and should be regarded as standard of care.

For patients with recurrent and metastatic bladder cancer, chemotherapy is usually the treatment of choice. The first major step in the modern era of chemotherapy was the development of the combination of methotrexate, vinblastine, doxorubicin and cisplatin by Sternberg et al [20]. Several series demonstrated median survival of about one year and 5-year survival of around 20% when patients with advanced and metastatic bladder cancer were treated with this regimen (Table 2). An international consortium compared single agent cisplatin to the MVAC regimen for advanced and metastatic disease [21]. The MVAC regimen produced a response rate of 39% with median survival of 12.5 months, which was statistically superior to the response rate of 12% and median survival of 8 months seen in the group that received cisplatin alone. The survival benefit persisted after a minimum follow-up of 6 years, although the vast majority of patients in both randomization arms had died by that time [22]. From this analysis, it was clear that the MVAC regimen was not sufficiently active to remain the permanent standard for advanced bladder cancer, opening the way for investigation of novel agents and approaches.

For example, paclitaxel [23], gemcitabine [24], ifosfamide [25], docetaxel [26] and pemetrexed [27] have been shown to produce response rates of approximately 25% when used as single agents. Carboplatin, mitoxantrone and trimetrexate have not found a routine management, and other agents, such as oxaliplatin and irinotecan, are currently undergoing evaluation. The use of some of these agents in combination with other standard or investigational drugs has resulted in response rates between 50% to 80%, with less toxicity than the CMV or MVAC regimens [28,29].

A phase III trial comparing the use of gemcitabine and cisplatin *versus* the standard MVAC regimen has suggested that there is no great difference in survival between the gemcitabine-cisplatin and MVAC regimens, but that the gemcitabine-cisplatin combination is associated with reduced toxicity [30]. It should be noted that this was not designed to assess equivalence of survival, and thus is under-powered to identify a small difference. Nevertheless, as a consequence of this study, the International Intergroup, comprising the EORTC, SWOG, NCI Canada, RTOG and several European groups, is comparing gemcitabine-cisplatin *versus* gemcitabine-cisplatin-paclitaxel for patients with previously untreated metastatic transitional cell carcinoma. These investigators have indicated that it is time to leave the MVAC regimen behind as the standard of care, unless late follow-up of the von der Maase trial [30] demonstrates an unexpected separation of survival curves. However, it is very important to emphasize that novelty of treatment does not necessarily equate with improved outcome. Two major trials to date have shown that the combination of paclitaxel and carboplatin, designed in an attempt to improve survival and reduce toxicity, has produced median survival values of only around 9 months, a significant reduction compared to what would be expected from the MVAC or gemcitabine-cisplatin regimens. The Eastern Cooperative Oncology Group attempted to test this issue formally in a randomized trial, but the study closed prematurely before sufficient cases had been accrued to

Table 2. International experience with the MVAC regimen

Institution	*References*	*No. of cases (%)*	*Complete remission (months)*	*Median survival*
Memorial Sloan Kettering*	[20]	121	26	13
MD Anderson Hospital	[35]	55	35	11
French Federation	[36]	67	19	13
International Intergroup	[21]	120	13	12
Memorial Sloan Kettering#	[37]	17	12	18

*Series published in 1989; # series published in 1997; note result of apparent stage migration

resolve this issue with certainty; it appears that many participating investigators believed the paclitaxel-carboplatin regimen to be inferior and discontinued support of the trial.

More recent approaches, such as the use of the ifosfamide-paclitaxel-cisplatin (ITP) combination, developed at the Memorial Sloan Kettering Cancer Center, and the combination of conventional cytotoxics with various growth factor inhibitors (such as those that interact with the epidermal growth factor receptor), while interesting and provocative, remain to be proven as major steps forward. The results from phase I-II testing are highly variable, and the encouraging early results may either represent real advances or equally could be due to stage migration or case selection, and thus will require validation in randomized clinical trials.

Finally, since the introduction of cisplatin-containing combination chemotherapy regimens, it has become clear that relatively predictable prognostic determinants can be identified for patients with metastatic bladder cancer [21,31]. Patients who are more likely to achieve objective remission and survival beyond 12-18 months include those who present with only nodal or pulmonary deposits, an ECOG performance status of 0, and normal liver function tests and serum alkaline phosphatase. Those with less favorable prognosis include patients who present with weight loss, impaired performance status, abnormal liver function tests and serum alkaline phosphatase, liver and bone metastases, and non-transitional cell cancer histology. It is thus clear that some patients may really benefit from active treatment of metastatic bladder cancer, and recent developments have provided less toxic alternatives for patients who are often elderly and have significant co-morbid illnesses.

SUMMARY AND ANSWERS TO QUESTIONS

This lesson has reviewed changes in approaches to the management of advanced bladder cancer that have occurred in the past decade. It is clear that cisplatin-based chemotherapy regimens have altered the natural history of invasive and metastatic bladder cancer, and that specific prognostic determinants have been identified which help to guide management. Novel compounds, such as the taxanes, gemcitabine and ifosfamide, have useful activity against bladder cancer and are being incorporated into clinical management in clinical trials and routine clinical settings.

For invasive bladder cancer, the use of systemic chemotherapy without definitive local treatment is not appropriate in view of the high relapse rate. Neoadjuvant MVAC chemotherapy followed by radical cystectomy constitutes one of the new standards of care, although other options that may also be appropriate include chemoradiation with attempted bladder preservation or radical cystectomy followed by adjuvant chemotherapy in certain circumstances.

Patients with metastatic bladder cancer have a 50-80% chance of tumor shrinkage when treated with cisplatin-containing regimens. Although the MVAC regimen has been a standard for many years, newer regimens, such as gemcitabine-cisplatin (with or without a taxane) are showing promise. Patients most likely to achieve sustained remission are those who present with an excellent performance status, no constitutional features, and lymph node or pulmonary metastases (without liver and/or bone involvement).

The correct answers are 1c, 1d and 2c.

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