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Bladder Cancer

Adjuvant and Neoadjuvant Chemotherapy in Muscle Invasive Bladder Cancer: Literature Review

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Abstract

Radical cystectomy is the standard treatment for patients with clinically localized muscle invasive bladder cancer, providing a 5-year survival rate of approximately 50%. Failure to cure is often due to the presence of occult metastases beyond the margins of local therapy, indicating a need for eradication of micrometastatic disease with systemic treatment, in order to improve survival. Combined chemotherapy regimens, such as methotrexate-vinblastine-cisplatin (CMV), methotrexate-vinblastine-cisplatin-doxorubicin (M-VAC) and gemcitabine-cisplatin (GC) have already demonstrated their effectiveness in patients with advanced or metastatic disease and have been considered as appropriate regimens in the peri-operative setting. Large randomized studies with a prolonged follow-up have been able to confirm a modest survival benefit with neoadjuvant therapy. A recent meta-analysis, including all previous reported randomized trials, concluded that neoadjuvant chemotherapy administration provides a significant survival benefit and can be administered without adverse outcomes resulting from delayed local therapy. Adjuvant chemotherapy trials, although promising, have failed to show statistically improved survival, mostly due to small sample sizes and absent or inconclusive data on overall survival. A multi-center randomized-controlled trial is currently ongoing, in order to elucidate the role of post-operative chemotherapy administration.

Keywords: Bladder cancer; Transitional cell carcinoma; Muscle invasive; Neoadjuvant therapy; Adjuvant therapy

1. Introduction

Bladder cancer is the fourth most commonly occurring cancer in men and the eighth in women, in United States and UK [1,2]. It is most common in the elderly with a peak incidence in the seventh decade. Transitional cell carcinoma (TIC) represents more than 90% of all bladder cancers, while squamous cell carcinoma and adenocarcinoma account for 5% and 2%, respectively [3]. About 20% of incident cases concern locally advanced, muscle invasive disease, although an additional 10–25% will occur in association with relapsed superficial bladder cancer [3,4].

Muscle-invasive bladder cancer may be treated with curative intent by either radical cystectomy or external beam radiotherapy. Despite local therapy with cystectomy and/or radical radiotherapy, the 5-year survival rate of patients with muscle invasive transitional cell carcinoma, is approximately 50% [5,6]. Recurrence is mostly related to tumor stage, grade and nodal status at the time of cystectomy. Nodal involvement is associated with a 5-year survival of 20–40%, while direct invasion into adjacent viscera reduces the rate to less than 10% [7]. Most patients relapse, within 2 years, in distant sites, with only one third of patients relapsing in the pelvis alone [8]. The presence of lymphatic or vascular invasion is associated with an increased risk of invasion and metastasis [9]. Other adverse prognostic factors include the absence of expression of blood group antigens on the tumor cell surface, DNA aneu-

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ploidy, expression of epidermal growth factor receptor (EGFR), p53 mutations, absence of retinoblastoma (Rb) protein expression and absence of p21 expression [9].

Failure to cure is often due to the presence of occult metastases beyond the margins of local therapy, indicating a need for eradication of micrometastatic disease with systemic treatment in the peri-operative setting, as combination chemotherapy for metastatic disease has already proven its effectiveness.

Although several single agents have been successfully used in patients with advanced or metastatic disease, randomized clinical trials have favored combined chemotherapy regimens, such as methotrexate-vinblastine-cisplatin (CMV) and methotrexate-vinblastine-cisplatin plus doxorubicin (M-VAC) [10,11]. Recently, the combination of gemcitabine and cisplatin (GC) has demonstrated similar objective response and survival rates with less toxicity than M-VAC, in a large randomized trial and is also considered as a current therapeutic option [12].

This article will review the delivery of neoadjuvant and adjuvant systemic chemotherapy aimed at improving the outcome of muscle invasive TCC.

2. Neoadjuvant chemotherapy

Systemic chemotherapy combined with local modalities, has been studied extensively in the past two decades, in order to improve survival, or to preserve the bladder. The theoretical advantages of neo-adjuvant chemotherapy are the immediate treatment of micrometastatic disease, the ability to assess tumor response in vivo (this may permit the continuation of treatment to maximal response or discontinuation of ineffective therapy), more effective delivery of chemotherapy before surgical disturbance, lower toxicity due to better performance status and the possibility of bladder preservation in selected patients, as a result of tumor downstaging. The main disadvantages are the time delay to definitive local therapy and the possibility of exposing some patients to unnecessary cytotoxic therapy based on inaccurate clinical staging. Trials addressing this question must assess the efficacy of treatment in terms of long – term overall survival. Until recently there was no clear evidence for the use of neoadjuvant chemotherapy for potentially curable bladder cancer outwith the context of a clinical trial. Although several randomized trials with good patient accrual had been published, none had statistical power to demonstrate a statistically significant benefit in its own right.

Phase I and II trials of single agent chemotherapy have been promising, providing encouraging data on tumor downstaging and survival [13,14]. Randomized trials, though, failed to support statistical survival benefit from neoadjuvant cisplatin-based chemotherapy prior to radical cystectomy or radiotherapy, despite the prolongation of disease free interval [15–17]. These early reports were criticized because of the single agent chemotherapy regimen used, which is not currently accepted for advanced bladder cancer, and for insufficient number of patients enrolled.

The largest published single trial of neoadjuvant chemotherapy in bladder cancer, the MRC BA06/EORTC 30894 study [18], randomized 976 patients with locally advanced TCC (T2 G3, T3 or T4a) to receive either radical local therapy alone (cystectomy or full dose external beam radiotherapy), or three cycles of neoadjuvant CMV prior to local treatment, aiming to detect 10% difference in overall survival. After a median follow-up of 4 years, results showed an improved 3-year survival from 50.5% to 55.5% ($p = 0.075$) and an increased overall survival from 37.5 to 44 months, for the arm of neoadjuvant CMV. The trial though, failed to achieve the predefined level of 10% improvement in overall survival. However, updated results with a prolonged median follow-up of 7 years, finally revealed an overall survival benefit with a hazard ratio (HR) of 0.85 (95% confidence intervals 0.72–1.00) in favor of the neoadjuvant arm making this trial statistically significant in its own right ($p = 0.05$) [19].

Although CMV has never been compared to M-VAC, most clinicians support that M-VAC regimen appears to be superior in terms of efficacy. It might therefore be suggested that this trial utilized inadequate chemotherapy. Against this, the pathological complete response rate of 33% in 206 assessable patients is comparable to published results with the four-drug regimens [20,21]. The SWOG 8710 trial enrolled 317 patients with T2-T4a disease [22]. Patients were randomized either to undergo radical cystectomy alone or to receive three cycles of M-VAC followed by radical cystectomy. After a median follow-up of 8.4 years, median overall survival was 77 months for the combination therapy group compared to 46 months for those treated by cystectomy alone ($p = 0.05$ by one-sided t-test, $p = 0.06$ by two-sided stratified log-rank test). The hazard ratio for patients in the experimental arm was 0.74 (95% confidence intervals 0.55–0.99). In addition, pathological complete response rates were observed in 38% of patients having received neoadjuvant M-VAC chemotherapy, a result similar to that seen in the MRC/EORTC trial, versus 15% of patients in the

cystectomy arm ($p < 0.001$). This trial has also demonstrated that most of the survival benefit was identified in patients who achieved surgical complete remission after neoadjuvant treatment.

Another study, similar to the SWOG one, is the Italian GUONE trial, which enrolled 206 patients [23]. Patients were randomized to either four cycles of M-VAC before cystectomy, or cystectomy alone. The sample size was calculated to detect 15% benefit in 3-year survival. The trial was closed early because failed to achieve any difference in survival. This is a small trial in which no difference in survival was observed (The 3-year survival was 62% for the M-VAC arm, versus 68% for the cystectomy alone arm). Another Italian trial substituted doxorubicin with epirubicin and studied the neoadjuvant M-VEC regimen plus cystectomy versus cystectomy alone [24]. Again, no difference in survival was observed.

In the first Nordic cystectomy trial (NCT1), 325 patients were enrolled [25]. The experimental arm included two cycles of cisplatin-doxorubicin, while all patients both in the experimental and in the control arm were planned to receive 40 Gy irradiation plus cystectomy. The trial reported a small difference in a subgroup analysis of patients with T3-T4 disease. In the second Nordic cystectomy trial (NCT2), 317 patients were randomized to receive either three cycles of cisplatin-methotrexate and leucovorin as rescue, prior to cystectomy, or cystectomy alone [26]. Despite the lack of statistical power to detect a difference in overall survival when presented separately, the combined analysis of the two Nordic studies, showed a hazard ratio of 80% (95% confidence intervals 0.64–0.99, $p = 0.049$) for overall survival in favor of neoadjuvant treatment [27]. The 5-year survival was 56% in the experimental group versus 48% in the control group.

Several other published randomized trials of neoadjuvant chemotherapy [28,29], have failed to show survival difference, mostly because in order to detect a 10% survival benefit of investigational chemotherapy arm over standard therapy, a randomized trial requires approximately 1000 patients [30] (Tables 1 and 2).

The first meta-analysis, included 2688 patients from 9 randomized published plus one unpublished trial [31]. The SWOG trial, although eligible, could not provide individual patient data in this meta-analysis. In five trials the planned local treatment was radical cystectomy, two used radical radiotherapy and one used preoperative radiotherapy and cystectomy. Two trials used a combination of one or more of these local treatments. All the trials used platinum-based chemotherapy, nine of which used cisplatin, either as a single agent, or in combination. The combined HR for trials using combination chemotherapy was 0.87 (95% confidence intervals 0.78–0.97, $p = 0.016$), equivalent to a 13% relative reduction in the risk of death, and an absolute benefit of 5% at 5 years, improving survival from 45% to 50%. The HR for trials with single agent chemotherapy is in favor of local treatment alone, although the result is not statistically significant ($p = 0.264$).

A more recent meta-analysis, including the SWOG trial, concluded in similar results. The combined HR for the total of trials was 0.90 (95% confidence intervals 0.82–0.99), in favor of the chemotherapy arm [32]. Although the overall benefit is modest, and the conclusions of trials which necessitate extensive patient selection may not be directly relevant to all patients,

Table 1
Randomized trials of neoadjuvant chemotherapy for TCC

Trial	*n*	Med F/U (m)	CT arm	Standard arm	Overall survival	
					Standard vs. neoadjuvant	HR (95% CI)
CUETO [15]	122	78.2	CDDP	C	6.5-y 37.3% vs. 35.5% NS	0.97 (0.54–1.77)
WMURG [16]	159	16	CDDP	R/T	3-y 40% vs. 30% NS	1.11 (0.67–1.81)
ABCSG [17]	96	16	CDDP	R/T	3-y 41% vs. 38% NS	1.33 (0.68–2.62)
EORTC [18]	976	48	CMV	C or R/T	Median 37.5 vs. 44 mos 3-y 50% vs. 55.5%	0.85 (0.71–1.02) $p = 0.075$
EORTC [19]	976	78	CMV	C or R/T		0.85 (0.72–1.00) $p = 0.05$
SWOG 8710 [22]	317	85.2	M-VAC	C	5-y 42% vs. 57% Median 43.2 vs. 74.7 mos	0.78, $p = 0.044$
GUONE [23]	206	NR	M-VAC	C	5-y 54% vs. 55% NS	NR
GISTV [24]	171	37	M-VEC	C	NS	
Nordic I [25]	325	60	CDDP-doxorubicin	R/T + C	5-y 51% vs. 58% NS	NR
Nordic II [26]	316	40.8	CDDP-MTX	C	NS	NR
DAVECA 8901 [28]	33	91.8	CDDP-MTX	C	5-y 46% vs. 64% NS	NR
DAVECA 8902 [28]	120	77	CDDP-MTX	R/T	5-y 24% vs. 19% NS	NR
RTOG 8903 [29]	126	60	CMV	R/T + CDDP	5-y 49% vs. 48% NS	NR

Table 2
Randomized trials of adjuvant chemotherapy for TCC

Trial	*n*	CT arm	Standard arm	Overall survival
Skinner et al. [43]	91	CAP	C	Benefit, Wilcoxon statistics
Stockle et al. [44]	49	M-VAC/M-VEC	C	Benefit, no treatment at relapse
Freiha et al. [46]	50	CMV	C	No benefit (only benefit in DFS)
Studer et al. [47]	77	Cisplatin	C	No benefit/single agent CT
Bono et al. [48]	83	Cisplatin/MTX	C	No benefit (for N0M0)
Otto et al. [51]	108	M-VEC	C	No benefit

this update analysis provides the first clear view of a significant benefit for chemotherapy in this setting and may represent a new standard of care for those patients with muscle – invasive TCC who are able to tolerate relatively aggressive chemotherapy. Future trials must now address the optimum chemotherapy regimen, determine whether the addition of new agents will add to the benefit of neoadjuvant chemotherapy and whether the benefit can also be transferred to patients who are unable to tolerate cisplatin – based combination chemotherapy.

Large randomized studies with a prolonged follow-up have been able to confirm a modest survival benefit with neoadjuvant therapy. Moreover, the response to chemotherapy may be the most important predictor of survival. Data collected from 147 patients with muscle invasive TCC [33], showed that the 5-year survival was 75% in patients achieving tumor downstaging to pT0 or superficial disease with neoadjuvant therapy, versus only 20% in patients with residual muscle invasive disease (>pT2).

3. Neoadjuvant chemotherapy and bladder preservation

Although radical cystectomy remains the standard treatment option for muscle invasive bladder cancer and since orthotopic bladder substitution has become available, the chance of organ preservation should not be dismissed. The advantages of bladder preservation include less surgery, no need for urinary diversion and normal sexual life. Several phase II trials have supported the combined modality therapy with TUR-B, chemotherapy and irradiation, especially for patients with T3b and T4 disease [34,35].

The combination of neoadjuvant chemotherapy and radiotherapy is capable of producing 5-year survival rates of 42–63%, with organ preservation in approximately 40% of patients [29]. Prognostic factors for local curability are a small tumor, absence of hydronephrosis, papillary histology, a visible complete TUR-B and a complete response to induction chemotherapy.

The evaluation of neo-adjuvant chemotherapy and bladder preservation was investigated in a series of 87 patients with T2-T4a TCC, who were treated with three cycles of M-VAC chemotherapy, followed by TUR-B ($n = 42$), or partial cystectomy ($n = 13$), or radical cystectomy ($n = 32$) [36]. In the first group, the 42 patients have attained a clinical complete response or a downstaging to superficial disease and they underwent a TUR-B. The 5-year survival for this group was 69%, while 57% have maintained an intact bladder. In another trial, with 111 surgical candidates who received neoadjuvant M-VAC, 10 year-survival of patients who underwent TUR-B or partial cystectomy is 74%, with 58% bearing an intact bladder [37].

Bladder preservation in patients based on the response to neoadjuvant chemotherapy is a feasible approach which must be confirmed in prospective randomized trials. The real value of bladder preservation need to be estimated in large randomized studies, as the goal of treatment remains the cure of patient with respect to the quality of life.

4. Adjuvant chemotherapy

For high risk patients with pT3-pT4 and/or pN+ M0 disease, 5 year survival after radical cystectomy is only 25–35% [3,38–40]. Post-operative chemotherapy has led to increased survival in patients with several malignancies. As a result, adjuvant chemotherapy has been used after cystectomy in high risk patients in an effort to delay recurrence and prolong survival.

The principal advantage of adjuvant setting is the immediate, without any delay performance of the definitive local treatment, especially for patients who do not respond to chemotherapy. Pathological evaluation of the cystectomy specimen offers the chance of accurate staging and detection of molecular prognostic markers. Moreover, the decreased morbidity of cystectomy because of orthotopic bladder substitution, is in favor of the immediate cystectomy and adjuvant chemotherapy.

Disadvantages of adjuvant chemotherapy include the delay of administering systemic chemotherapy, the lack of in vivo response assessment and the difficulty to administer chemotherapy after cystectomy.

A number of randomized trials have assessed the role of adjuvant chemotherapy following either radiotherapy or cystectomy against an observation controlled arm. The first comparative, nonrandomized trial was reported by Logothetis et al. [41], who divided patients into three groups, i.e. low risk controls, high risk controls (did not receive adjuvant chemotherapy because of refusal or medical reasons) and high risk patients treated with adjuvant chemotherapy. Follow-up of high-risk patients treated with five cycles of CISCA (cisplatin, cyclophosphamide, adriamycin) regimen after radical cystectomy demonstrated a significantly improved 2-year DFS (79% vs. 37%, $p = 0.0012$). These high-risk patients who were defined by vascular invasion, extravesical involvement or direct invasion into adjacent prostate or vagina (pT3-pT4, pN+), had a similar DFS to that of untreated low risk patients (70% vs. 76%, $p = 0.33$).

A single-center randomized trial of five cycles of M-VAC chemotherapy, given either as two neoadjuvant and three post-operative cycles, or five cycles of adjuvant therapy has recently been published [42]. 140 patients with T3b or T4a were enrolled. Significant difference in overall survival was not observed between the two arms. A disadvantage of this trial was that no observation-only arm was included.

A small number of randomized trials have evaluated the role of adjuvant chemotherapy following either cystectomy, or radiotherapy, against an observation-only control arm.

The first randomized trial that showed at 5 years a benefit in DFS (51% vs. 34%) and survival (44% vs. 39%, n.s.) for the arm of adjuvant chemotherapy, was reported by Skinner et al. [43]. Ninety-one patients with pT3-pT4 or N+ were randomized to receive either the combination of cyclophosphamide, doxorubicin and cisplatin (CAP) after cystectomy, or cystectomy alone. The median survival for patients in the experimental group was 4.3 years versus 2.4 years in the control group. The trial marked as important prognostic factors the age, gender and lymph-node status, with the latter as the most important variable. However, after 7 years the DFS curves of the two patient groups crossed. This was somewhat unexpected, as cystectomy patients rarely relapse beyond 3 years after treatment. It has been speculated that the chemotherapy used in this study was too weak to cure the disease, but was strong enough to prolong DFS. The trial was criticized due to the small number of cases, the deviation from the predefined chemotherapy regimen and its statistical methodology (while chemotherapy appeared to prolong the median time to recurrence by 14 months, there was no residual advantage at 2 years).

In another trial of adjuvant therapy, 49 patients were finally randomized either to observation-only after cystectomy, or to adjuvant chemotherapy with 3 cycles of M-VAC or M-VEC regimen in patients with locally advanced bladder cancer (pT3-pT4, pN+) [44]. This trial was designed to demonstrate a 35% improvement of DFS from 25% to 35%. Twenty-six patients were randomized to the adjuvant treatment arm and 23 to cystectomy alone. Those patients who underwent cystectomy only had a very high-rate of progression (12 out of 13 node-positive patients), while only 3 out of 11 node-positive patients who received post-cystectomy chemotherapy were free of disease. In this study, patients randomized to observation after cystectomy, were not permitted to receive chemotherapy at any time (neither adjuvant, nor salvage). The study was prematurely closed because of a dramatic difference in progression free survival between the two arms (the 5-year progression free survival was 59% for the adjuvant group, versus 13% for the observation group). The authors later added non-randomized cases in order to increase the total number of cases, but this attempt reflected a serious error of statistical methodology and potential case selection bias. A later comparative analysis of 166 patients, including the initially treated 49 patients, found a significant difference ($p = 0.0002$) in DFS for 89 patients treated with 3 cycles of adjuvant MVAC or MVEC, as compared to 86 patients who had only cystectomy. [45]. When stratifying patients, by the extend of lymph node involvement, it was found that adjuvant chemotherapy achieved the highest benefit in patients with pN+ disease. However, strong methodological problems of these studies may consider the conclusion as doubtful.

Another prospective, randomized trial which was reported by Freiha et al. investigated the benefit of CMV after radical cystectomy in 50 patients with pT3b-T4, N0/+, M0 [46]. Patients were treated with 4 cycles of CMV and those who did not have adjuvant therapy, received salvage chemotherapy after progression, thus decreasing the tumor-specific survival difference between the two arms. The study showed a statistically significant DFS benefit for the experimental arm (median 37 versus 12 months, $p = 0.01$), and concerning the overall survival benefit, a trend in favor of adjuvant therapy (median 63 versus 36 months, $p = 0.32$). The lack of significant difference in overall survival was attributed to the unexpected ability to salvage patients with relapse on the observation arm.

This trial was also terminated prematurely before having included the full number of intended patients, due to an obvious progression-free survival, leaving the most important endpoint of an adjuvant trial (overall survival) unresolved.

Two studies out of 5 found no statistical difference between adjuvant treatment and cystectomy alone, but criticism addresses the inclusion of patients with organ-confined disease (pT2, pN0) [44,45]. Studer et al. [47] treated 37 of 77 patients with single-agent cisplatin postcystectomy and no difference between the two groups was detected. More than 50% of patients had only organ-confined disease and patients who were diagnosed as node-positive disease, by imaging techniques, were excluded from the study. Bono et al. [48] randomized only pN0 patients to 4 cycles of adjuvant cisplatin and methotrexate post-cystectomy vs. cystectomy alone. They found a 10% (n.s.) advantage in DFS in favor of the adjuvant treatment after 18-month follow-up.

Although these trials appear to show a benefit in favor of adjuvant chemotherapy, they do not provide sufficient evidence to support its routine use in clinical practice for patients with locally advanced, particularly lymph-node-positive disease, due to small sample sizes and absent or inconclusive data on overall survival.

Therefore, EORTC and collaborating groups have developed a multi-center randomized-controlled trial (EORTC 30994) for pT3-pT4, and/or N+, M0 patients. Patients are randomized to either immediate chemotherapy following cystectomy, or delayed chemotherapy following relapse. M-VAC, dose-intense M-VAC with G-CSF support, or gemcitabine-cisplatin (GC) are considered acceptable regimens, providing that the same regimen is used for immediate and delayed chemotherapy within each institution. 1344 patients are required to detect the designed trial accrual, which is 20% relative increase in 5-year overall survival, at 80% power, using a two-sided log-rank test. A current adjuvant trial by the German Genito-Urinary Group was designed to demonstrate improved tolerability of 3 cycles of adjuvant cisplatin and methotrexate (CM) without loss of efficacy, when compared with 3 cycles of MVEC. The trial was recently closed (320 patients) including 120 patients with tumor-positive lymph-node disease. Preliminary results showed that the median survival was 25 months in patients receiving the intended-dose of either MVEC or CM, in contrast to 11 months after receiving either incomplete adjuvant chemotherapy or none at all. This was also observed in patients with node-positive disease [49]. It should be interesting to wait for the final results, concerning the two clear arms of the study. Another German study, that randomized 138 patients to receive MVEC as adjuvant chemotherapy or cystectomy alone was closed and the results are awaited. Another adjuvant study was conducted by the University of Chicago, in which 33 high-risk patients (pT3-pT4a, pN+) were treated with cisplatin and gemcitabine. The outcome data of this study were limited, since only 8 patients included in the study after 15 months [50]. Other current adjuvant phase III trials which include modern antineoplastic agents for locally advanced bladder cancer were performed by the Spanish Oncology Genito-Urinary Group (SOGUG) comparing 4 cycles of paclitaxel, cisplatin and gemcitabine post-cystectomy vs. cystectomy only and by the ECOG (Eastern Cooperative Oncology Group) that randomized 490 patients to 4 cycles of carboplatin and paclitaxel post-cystectomy vs. cystectomy only.

5. Novel cytotoxic agents

The recent introduction of gemcitabine and the taxanes as treatment options for bladder cancer is a promising development. Gemcitabine, a nucleoside antimetabolite that inhibits DNA synthesis, has shown single agent overall response (OR) rate of about 25%, with a complete response rate of 9% [52–55]. Disposing a synergistic action with cisplatin, the combination GC has already demonstrated similar objective response and survival rates with less toxicity than M-VAC, in patients with metastatic bladder cancer [12]. As it is considered an option for first line treatment, clinical randomized trials may use this combination in adjuvant and neoadjuvant settings. The currently ongoing EORTC trial (EORTC 30994), testing the benefit of adjuvant chemotherapy, has already included this combination as acceptable along with M-VAC (intensified, or standard doses).

The taxanes, as single agents, have yielded overall response rates of 7% to 56%, depending on whether the patients have received prior chemotherapy for metastatic disease, while in combination with cisplatin the OR rates are 61% for paclitaxel and 54% for docetaxel [55]. They have also been assessed in neoadjuvant regimens in combination with cisplatin, in phase II clinical trials. Three cycles of paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2) were administered before radiotherapy or radical surgery in 42 patients with locally advanced bladder cancer (T3a-T4a) [56]. Thirty-two out of 42 patients (76%) achieved a major response, while 20 patients (47.6%) remain free of disease at a median follow-up of three years. In another

phase II trial, 50 patients were treated with docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) for 3 cycles prior to cystectomy [57]. Chemotherapy was well tolerated. The 5-year survival and progression free survival were 51.92% and 52.47% respectively.

6. Conclusions

Muscle invasive bladder cancer is a chemosensitive disease and should be dealt with in a multimodality approach. Cisplatin-based combination chemotherapy has recently demonstrated to improve overall survival prior to definitive local treatment and may become the standard of care for patients who have undergone radical cystectomy. Results from the EORTC 30994 trial will probably clarify any survival benefit from post-operative chemotherapy.

Newer drugs such as gemcitabine and the taxanes, combined with cisplatin, may represent effective and less toxic regimens. The use of molecular markers, although investigational at present, may permit the detection of selected populations that could benefit from peri-operative therapy in the future.

References

[1] Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer Statistics, 2001. CA Cancer J Clin 2001;51:15–36.

[2] Cancer Research UK. CancerStats: Incidence, UK; 1998.

[3] Sternberg CN, Calabro P. Chemotherapy and management of bladder tumors. BJU Int 2000;85:599–610.

[4] Raghavan D. Chemotherapy and cystectomy for invasive transitional cell carcinoma of bladder. Urol Oncol 2003;21:468–74.

[5] Raghavan D, Shipley WU, Hall RR, Richie JP. Biology and management of invasive bladder cancer. In: Raghavan D, Scher HI, Leibel SA, Lange PH, editors. Principles and Practise of Genitourinary Oncology. Philadelphia: Lippincott-Ravel; 1997. p. 281–98.

[6] Ghonheim MA, El-Mekresh MM, Mokhtar AA, Gomha MA, El-Baz MA, El-Attar IA. A predictive model of survival after radical cystectomy for carcinoma of the bladder. BJU Int 2000;85:811–6.

[7] Vieweg J, Whitmore Wf Jr, Herr HW. The role of pelvic lymphadenectomy and radical cystectomy for lymph node positive bladder cancer. Cancer 1994;74:3020–8.

[8] Sternberg CN. The treatment of advanced bladder cancer. Ann Oncol 1995;6:113–26.

[9] Raghavan D, Quinn D, Skinner DG, Stein JP. Surgery and adjunctive chemotherapy for invasive bladder cancer. Surg Oncol 2002;11:55–63.

[10] Loehrer Sr PJ, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, 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;10:1066–73.

[11] Harker WG, Meyers FJ, Freiha FS, Palmer JM, Shortliffe LD, Hannigan JF, et al. Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. J Clin Oncol 1985;3:1463–70.

[12] von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, 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;18:3068–77.

[13] Scher HI. Should single agents be standard therapy for urothelial tract tumors? J Clin Oncol 1989;17:694–7.

[14] Raghavan D. Premptive (neo-adjuvant) intravenous chemotherapy for invasive bladder cancer. Br J Urol 1988;61:1–8.

[15] Martinez-Pineiro JA, Martin MG, Arocena F, Flores N, Roncero CR, Portillo JA, et al. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. J Urol 1995;153:964–73.

[16] Wallace MA, Raghavan D, Kelly KA, Sandeman TF, Conn IG, Teriana N, et al. Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. Br J Urol 1991; 67:608–15.

[17] Ghersi D, Stewart LA, Parmar MKB. Coppin C, Martinez-Pineiro J, Raghavan D, et al., Advanced Bladder Cancer Overview Collaboration. Does neoadjuvant cisplatin-based chemotherapy improve the survival of patients with locally advanced bladder cancer: a meta-analysis of individual patient data from randomized clinical trials. Br J Urol 1995;75:206–13.

[18] Medical Research Council, European Organization for Research and Treatment of Cancer, Australian Bladder Cancer Study Group et al. Neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. The Lancet 1999; 354:533–40.

[19] Hall RR. Updated results of a randomised controlled trial of neoadjuvant cisplatin (C), methotrexate (M) and vinblastine (V) chemotherapy for muscle-invasive bladder cancer. Proc Am Soc Clin Oncol 2002;21:178A abstract 710.

[20] Scher HI, Yagoda A, Herr HW, Sternberg CN, Bosl G, Morse MJ, et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. J Urol 1988;139:470–4.

[21] Scher HI. Systemic chemotherapy in regionally advanced bladder cancer. Theoretical considerations and results. Urol Clin North Am 1992;19:747–59.

[22] Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.

[23] Bassi P, Pappagallo GL, Sperandio P, Monfardini S, Pagano F, Cosciani S. Neoadjuvant M-VAC chemotherapy for invasive bladder cancer: results of a multicenter phase III trial. J Urol (Suppl) 1999;161:264 abstract 1021.

[24] Cortesi E. Neoadjuvant treatment for locally advanced bladder cancer: a randomized prospective clinical trial. (meeting abstract);1995.

[25] Malmstrom PU, Rintala E, Wahlqvist R, Hellstrom P, Hellsten S, Hannisdal E. Five year follow-up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. J Urol 1996;155:1903–6.

[26] Sherif A, Rintala E, Mestad O, Nilsson J, Holmberg L, Nilsson S, et al. Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer-Nordic cystectomy trial 2. Scand J Urol Nephrol 2002; 36:419–25.

[27] Sherif A, Holmberg L, Rintala E, Mestad O, Nilsson J, Nilsson S, et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic Studies. Eur Urol 2004;45:297–303.

[28] Sengelov L, von der Maase H, Lundbeck F, Barlebo H, Colstrup H, Engelholm SA, et al. Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle invasive bladder tumours. Acta Oncol 2002;41:447–56.
[29] Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester BJ, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with elective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. J Clin Oncol 1998;16: 3576–83.
[30] Parmar MK. Neoadjuvant chemotherapy in invasive bladder cancer. Trial Design Prog Clin Biol Res 1990;353:1115–8.
[31] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer; a systematic review and meta-analysis.
[32] Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol 2004;171:561–9.
[33] Splinter TA, Scher HI, Denis L, Bukowski R, Simon S, Klimberg I, et al. The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. European Organization for Research on Treatment of Cancer-Genitourinary Group. J Urol 1992;147:606–8.
[34] Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder sparing surgery for invasive bladder cancer: ten year outcome. J Clin Oncol 1998; 16:1298–30.
[35] Kachnic LA, Kaufman DS, Heney NM. Bladder preservation by combined modality therapy for invasive bladder cancer. J Clin Oncol 1997;15:1022–9.
[36] Sternberg CN, Pansadoro V, Calabro F, Marini L, van Rijn A, de Carli P, et al. Neoadjuvant chemotherapy and bladder preservation in locally advanced transitional cell carcinoma of the bladder. Ann Oncol 1999;10:1301–5.
[37] Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. J Clin Oncol 1998;16:1298–301.
[38] Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer; long term results in 1054 patients. J Clin Oncol 2001;19:666–75.
[39] Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, et al. Cystectomy for bladder cancer: a contemporary series. J Urol 2001; 165:1111–6.
[40] Bassi P, Ferrante GD, Piazza N, Spinadin R, Carando R, Pappagallo G, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol 1999;161:1494–7.
[41] Logothetis CJ, Johnson DE, Chong C, Dexeus FH, Sella A, Ogden S, et al. Adjuvant cyclophosphamide, doxorubicin, and cisplatin chemotherapy for bladder cancer: an update. J Clin Oncol 1988;6:1590–6.
[42] Millikan R, Dinney C, Swanson D, Sweeney P, Ro JY, Smith TL, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with preoperative and postoperative M-VAC. J Clin Oncol 2001;19:4005–13.
[43] Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 1991;145:459–64.
[44] Stockle M, Meyenburg W, Wellek S, Voges GE, Rossmann M, Gertenbach U, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long term results of a controlled prospective study and further clinical experience. J Urol 1995;153:47–52.
[45] Stockle M, Wellek S, Meyenburg W, Voges GE, Fischer U, Gertenbach U, et al. Radical cystectomy with or without adjuvant polychemotherapy for non-organ-confined transitional cell carcinoma of the urinary bladder: prognostic impact of lymph node involvement. Urology 1996; 48:868–75.
[46] Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cosplatin, vinblastine and methotrexate chemotherapy for muscle-invasive bladder cancer. J Urol 1996;155: 495–9.
[47] Studer UE, Bacchi M, Biedermann C, Jaeger P, Kraft R, Mazzucchelli L, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol 1994;152:81–4.
[48] Bono AV, Benvenuti C, Reali L, Pozzi E, Gibba A, Cosciani-Cunico S, et al. Adjuvant chemotherapy in advanced bladder cancer. Italian Uro-Oncologic Cooperative Group. Prog Clin Biol Res 1989;303: 533–40.
[49] Lehmann J, Stockle M. Adjuvante chemotherapie nach cystectomie MVEC vs. CM. Urologe A 2000;39(Suppl 1) SA.
[50] Stadler WM, Steinberg GS, Vogelzang NJ. Low rate of patient (pt) enrollement in an adjuvant study of gemcitabine (G), cisplatin (C) and amifostine in high-risk localized bladder cancer. Proc Am Soc Clin Oncol 2000;19:1409 (abstract).
[51] Otto T, Borgemann C, Krege S. Adjuvant chemotherapy in locally advanced bladder cancer (pT3/pN1-2, M0): a phase III study. Eur Urol 2001;39(Suppl 5):147 (abstract).
[52] Moore MJ, Tannock IF, Ernst DS, Huan S, Murray N. Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. J Clin Oncol 1997;15:3441–5.
[53] Stadler WM, Kuzel T, Roth B, Raghavan D, Dorr FA. Phase II study of single agent gemcitabine in previously untreated patients with metastatic urothelial cancer. J Clin Oncol 1997;15:3394–8.
[54] von der Maase H. Gemcitabine in transitional cell carcinoma of the urothelium. Expert Rev Anticancer Ther 2003;3:11–9.
[55] von der Maase H. Current and future perspectives in advanced bladder cancer: is there a new standard? Semin Oncol 2002 Feb;29:3–14.
[56] Sousa-Escandon A, Vasquez S, Quintero-Aldana G, Picall JA, Neira J, Garcia-Novio F, et al. Neo-adjuvant treatment of infiltrating transitional cell carcinoma of the bladder with paclitaxel and cisplatin: a phase II study. Int J Urol 2002;9:162–6.
[57] Bamias A, Deliveliotis C, Karayiannis A, Varkarakis I, Zervas I, Pantazopoulos D, et al. Neoadjuvant chemotherapy with docetaxel and cisplatin in patients with high-risk resectable bladder carcinoma: long term results. Eur Urol 2004;46:344–50 discussion 350–51.

Editorial Comment

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More than 20 years after the first reports on systemic chemotherapy such as the M-VAC regimen, the role of systemic treatment for transitional cell carcinoma remains more or less undefined in spite of thousands of treated patients: In patients with *metastatic* disease, long term survival is exceptional, the treatment intention is therefore often described as ''palliative''.

In the situation of patients undergoing cystectomy for *muscle invasive or locally advanced disease*, it was the matter of a long-lasting controversy, wether peri-

operative chemotherapy can improve their doubtful prognosis by sterilizing potential micrometastases. The large meta-analysis of the neo-adjuvant trials gave a clear answer to this question: Eradication of micrometases is possible. However, the survival probability was only improved by 5%, which indicates that 19 of 20 treated patients have to accept treatment without efficacy: They would either be cured by cystectomy alone or they will die in spite of additional treatment.

The question therefore arises, if this small 5% difference reflects the weakness of chemotherapy itself or the weakness of the neo-adjuvant trials that were summarized for the meta-analysis. And indeed, the trials as well as the concept of neo-adjuvant chemotherapy are characterized by two flaws that may have significantly contributed to this borderline result.

1. *Dilution* of ''informative'' patients (Namely those who would develop progression after cystectomy) by a high percentage of ''non-informative'' patients (Those who are cured by cystectomy alone): Almost all neo-adjuvant protocols called for patients with T2 or T3 disease. Patients with T2 disease are characterized by a cure rate of up to 80%. A significant improvement of such a favourable prognosis is extremely unlikely. Even the optimistic assumption that neo-adjuvant chemotherapy can prevent one out of three tumor-related deaths would only translate into a 6% survival advantage in a patient group with a progression risk as low as 20%. Including such patients will therefore probably ''dilute'' the potential benefit that might be observed in patients with a higher risk of progression, but will not add useful additional information. The inclusion of patients with T2 disease probably adds nothing but a significant increase of the number of patients necessary to detect a significant survival advantage and a decrease in survival difference.
2. Patients with *non-responding tumors* may not only not benefit from systemic pre-treatment, prognosis may even become worse by the delay of definitive treatment in favour of an ineffective pre-treatment. The 5% survival advantage must therefore be read as the summary effect of a prognostic improvement in patients with a tumor response minus the worsening in patients with non-responding tumors.

The majority of adjuvant trials focused on high risk patients based on the histopathological tumor stage, thus circumventing the dilution problem. Furthermore, adjuvant trials are not biased by the non-responder-problem, because adjuvant treatment does not lead to a delay of definitive treatment. For theoretical reasons, adjuvant trials should therefore be expected to reveal larger survival differences as compared to neo-adjuvant trials and it is regrettable that not more efforts were invested in large adjuvant trials during the late 1980s, when almost all international trial organisation planned for neo-adjuvant studies. The authors correctly state that all available adjuvant trials are characterized by small patient numbers, but on average, they concluded with a larger survival advantage as could be predicted by simple considerations.

How can these experiences be translated into the decision making process of the individual patient? The poorer his baseline prognosis, the higher is the probability that the patient will benefit from perioperative systemic treatment. When clear signs of lymph node involvement are seen on a preoperative CT or MRI, inductive chemotherapy should be seriously considered prior to cystectomy, because the prognosis of such a patient must be regarded as extremely poor with a pure surgical approach. When lymph node involvement is detected during cystectomy, adjuvant chemotherapy should also seriously be considered because of a progression risk as high as 80%.