Muscle invasive and metastatic bladder cancer

C. N. Sternberg
Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy

Introduction

Bladder cancer is the second most common cancer of the genitourinary tract with approximately 350,000 new cases worldwide [1]. It is an aggressive epithelial tumor with a high rate of early systemic dissemination. One third of patients develop locally invasive or metastatic disease. In patients with locally advanced bladder cancer (infiltrating the musculature) 5-year survival is dependent upon pathologic stage, grade and nodal status. With increasing tumor (T) stage, especially when cancer extends outside of the bladder wall, prognosis worsens. Failure is usually due to occult metastatic disease present at the time of initial diagnosis.

Cystectomy is the gold standard of treatment for muscle invasive bladder cancer in most countries, although definitive radiotherapy (RT) is another suitable alternative. Five-year survival after cystectomy is at best 50%. In large series from the University of Padua, Memorial Sloan Cancer Center and the University of Southern California survival varies between 36% and 48% [2–5]. High-risk patients with pathologic stage pT3–pT4 and/or pN+ M0 bladder cancer have inferior 5-year survival between 25–35%.

Advantages and disadvantages of neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy is intended for patients with operable clinical stage cT2 to cT4a muscle invasive disease. The rationale for giving chemotherapy prior to cystectomy or definitive RT is based on the intent to treat micrometastatic disease, present at diagnosis.

The main advantages of neo-adjuvant therapy are that systemic chemotherapy is delivered early when the burden of metastatic disease is minimal; therapy is tolerated better prior to surgery or radiation than after cystectomy or RT; and toxicity is usually less than that seen in patients with metastatic disease, as subjects with localized disease usually have a better performance status. In addition, neo-adjuvant chemotherapy has been so effective that it has been incorporated in programs where bladder preservation is planned [6, 7].

The main disadvantages of neo-adjuvant chemotherapy are that transurethral resection of the bladder (TURB) staging is clinical which may lead to difficulty in assessing response to therapy [a discrepancy between clinical and pathological staging can be seen in approximately 30% of cases [8, 9]; and there is also a delay in cystectomy or RT during neo-adjuvant therapy.

Randomized trials of neo-adjuvant chemotherapy

Whether neo-adjuvant chemotherapy improves survival has been addressed in randomized trials. Initial studies were with single agent cisplatin, but most recent trials have been with cisplatin-containing combination chemotherapy.

These trials have either shown a trend towards a small benefit or no survival benefit. What has emerged is that most of the trials did not enlist sufficient numbers of patients to detect differences in survival. Randomized trials in the literature can be found in Table 1.

Results from the Intergroup trial conducted by the Southwest Oncology Group (SWOG) were published in the New England Journal of Medicine [14]. Patients with cT2 to cT4a were randomized between three cycles of neo-adjuvant methotrexate-vinblastine-doxorubicin-cisplatin (M-VAC) chemotherapy + cystectomy or cystectomy alone. Enrollment took place over an 11-year period. Three hundred and seven patients were eligible. Some 82% in the M-VAC group and 81% in the surgery group actually underwent cystectomy. Median survival was 77 months in patients who received neo-adjuvant M-VAC as compared to 46 months in patients who underwent cystectomy alone. The results are not statistically significant in terms of overall survival (P = 0.06; 2-sided testing), but demonstrate a trend towards improved survival in M-VAC treated patients. The estimated risk of death was reduced by 25% (HR 1.33) [15]. Unfortunately, the size of the study has limited potential to discern a clinically meaningful difference and as such does not rule out the relevance of this approach.

The European Organization for Research and Treatment of Cancer/Medical Research Council (EORTC/MRC) trial is the largest neo-adjuvant randomized trial. This trial accrued over 5½ years and 976 patients were accrued. CMV neo-adjuvant

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chemotherapy prior to cystectomy or RT was evaluated. There was a non-significant trend towards improvement in survival in patients on the CMV arm [16]. In an unpublished ASCO update, with follow-up of 7.4 years, the data reached statistical significance ($P = 0.048$). There was a 5.5% benefit in favor of patients treated with CMV [17]. Survival at 5 years was 50% compared to 44%, and at 8 years was 43% versus 37%. The authors concluded that there was no change in absolute benefit.

The Nordic cystectomy I trial evaluated neo-adjuvant adriamycin, cisplatin + pre-operative RT prior to cystectomy versus pre-operative RT + cystectomy. A 15% survival difference in favor of patients treated with chemoradiotherapy was seen only in a subset of patients with T3–T4 disease [18]. This advantage was not confirmed in the subsequent Nordic cystectomy II trial in which 317 patients were randomized between cystectomy or cystectomy preceded by methotrexate + cisplatin (without RT) [19].

The Advanced Bladder Cancer (ABC) Meta-Analysis Collaboration, an ad hoc group has retrospectively evaluated several randomized studies of neo-adjuvant chemotherapy [20]. The neo-adjuvant study updates a prior meta-analysis done in 2003 by the same group [21], which had very similar results, but did not include data from the SWOG trial [14].

With individual patient data from 3005 patients in 11 randomized trials treated with neo-adjuvant chemotherapy, the overall analyses was not significantly in favor of chemotherapy [HR = 0.89 (95% CI 0.81–0.98), $P = 0.022$]. In patients who received single agent cisplatin chemotherapy, neo-adjuvant chemotherapy was detrimental. However, in a subset analysis of patients who received cisplatin based combination chemotherapy, a 5% absolute benefit improving survival from 45% to 50% at 5 years (HR = 0.86, 95% CI 0.77–0.95, $P = 0.003$) was observed in those who received neo-adjuvant therapy prior to cystectomy.

The study includes many studies that were underpowered and that showed no difference in survival with neo-adjuvant chemotherapy. It includes the two Nordic studies that were individually negative [18, 19], but in a combined analysis had positive results in favor of combination chemotherapy [22].

In addition to chemotherapy, surgical factors were evaluated in 268 patients who underwent radical cystectomy in the SWOG Intergroup trial [23]. The quality of surgery was an independent prognostic factor for outcome after adjustment for pathologic factors and was just as important as the use of neoadjuvant chemotherapy.

Available data suggest that for ‘average risk’ cT2 patients, there is at best a modest benefit of adding chemotherapy to definitive local therapy. Available studies also suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers.

**neo-adjuvant chemotherapy and bladder preservation**

Up to 15% of patients with muscle-invasive disease have no pathologic residual disease at the time of cystectomy, indicating the potential curability of select patients with TURB alone. These findings suggest that while bladder preservation can be a viable option to radical cystectomy in selected patients, surgery alone will be successful in only a small percentage of patients. The limited effectiveness of surgery alone, and the advent of more effective combination chemotherapy has led to a multidisciplinary approach to bladder preservation.

The goal of bladder preservation is to achieve equivalent cancer survival to surgery, while maintaining quality of life. Improvement in surgical techniques and the development of continent urinary diversions have resulted in decreased morbidity and better postoperative quality of life after radical cystectomy [32], speaking against bladder preservation.

Prior to effective chemotherapy, early attempts at bladder preservation included TURB or partial cystectomy alone for solitary tumors amenable to complete surgical resection.

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**Table 1. Randomized Phase III trials of neo-adjuvant chemotherapy**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Neo-adjuvant arm</th>
<th>Standard arm</th>
<th>Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin chemotherapy trials</td>
<td>DDP/RT</td>
<td>RT</td>
<td>255</td>
<td>No difference</td>
</tr>
<tr>
<td>Aust/UK [24]</td>
<td>DDP/RT or preop RT+Cyst</td>
<td>RT or preop RT+Cyst</td>
<td>99</td>
<td>No difference</td>
</tr>
<tr>
<td>Canada/NCI [25]</td>
<td>DDP/Cyst</td>
<td>Cyst</td>
<td>121</td>
<td>No difference</td>
</tr>
<tr>
<td>Spain [CUETO] [26]</td>
<td>CMV/RT or Cyst</td>
<td>RT or Cyst</td>
<td>976</td>
<td>5.5% difference in favor of CMV</td>
</tr>
<tr>
<td>Combination chemotherapy trials</td>
<td>M-VAC/Cyst</td>
<td>Cyst</td>
<td>298</td>
<td>Trend in benefit with M-VAC [$P = 0.06$]</td>
</tr>
<tr>
<td>EORTC/MRC [16]</td>
<td>M-VAC/Cyst</td>
<td>Cyst</td>
<td>206</td>
<td>No difference</td>
</tr>
<tr>
<td>SWOG Intergroup [27]</td>
<td>M-VEC/Cyst</td>
<td>Cyst</td>
<td>171</td>
<td>No difference</td>
</tr>
<tr>
<td>Italy [GUONE] [28]</td>
<td>DDP/FU/RT/Cyst</td>
<td>RT/Cyst</td>
<td>104</td>
<td>No difference</td>
</tr>
<tr>
<td>Italy [GISTV] [29]</td>
<td>ADM/DDP/RT/Cyst</td>
<td>Cyst</td>
<td>311</td>
<td>No difference, 15% benefit with ADM+ DDP in T3-T4a</td>
</tr>
<tr>
<td>Genoa [30]</td>
<td>MTX/DDP/Cyst</td>
<td>Cyst</td>
<td>317</td>
<td>No difference</td>
</tr>
<tr>
<td>Nordic 2 [19]</td>
<td>CarboMV/Cyst</td>
<td>Cyst</td>
<td>194</td>
<td>Benefit with CarboMV</td>
</tr>
<tr>
<td>Abol-Enein [31]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DDP or C, Cisplatin; MTX, Methotrexate; ADM, Doxorubicin; E, Epirubicin; V, Vinblastine; Carbo, Carboplatin; Cyst, cystectomy; RT, radiation therapy.
There are no randomized trials comparing survival with TURB alone versus cystectomy. Two large series have reported similar long-term 10-year survival rates indicating TURB alone may be an effective bladder-sparing technique in select patients with small tumors [33, 34].

It is difficult to interpret the contribution of each component of a multi-modality bladder-sparing approach to survival. Restaging TURB has not been performed as standard practice in all series, therefore it is difficult to know what is the impact of TURB alone. One would expect patients who have been rendered clinical p0 by either TURB alone or TURB plus chemotherapy prior to radiation or cystectomy to have better long-term survival [35]. This has been demonstrated in several phase II series [36–41]. Clinical factors associated with a better chance of a complete clinical response to TURB alone or TURB + chemotherapy are clinical stage (organ-confined), tumor size < 3–5 cm, no hydronephrosis, no palpable mass, and unifocal disease, although none have been prospectively verified in a randomized trial.

In Rome, 104 patients with clinical T2–T4N0M0 tumors of the bladder were treated with neoadjuvant M-VAC [8]. Median survival for the entire group was 7.49 years (95% confidence interval, 4.86–10.00 years). At the TURB following M-VAC, 49 (49%) patients were T0. Responding patients underwent TURB or partial cystectomy alone. 60% of the patients treated with M-VAC and TURB alone were alive at a median follow-up of 56 months (10–160+). 44% of the patients in the TURB group maintained an intact bladder. Of the responding patients with monofocal lesions who underwent partial cystectomy, 5-year survival was 69% and only one patient required salvage cystectomy.

Combining systemic chemotherapy with RT also allows bladder preservation while sensitizing the tumor to radiation and treating occult metastases. This approach has been advocated by the Radiation Therapy Oncology Group (RTOG) at Massachusetts General Hospital [42] and by others [43, 44]. Selection criteria are similar to those that predict a good prognosis after cystectomy. Patients with small T2–T3 lesions without hydronephrosis who undergo a thorough TURB tend to fare best.

Five-year survival rates from 42–63%, with organ preservation in approximately 40% of patients, are reported. Although survival is similar to that in contemporary cystectomy series, the combined morbidity of chemotherapy and radiation therapy can be significant.

Patients who undergo neo-adjuvant chemotherapy and bladder preservation should be highly informed, willing to undergo frequent follow-up and multiple cystoscopies, and understand the possibility that cystectomy may become necessary. It is in patients with residual disease at the first cystoscopy (within 3 months) after neo-adjuvant chemotherapy, with or without radiation therapy, in whom we must critically assess the effectiveness of combined modality approaches in comparison to immediate radical cystectomy.

The use of agents such as gemcitabine and the taxanes in the neo-adjuvant setting or with radiation remains experimental, but is being incorporated into treatment protocols. Patients should be highly motivated to preserve their bladders and understand the possible side effects of combined therapy.

### advantages and disadvantages of adjuvant chemotherapy

Adjuvant chemotherapy is given after cystectomy in patients with pT3–pT4a and/or pN+ M0 disease in an effort to delay recurrence and prolong survival. The advantage of giving adjuvant chemotherapy, is that local definitive treatment is performed immediately. Treatment decisions are based on pathologic criteria, after careful examination of the cystectomy specimen. The availability of sufficient tissue for increasingly sophisticated analysis of reputed molecular prognostic and predictive markers is also an advantage. Surgery is not delayed, and there is no time wasted in those patients who would not respond to chemotherapy. If micrometastases are present, they are treated when at a low volume, rather than waiting for overt metastatic disease.

The advent of orthotopic bladder substitutions and the decreased morbidity of cystectomy has increased the tendency of urologists to operate early and then to consider adjuvant chemotherapy.

The major disadvantage is that the bladder is not preserved and that there is a delay in starting systemic therapy for occult metastases while focusing first upon the primary tumor. Response cannot be easily evaluated, and the only clinical endpoint that can be assessed is the time to tumor recurrence. An additional disadvantage is the difficulty in administering chemotherapy to patients following cystectomy.

Despite its appeal, there have been few randomized trials evaluating adjuvant chemotherapy. Table 2 defines the results of randomized adjuvant chemotherapy trials in the literature. Two studies have received the most attention. In an American phase III trial, Skinner showed a significant increase in time to progression and survival in patients randomized to receive chemotherapy following cystectomy [45]. This study has been criticized for its methodology.

Another adjuvant chemotherapy trial conducted in Germany was performed by Stockle [46, 47]. Patients were randomized to cystectomy or cystectomy followed by M-VAC or M-VEC.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Chemo</th>
<th>Chemo</th>
<th>No chemo</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logothis</td>
<td>1988</td>
<td>CISCA</td>
<td>62</td>
<td>71</td>
<td>Benefit but not randomized</td>
</tr>
<tr>
<td>Skinner</td>
<td>1991</td>
<td>CAP</td>
<td>47</td>
<td>44</td>
<td>Benefit, few pts received therapy</td>
</tr>
<tr>
<td>Stockle</td>
<td>1992</td>
<td>M-VAC</td>
<td>26</td>
<td>23</td>
<td>Benefit, few pts, no treatment at relapse</td>
</tr>
<tr>
<td>Studer</td>
<td>1994</td>
<td>DDP</td>
<td>40</td>
<td>37</td>
<td>No benefit, DDP alone inadequate</td>
</tr>
<tr>
<td>Bono</td>
<td>1995</td>
<td>CM</td>
<td>48</td>
<td>35</td>
<td>No benefit for N0M0</td>
</tr>
<tr>
<td>Freiha</td>
<td>1996</td>
<td>CMV</td>
<td>25</td>
<td>25</td>
<td>Benefit in relapse free survival only</td>
</tr>
<tr>
<td>Otto</td>
<td>2001</td>
<td>M-VEC</td>
<td>55</td>
<td>53</td>
<td>No benefit</td>
</tr>
</tbody>
</table>
Patients had poor risk factors; 60% had positive nodes and most were stage T4. The study was prematurely discontinued with only small patient numbers after an interim analysis showed a benefit for patients randomized to chemotherapy. At 10 years overall survival is 17.4% vs. 26.9% and tumor-specific survival 17.4% vs. 41.7%, respectively [48]. Biases introduced by early stopping of non-blinded phase III trials have been well recognized. In addition, and contrary to current standard practice, the investigators did not offer chemotherapy to patients in the observation group at the time of recurrence. Of note, in a more recent German series comparing M-VEC to observation after cystectomy, no differences in survival were found [49].

Due to the difficulty in interpretation of adjuvant chemotherapy trials, a systematic review of adjuvant combination chemotherapy trials was undertaken. Serious methodological flaws were found in all studies. Major deficiencies included insufficient sample sizes, inappropriate early stopping of patient entry, inappropriate statistical analyses, and insufficient reporting of results: all leading to poorly substantiated and supported conclusions [50]. The ABC meta-analysis sought to better understand the value of adjuvant chemotherapy [51], but although 11 randomized controlled trials were identified, individual patient survival data from only 6 adjuvant trials comprising 283 events in 491 patients was eventually included and 4/6 of these trials were stopped early. Although the results suggest a 9% improvement in absolute survival at 3 years (HR = 0.75, 95% CI 0.60–0.96, P = 0.019), the paper is notable for its underpowered survival curves. In publishing, the authors clearly recognize that there are problems with interpretation of these results and make a plea to the urological oncology community for continued recruitment in adjuvant chemotherapy trials.

The current data have been unable to reliably support the routine use of adjuvant chemotherapy. To further address this question, it is fundamental to continue to support the ongoing EORTC 30994 and the Spanish and Italian adjuvant chemotherapy trials. Another international study seeks to evaluate adjuvant chemotherapy after cystectomy in pT1–PT2 patients with altered p53 status, who are at high risk [52].

**metastatic disease**

Systemic chemotherapy is the only modality shown to improve survival in phase III trials [53, 54]. The M-VAC regimen, first reported in 1985 by Sternberg et al. at Memorial Sloan Kettering Cancer Center, demonstrated that urothelial carcinoma was sensitive to chemotherapy [55]. Patients with measurable lesions had a 72% response rate (RR) and 36% attained complete response (CR) [56]. Long-term survival was achieved in patients who attained CR. Patients who achieved CR with M-VAC and surgery had twice the survival of patients who had only a partial response (PR). Chemotherapy was more effective in nodal disease than in visceral metastases [54, 56].

In an update of M-VAC results at MSKCC in 194 evaluable patients, median survival was 14.8 months, with a 5-year survival rate of 17% [57]. The 5-year survival rate for 46 patients with a CR after chemotherapy was 40%. An additional 30 patients achieved CR after chemotherapy followed by surgery with a 5-year survival rate of 33% [58].

Three risk categories were established on the basis of Karnofsky Performance Status (KPS) and the presence or absence of visceral (lung, liver, or bone) metastasis. Median survival times for patients who had 0, 1, or 2 risk factors were 33, 13.4, and 9.3 months, respectively (P = 0.0001). The median survival time of patient cohorts could vary from 9 to 26 months by altering the proportion of patients from different risk categories [57].

More recent combination regimens may show slightly better survival than what was seen in the original M-VAC series (in the range of 14 to 15 months) [59]. This may be the case for multiple reasons including case selection, stage migration (patients with locally-advanced disease mixed together with advanced metastatic disease), better radiological techniques, increased patient awareness, increased use of post-chemotherapy surgery, and newer active agents [60, 61].

**single agents**

Several novel chemotherapeutic agents have activity in urothelial carcinoma including gemcitabine, the taxanes (paclitaxel and docetaxel), pemetrexed, the epothilones, and vinflunine [62, 63, 66–69].

Gemcitabine and cisplatin (GC) have been combined in a randomized international trial and compared to M-VAC. Eligibility criteria included patients with T4b, N2 or N3, or M1 disease. The trial revealed a similar efficacy with respect to response, time to progressive disease, and survival between the two treatment arms, whereas GC was less toxic than M-VAC [70]. Overall survival was similar in both arms with a median survival of 14.0 months for GC and 15.2 months for M-VAC. The 5-year overall survival rates were 13.0% and 15.3%, respectively. Although the study was not powered to demonstrate that the regimens were equivalent (n = 405), GC is now considered an alternative to M-VAC as a standard of care in patients with locally advanced and metastatic urothelial cancer.

High-dose paclitaxel at 250 mg/m² by 24-hour continuous infusion every 3 weeks [71] resulted in a RR of 42%, including a 27% CR rate. Since the kidneys are only minimally involved in the excretion of paclitaxel, it can be utilized in patients with impaired renal function [72]. Regimens of combined paclitaxel and cisplatin, usually every 3 weeks, have been evaluated in several phase II studies [73–75] including more than 100 patients, with an overall RR rate ranging from 50% to 70% (CR rates from 15–32%).

Docetaxel, another widely used taxane, has likewise displayed activity in urothelial carcinoma. In previously treated patients, the RR was 13% with a median overall survival of 9 months [76]. In untreated patients, the RR was higher (38%) with a response duration of 6 months [77]. The combination of docetaxel and cisplatin every 3 weeks has been evaluated in 3 studies [78–80]. In more than 120 patients, the overall RR was 52% to 62% and the median overall survival ranged from 8.2 to 13.6 months.

A randomized study by the Hellenic Group has shown inferior activity of the docetaxel and cisplatin (DC)
combination compared to M-VAC. Although this study was designed to detect a survival advantage for DC, survival was inferior for patients treated with DC.

In a phase III EORTC Genitourinary Group trial, high-dose M-VAC (HD-M-VAC) given every 2 weeks with G-CSF (granulocyte colony stimulating factor) was compared to M-VAC [81]. It was possible to deliver twice the dose of cisplatin and doxorubicin with less toxicity, fewer dose delays, and in half the time if granulocyte colony stimulating factor (G-CSF) was routinely added. This trial revealed less toxicity with high dose M-VAC due to the addition of G-CSF. Although there was not a significant difference found in median survival (more than 14 months in both arms), there was a significant difference in favor of high dose M-VAC in RR and CR rate. In an intention to treat analysis, there was a 64% RR on the HD-M-VAC arm as compared to 50% with M-VAC. After a median follow-up of 7.3 years, 24.6% are alive on the HD-M-VAC arm vs. 13.2% on the M-VAC arm. HD-M-VAC produces a borderline statistically significant relative reduction in the risk of progression and death compared to M-VAC. This regimen may be useful in the neoadjuvant or adjuvant setting since the cycle length is much shorter and it is delivered in half the time of traditional M-VAC.

The combination of paclitaxel and carboplatin has been routinely used in advanced bladder cancer [82]. Several studies with carboplatin (AUC 5–6) and paclitaxel (150–225 mg/m²) have reported RRs ranging from 21% to 63%, though many of the responses were partial [83–85]. In the SWOG study, the RR was only 14% with a very poor median survival of only 9 months [83]. This may have been due to a predominance of patients with poor PS and visceral metastases. Since no phase III trials have compared carboplatin and paclitaxel to the standard regimens of M-VAC or GC (the ECOG trial of M-VAC versus carboplatin and paclitaxel was closed due to poor accrual), it is probably best not to use this regimen except in patients with extremely poor renal function who cannot tolerate cisplatin.

Gemcitabine and paclitaxel combination chemotherapy has been evaluated in several studies with favorable results, even in pretreated patients [86–91]. In a phase II Italian and Israeli study, 40 patients who had been pretreated with M-VAC had a 60% overall RR (28% CR and 33% PR) when treated with paclitaxel 150 mg/m² and gemcitabine 2500–3000 mg/m² every 2 weeks on an outpatient basis [86]. Of note, the RR was 27% in patients who had failed prior chemotherapy for metastatic disease within the last year as compared to 80% for patients who received prior neoadjuvant or adjuvant M-VAC. The median survival for all patients was 14.4 months, equal to that seen in another American study [87].

The combination of docetaxel and gemcitabine every 3 weeks has been evaluated in pretreated patients by the ECOG [92]. Of 29 patients, 25 were evaluable for response. The authors concluded that this regimen was active with five patients attaining a PR (20% overall RR) and 10 having stable disease. A combination of doxorubicin and gemcitabine has been reported to lead to a 36% CR rate, but this has not been confirmed.

The combination of gemcitabine and a taxane is active and well-tolerated as first- or second-line treatment of patients with advanced urothelial carcinoma, as well as in patients with compromised renal function. Other combinations using the taxanes and gemcitabine have been put forth as possible alternatives to M-VAC. Both gemcitabine and paclitaxel have been incorporated into multi-agent chemotherapy combinations with cisplatin or carboplatin [93].

Phase II data from several gemcitabine-based triplet combination regimens are available. The Spanish regimen of gemcitabine, cisplatin, and paclitaxel (GCP) has led to a 78% RR [94]. In the multi-center phase II study, the median survival was 15.6 months, consistent with other currently available regimens [95]. The American combination of gemcitabine, paclitaxel, and carboplatin (rather than cisplatin) compared favorably to the Spanish regimen with a 14.7 month median survival and 1-year survival of 59%. The RR was 68% (CR 32% and PR 36%) [96]. In a third study from MSKCC, the triplet ifosfamide, paclitaxel, and cisplatin (ITP) revealed a 68% overall RR (CR 23% and PR 45%). Median survival was 20 months in this single center study [97]. Whether or not newer triplet regimens can improve survival remains to be seen in ongoing phase III trials.

conclusions

Cystectomy remains the gold standard of treatment for localized muscle-invasive bladder cancer. For patients with cT2 there is at best a modest benefit in adding neoadjuvant chemotherapy to local therapy. Available data suggest a more substantial benefit for patients with high-risk disease, such as cyst3b cancers. The quality of the surgery is extremely important. Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials reveal a 5% difference in favor of neoadjuvant chemotherapy.

The goal of organ preservation is to achieve equivalent cancer survival to radical cystectomy while maintaining quality of life. Randomized trials have not compared TURB alone and cystectomy in terms of survival. Clinical factors associated with a better possibility of attaining a complete clinical response to TURB alone or TURB plus chemotherapy are clinical stage (organ-confined), tumor size less than 3–5 cm, no hydroureterohydronephrosis, no palpable mass, and unifocal disease. Patients with residual disease at the first cystoscopy (within 3 months) after TURB alone or neoadjuvant chemotherapy plus TURB should undergo cystectomy.

The rationale for giving adjuvant chemotherapy is that local treatment is performed immediately. Treatment decisions are based on pathologic criteria after careful examination of the cystectomy specimen. The availability of sufficient tissue for increasingly sophisticated analysis of putative molecular prognostic and predictive markers is also an advantage. Surgery is not delayed, and there is no time wasted for those patients who would not respond to chemotherapy. If micrometastases are present, they are treated when at a low volume, rather than waiting for overt metastatic disease. Available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice. The results of larger collaborative international adjuvant chemotherapy trials will
be needed in order to determine the true value of adjuvant chemotherapy.
Systemic cisplatin-based combination chemotherapy is the only current modality shown to improve survival in metastatic bladder cancer. Prognostic factors can be as important as the therapy actually given and can determine both response and survival. GC is now considered an alternative to M-VAC as a standard of care in patients with locally advanced and metastatic urothelial cancer. Whether or not newer triplet regimens can improve survival remains to be seen in ongoing phase III trials.

References