Annals of Oncology 16 (Supplement 4): iv85–iv89, 2005
doi:10.1093/annonc/mdi914

Systemic chemotherapy for patients with advanced and metastatic bladder cancer: current status and future directions

V. Lorusso[1]* & N. Silvestris[2]

[1]*Operative Unit of Medical Oncology, Oncology Institute of Bari;* [2]*Operative Unit of Medical Oncology, Hospital Santa Maria Goretti, Latina, Italy*

Bladder cancer is the second most common genitourinary cancer and is a significant cause of morbidity and mortality with an estimated 63 210 new cases and projected 13 180 deaths in 2005 in the USA [1]. This malignancy occurs more frequently in men while the median age at diagnosis is 68 years. Transitional cell carcinoma (TCC) comprises more than 90% of all bladder cancers with the remainder consisting of squamous cell carcinoma (3%), adenocarcinoma (2%), and small cell carcinoma (less than 1%). TCCs with focal areas of squamous or glandular differentiation are common and are classified and managed as TCC. On the contrary, the biology and management of pure non-TCC bladder cancers differ from those of TCC. Four clinical distinct entities of TCC are recognised: superficial papillary tumors (T_a and T_1), carcinoma in situ (T_{is}) muscle-invasive (T_2 to T_4) and advanced (involved extra-pelvic nodal or distant metastatic) disease. About 75% of patients present with superficial disease that can be generally managed with local therapy, such as transurethral resection and intravescical chemotherapy or immunotherapy. Once muscle invasion has occurred, the prognosis worsens, with 5-year survival of about 60% for patients with carcinoma macroscopically confined to the bladder and only 20–30% for patients with tumors extending beyond the bladder wall [2]. The standard treatment for invasive bladder cancer is radical cystectomy with bilateral pelvic lymphadenectomy. Although surgery may be curative, about 50% of patients with muscle-invasive bladder cancer develop metastases within 2 years because of micrometastatic disease probably present at the time of local treatment [3].

Herein we discuss the role of systemic chemotherapy, aimed at improving survival for muscle-invasive disease, and palliation for metastatic TCC of the bladder.

Chemotherapy for metastatic disease

TCC is moderately sensitive to chemotherapy with a variety of drugs shown to have single-agent activity. In fact, with combination chemotherapy, an overall response rate of 12–73%, with 0–35% complete response can be achieved in patients with metastatic disease [4]. Cisplatin and methotrexate are traditionally considered the most active agents; other cytotoxics which have demonstrable single-agent activity include doxorubicin, cyclophosphamide, ifosfamide, gemcitabine, and taxanes. However, although antitumor activity has been shown with these drugs, the median duration of survival associated with single-agent therapy varies between 4 and 6 months [5].

Conversely, combination chemotherapy has been found to be superior to single agents. In particular, combination chemotherapy including cisplatin is superior to cisplatin alone, even if with greater toxicity [6]. Indeed, combination chemotherapy containing cisplatin is superior to the same combination without cisplatin [7]. Until recently, the two most commonly used cisplatin-based combination chemotherapies for advanced TCC were MVAC (methotrexate, vinblastine, cisplatin and doxorubicin) and CMV (cisplatin, methotrexate and vinblastine). In 1985, Sternberg et al. reported the results of a phase II study of MVAC in which they had found and overall response rate of 71%, albeit in a selected patient population [8]. A second study later confirmed that significant tumor regression was achieved in a series of 121 valuable patients: overall response in 72% with complete remission in 36% of cases, respectively [9]. Nevertheless, toxic effects were significant with 4 drug-related deaths (3%), nadir sepsis (25%), grade 3 or higher myelosuppression (58%), and mucositis (49%). CMV is a better tolerated combination which has shown similar response rates to those reported with MVAC [10]; unfortunately, a randomised-controlled trial comparing the two has not been performed.

The efficacy of the MVAC regimen has been assessed in a prospective randomised trial versus cisplatin alone, with response rates (39% versus 12%), progression-free survival (10 versus 4.3 months) and overall survival (12.5 versus 8.2 months) significantly better for patients given the combined therapy [11]. Moreover, in a prospective randomised trial comparing MVAC with a combination of cisplatin, cyclophosphamide, and doxorubicin (CISCA), the former was found to be superior achieving a significantly higher response rate and a longer survival [12]. For these phase III studies overall response using MVAC have varied between 39% and 65% with median survival up to 16 months.

**Correspondence to*: Dr Vito Lorusso, Operative Unit of Medical Oncology, Oncology Institute of Bari, Via Amendola, 209, 70126 Bari, Italy.

High-dose MVAC in 2-week cycles with granulocyte colony-stimulating factor (G-CSF) has been compared with standard MVAC [13]. The complete and partial response rates were 21% and 55% for dose-intense MVAC, versus 9% and 41% for standard MVAC, respectively. There was no statistically significant difference in survival or time to progression, though progression-free survival was superior in the high dose arm. The toxic death rates were also comparable. Nevertheless, the clinical benefits were not believed to be sufficiently large to justify the adoption of this regimen as standard therapy.

Cisplatin has been demonstrated to have synergistic interaction with gemcitabine, and gemcitabin/cisplatin (GC) combination has been shown to be safe and effective in phase II trials [14–15]. In a phase III randomised study Von der Maase et al. compared GC with classic MVAC in 405 patients with T_{4b} and/or node-positive and/or distant metastatic disease [16]. At a median follow-up of 19 months, the regimens were not statistically different in terms of overall survival, time to progression, time to treatment failure, and response rate. The GC regimen was superior in terms of tolerability with a lower incidence of treatment-related mortality and fewer episodes of neutropenic fever and mucositis (resulting in fewer dose adjustments) and lesser effects on performance status and fatigue. As a consequence, many researchers interpreted these results as showing therapeutic equivalence and adopted GC regimen as a (second) standard of care.

A significant proportion of patients with advanced TCC of the bladder are not eligible to receive cisplatin-based chemotherapy because of several reasons including impaired renal function, cardiopathy, poor performance status and a variety of co-mobid conditions. A strategy to improve the tolerability of platinum-based chemotherapy regimens is to substitute carboplatin for cisplatin. However, the results achieved with carboplatin containing regimens are generally worse. In fact, MVEC (methotrexate, vinblastine, epirubicin and cisplatin) has been compared with MVECa (methotrexate, viblastine, epirubicin and carboplatin) with an overall clinical response rate of 71% and 41%, respectively [17]. Similarly, cisplatin also seemed to be more effective than carboplatin in a phase II study comparing GC versus carboplatin/gemcitabine with response rates of 66% and 35%, respectively [18]. Paclitaxel, a drug that stabilizes microtubules and promotes their assembly resulting in a M-phase cell-cycle arrest [19], has been shown to be active against TTC both in preclinical as well in clinical studies [20–21]. The combination of paclitaxel with cisplatin was also tested in at least three clinical trials: response rates of 62% to 72% and complete response rates of 10% to 34% have been reported [22–24]. The Spanish Oncology Genitourinary Group conducted a phase I/II trial combining gemcitabine, cisplatin and paclitaxel [25]. Fifteen patients were entered at four different dose levels in the phase I part of the study. Dose-limiting toxicity was grade 2 and 3 asthenia at dose level 4. The recommended doses for the phase II part of the study were gemcitabine, 1000 mg/m^2, on days 1 and 8; paclitaxel, 80 mg/m^2 as a 3 h infusion, on days 1 and 8; and cisplatin, 70 mg/m^2, on day 1, every 21 days. An additional 46 patients were entered in the phase II portion, resulting in a total of 49 patients at the specific dose level (three patients from the phase I part). A total of 58 patients were evaluable for response, with an overall response rate of 78% and a CR rate of 28%. Responses were observed at all dose levels and in all disease sites. The median survival for the phase I portion of the study was 24 months, subsequently reduced to 15.8 months when enough follow up was available for the entire group of the patients [26]. However, this regimen was very toxic. In fact, full dose was possible only in 15/46 patients (32.6%), 9 patients were removed from the study for toxicity (1 death due to neutropenic sepsis, 1 because of haematological toxicity, 3 because of renal toxicity and 4 because of non-haematological toxicity). Moreover, G-CSF were given to 18 patients in 42 cycles. Another triple combination was reported by Bajorin et al [27] who combined ifosfamide, 1.5 g/m^2 daily, on days 1 through 3; paclitaxel, 200 mg/m^2 in 3 hours on day 1; and cisplatin, 70 mg/m^2 on day 1 with granulocyte colony stimulating factors administered during each 28-day treatment cycle. A total of 44 patients were evaluable for response, with an overall response rate of 68% and a CR rate of 23%. The median survival was 20 months. Toxicity seemed to be independent of whether the treatment was recycled at 3 or 4 weeks. The most important grade 3/4 toxicity was myelosuppression. Seven patients (16%) had neutropenic fever. Non-haematological toxicities included grade 3 renal insufficiency (11%), and grade 3 neuropathy occurred in 9% of the patients. In a study by Hussain and co-workers [28], 49 patients received gemcitabine 800 mg/m^2 on day 1 and 8, paclitaxel 200 mg/m^2 in 3 h on day 1 and carboplatin AUC 5 on day 1 every 21 days. Prior chemotherapy for metastatic disease was not allowed. The overall response rate for 47 evaluable patients was 68% with CR rate of 32%. Responses were observed in all sites and within 15 of 22 patients with visceral metastases. The median survival was 14.7 months. The major toxicities were grade 3–4 neutropenia and grade 3–4 thrombocytopenia in 73% and 43% of patients, respectively. There were no toxicity related deaths. Recently a phase II randomised trial suggested that the combination of cisplatin, paclitaxel, and gemcitabine (CPG) may not achieve results superior to those reported in literature in studies with GC comprising doublet [29]. On the other hand, toxicity of the triplet was relevant. The standard treatment is still MVAC or GC. However, only the results of the large randomised phase III trial ongoing by EORTC, comparing CPG with GC in a large number of patients will definitely state if the addition of paclitaxel to GC will really improve the response and survival of these patients, or only add toxicity, abolishing any potential advantage over MVAC.

Chemotherapy for patients with muscle-invasive disease

As indicated earlier, radical cystectomy with lymphadenectomy alone cannot achieve satisfactory survival for patients

with pT_3, pT_4 and node-positive disease. Failure to cure is most often due to the presence of occult metastatic disease at sites beyond the margins of local therapy [30]. Therefore, the efficacy of combination chemotherapy in patients with metastatic disease has led to the assessment of chemotherapy delivered either before local therapy (neoadjuvant), after local therapy (adjuvant), or concurrently with radiotherapy (bladder-preserving therapy).

Neoadjuvant chemotherapy

The theoretical advantages of neoadjuvant chemotherapy include information about the response to chemotherapy, possible treatment of micrometastases without delay, more effective delivery of chemotherapy before surgical disturbance and compromised patient performance status, and the potential for down-staging inoperable tumors to respectable disease. Among the concerns regarding neoadjuvant therapy are: the time delay to definitive local therapy (particularly damaging to those who do not respond to chemotherapy), and the possibility of exposing some patients to unnecessary cytotoxic therapy based on inaccurate clinical staging of the disease [31].

Until recently there was no clear evidence for the use of neoadjuvant chemotherapy for potentially curable bladder cancer outwit the context of a clinical trial. The MRC BA06/EORTC 30 894 study randomised 976 patients with locally advanced TCC who were planned for radical local treatment to receive either local therapy alone or three cycles of CMV prior to local therapy [32]. At a median follow up of 4 years, although there was a trend in favour of the addition of neoadjuvant chemotherapy, the trial did not demonstrate a statistically significant improvement in overall survival. Nevertheless up-dated results indicate that, with prolonged follow-up to a median of more than 7 years, there is a hazard ratio of 0.848 in favour of the addition of neoadjuvant chemotherapy, making this trial statistically significant in its own right [33]. The SWOG 8710 (Intergroup 0080) trial randomised 317 patients with node-negative T_2-T_{4a} bladder cancer to receive either 3 cycles of neoadjuvant MVAC chemotherapy, followed by cystectomy, or cystectomy alone [34]. The median survival among patients assigned to surgery alone was 46 months, as compared with 77 months among patients assigned to combination therapy. This result was statistically significant when assessed using the one-side t-test, but failed to reach statistical significance when assessed by the more widely accepted two-side t-test. In addition to the improvement in overall survival, significantly more patients in the combination-therapy group had no residual disease than patients in the cystectomy group (38% versus 15%). An updated meta-analysis which demonstrated an absolute overall survival benefit of 6.5% (from 50% to 56.5%) for patients treated with cisplatin-based combination chemotherapy was recently reported [35]. Major pathological response occurred in 30 to 40% of patients and it was associated with improved survival. However, reliable pre-treatment determinant of benefit remained to be identified, and neoadjuvant therapy has still not become a *standard* in the treatment of TCC.

Adjuvant chemotherapy

Despite radical cystectomy, 40% of the patients with locally advanced disease and more than 80% of the patients with lymphatic metastases, die tumor related. This provides the rationale for additional effective systemic therapy following surgery. The advantages of adjuvant chemotherapy consist of accurate stage diagnosis, more appropriate selection of patients based on full pathological information, and no delays to surgery. On the contrary, its disadvantages include relative delay for treatment of micrometastases, difficulties in giving chemotherapy with a planned dose intensity and, mostly, no possibility of organ-sparing treatment.

A number of randomised trials have assessed the role of adjuvant chemotherapy following either radiotherapy or chemotherapy, against an observational control arm [36–39]. None of these trials has sufficient power to draw statistically significant conclusions. Therefore, in the absence of conclusive evidence for a survival benefit; there is insufficient evidence to support routine use of adjuvant chemotherapy for muscle-invasive/locally advanced bladder cancer. A conclusive answer to this key question could be provided by the EORTC multicentre randomised-controlled trial 30 994 in which patients with pT_3 or pT_4 and/or node-positive TCC of the urothelium are randomised to receive either chemotherapy (MVAC, dose-intense MVAC with G-CSF support of GC) within 90 days following cystectomy, or delayed chemotherapy following relapse.

Another ongoing multicenter American and international adjuvant trial seeks to make therapeutic decisions based on p53 status [40]. Patients with mutant p53 T_1-T_2 tumors are randomised after surgery to MVAC versus observation. This study is based on the observation that tumor expressing alterations in pRb and p53 had significantly increased rates of recurrence and decreased survival compared with patients without these alterations [41].

Bladder-preserving therapy

Radiotherapy alone or transurethral resection of the bladder tumor (TURBT) alone provide only 20% to 40% success at local control [42]. Similarly systemic chemotherapy alone has the same efficacy of radiation therapy [43]. This situation has led to a next stage where combination treatments have been tried. Initial treatment involves TURBT, with removal of all visible tumors cystoscopically. The next stage of treatment, termed induction, combines radiation therapy with platinum-based radiosensitizing chemotherapy. Response to therapy is assessed through cystoscopy biopsy, and patients without a complete response to induction therapy are immediately referred for radical cystectomy. Patients with a complete response after induction undergo additional combined therapy with radiation and chemotherapy, in the consolidation stage of treatment. Several reports involving trimodality therapy have

shown survival rates comparable with those reported in radical cystectomy series [44–45]. Although superficial relapse occurs in 20% of cases, it remains responsive to bacillus Calmette–Guerin, as does *de novo* superficial disease. Indeed, quality of life studies show the retained bladder functions well. Nevertheless, to date, there have been no randomised studies that directly compare radical cystectomy with bladder-sparing treatment. As a consequence, although some patients with invasive disease can be managed with this strategy, the indication for the treatment may be limited to patients with early-stage and unifocal tumors in whom a microscopically or at least visibly complete TURBT was accomplished [46].

Target molecular therapies

A major focus of current research on bladder cancer is based on the identification and suppression of mechanisms of angiogenesis [47]. Endostatin, an endogenously produced inhibitor of angiogenesis, has been tested as a potential agent for the inhibition of bladder cancer growth [48]. TNP-470, a compound derived from *Aspergillus fumigatus*, has been shown to inhibit development of lymph node metastases in a murine model of human bladder cancer [49]. Indeed, in vitro studies antisense oligonucleotide gene therapy directed at bcl-2 mRNA has been demonstrated to reverse cisplatin resistance in bladder tumor cell lines [50]. Moreover HER2/neu, a receptor protein overexpressed in invasive bladder cancer, has been suggested as a therapeutic target [51]. All these new agents are in early clinical trials.

Conclusions

Advanced bladder cancer is a moderately chemotherapy-sensitive disease and cisplatin-based combination chemotherapy improves survival of these patients. Gemcitabine plus cisplatin is equal effective and less toxic than MVAC. For patients not suitable for cisplatin-containing regimens, chemotherapy may be based around carboplatin or newer agents such as gemcitabine and taxanes. Even if neoadjuvant chemotherapy may provide a small survival advantage, this approach has not been universally adopted. Adjuvant studies have been less definitive than neoadjuvant studies; nevertheless, the evaluation of molecular prognostic markers, such as p53, has led to new adjuvant chemotherapy trials. Bladder-preserving therapy remains a controversial topic, as radical cystectomy is still regarded as the gold standard. Progress in the molecular characterization of bladder cancer and identification of new target therapies will provide new opportunities to tailor treatments to specific needs of the patients.

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