Gemcitabine in the treatment of advanced transitional cell carcinoma of the urothelium

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M-VAC (cisplatin, methotrexate, Adriamycin, vinblastine) combination chemotherapy has been for long time the standard of care in fit patient with advanced urothelial tumors. Gemcitabine/cisplatin with similar results and an improved toxicity profile has proved to be a new standard alternative. Whether or not we can improve survival with newer triplet regimens will depend upon the results of ongoing phase III trials. In addition to the new active drug combinations and targeted therapies, new approaches are emerging for treatment. Chemotherapy optimization using molecular markers predicting chemosensitivity are being applied. There is an obvious need to incorporate in clinical trials a systematic translational approach to explain both our successes and our failures.

Key words: bladder cancer, chemotherapy, gemcitabine, urothelial cell cancer

Systemic chemotherapy is the only modality that has been shown to improve survival in responding patients with advanced bladder cancer [1, 2]. In randomized trials, M-VAC (cisplatin, methotrexate, Adriamycin, vinblastine) has produced a modest, though significant survival benefit when compared to cisplatin as a single agent, CISCA or carboplatin-based regimens [1–3]. Other extensively studied combination regimens in metastatic urothelial carcinoma are cisplatin and methotrexate (CM) and CMV (with vinblastine) [4–6]. CMV has been shown to be superior to MV (methotrexate and vinblastine) in a randomized study of 214 patients undertaken by the Medical Research Council [7]. This study demonstrated the significant survival impact of cisplatin and has helped to justify the routine use of cisplatin in all designed combination chemotherapies. Although CM, CMV, and M-VAC have never been compared in randomised studies, the majority of the clinicians consider M-VAC as the standard regimen. However, the limited results with the classical M-VAC combination led in the nineties to the search for new treatment approaches aiming to improve outcome and treatment tolerance.

gemcitabine as single agent in bladder cancer

Anti-tumor activity has been demonstrated with several single agents including gemcitabine, the taxanes (paclitaxel and docetaxel), ifosfamide and recently, pemetrexed, the epothilones, and vinflunine [8–15], although these have rarely produced an improvement in survival when used alone [16–18]. Among these new active chemotherapy agents, gemcitabine was shown and is still, the most highly promising single-agent activity in this disease.

Gemcitabine was initially evaluated in an Italian phase I study conducted in 15 patients with metastatic bladder cancer [19]. The doses ranged from 875 to 1,370 mg/m². One complete response and 2 partial responses were seen in 14 previously treated patients and 1 partial response was observed in a chemotherapy-naive patient. The overall response rate was 27% (4.3–49.1%, 95% CI). In two phase II trials in previously treated patients, a response rate of 28% and 50% was reported [20, 21]. Two trials evaluating gemcitabine in previously untreated patients confirmed the high activity of this agent. Stadler et al. [22] treated 40 patients with gemcitabine 1200 mg/m² weekly times three, repeated every 28 days, and reported an overall response rate of 28% (15–45%, 95% CI). Three complete responses were obtained in patients with liver metastasis. Additionally, Moore et al. [23] confirmed in 37 non treated patients an overall response rate of 24.3% (12–41%, 95% CI).

gemcitabine containing combination regimens

Because of the high antitumor activity reported with various of the previously mentioned new agents, particularly the gemcitabine but also with the taxanes, a great deal of effort was aimed at integrating these agents into combination regimens, mainly with cisplatin and, in some instances, with carboplatin. These newly designed double and triple combination therapies have been evaluated in patients with advanced disease in several phase II and III trials.
cisplatin-Gemcitabine vs. M-VAC

Following several phase II studies [24–27] gemcitabine and cisplatin (GC) were combined in a randomized international trial and compared to M-VAC. The trial revealed a similar efficacy with respect to response, time to progressive disease and survival between the two treatment arms, whereas GC was significantly less toxic than M-VAC [28]. The median survival was 13.8 months for GC treated patients and 14.8 months for M-VAC treated patients with a hazard ratio of 1.04. The study was designed to demonstrate a 4 months improvement in survival benefit with GC and although this trial was not designed to show the equivalence of the two regimens, many researchers have interpreted the results as showing therapeutic non-inferiority and determined that any difference in survival was unlikely to be sufficiently large to offset the improvement in toxicity with GC. Based on the favorable balance in the risk-benefit ratio in favor of GC, this regimen is considered a standard alternative to M-VAC.

carboplatin-based regimens vs. M-VAC

Gemcitabine has been studied in combination with carboplatin in different studies.

The gemcitabine/carboplatin [29] trial was a dose finding study and it was evaluated in a clearly predefined ‘unfit’ bladder cancer patients: PS > 2 and or creatinine clearance less than 60 ml/min. Using this combination investigators reported an overall response rate of 43.5% with a median survival time of 14.4 months in 16 patients that were ineligible for a cisplatin-based regimen. The preliminary results found on this phase II trial using the carboplatin/gemcitabine doublet prompted an EORTC randomized phase II/III trial (EORTC protocol 30986) comparing carboplatin/gemcitabine with methotrexate/carboplatin/vinblastine (M-CAVI) in patients ineligible for cisplatin-based chemotherapy. This trial is presently ready to start the phase III.

triple combination chemotherapy

Several triple combinations with and without gemcitabine have been studied in urothelial cancer patients. Bajorin et al. have reported the activity of the combination of ifosfamide, paclitaxel, and cisplatin (ITP). They demonstrated a response rate of 68% and a median survival in the range of 20 months, which was reported initially as a 50% increment in survival compared historically to the original M-VAC series [30]. Based on these results, and on concepts derived from kinetic models studied in breast cancer, investigators at Memorial Sloan-Kettering have developed the concept of dose-dense-sequential chemotherapy in bladder cancer using the two-drug regimen of doxorubicin and gemcitabine (AG) followed by the three-drug regimen of ifosfamide, paclitaxel and cisplatin (ITP). In a phase I study with 15 patients, AG was well tolerated at all dose levels and no grade 3 or 4 myelosuppression was observed [31]. In a phase II trial in 21 patients, the overall response rate reported was 86%. ITP increased the response seen after AG in 6 patients. This suggests non-cross resistance for the two regimens. The same approach has been evaluated in patients with impaired renal function using AG, but followed by paclitaxel and carboplatin with a median survival time as high of 15 months in these unfit patients reported at recent ASCO meeting this year [32].

Taking in consideration the significant activity of paclitaxel and gemcitabine, either alone or in combination with cisplatin, their different mechanism of action, and their non-overlapping toxicities, the Spanish Group (SOGUG) studied the feasibility of adding paclitaxel to the doublet of gemcitabine/cisplatin in a phase I/II trial. In 58 patients, an overall response rate of 78% was observed with a median survival time of 24 months for the phase I segment of the trial and 15.6 months for the phase II part of the study [33]. Similarly, another triplet was evaluated but using carboplatin. Investigators at Wayne State University, Detroit incorporated gemcitabine in the carboplatin/paclitaxel combination in a phase II trial with 49 previously untreated patients with advanced urothelial malignancy and normal renal function. Of the 47 patients assessable for response, 15 obtained a CR and 15 obtained a PR, for an overall response rate of 68%. The median survival was 14.7 months [34].

To elucidate the role of paclitaxel when added to CG, a large Global International study (EORTC 30987/Intergroup Study) has now been closed to patient accrual (with 610 patients), comparing cisplatin/gemcitabine/paclitaxel with the conventional GC doublet. This trial will shed light on the role of the triplets in the management of advanced urothelial tumors. Whether or not we can improve survival with the newer triple regimen will depend upon the results of this phase III trial.

As shown, throughout the years, many phase III trials have evaluated new combinations such as, gemcitabine/cisplatin, carboplatin/paclitaxel, docetaxel/cisplatin and interferon-α/5-fluorouracil/cisplatin with M-VAC. Unfortunately, in all of these randomized trials, the new regimens have failed to demonstrate superiority in terms of overall survival when compared with the classical M-VAC [34–37].

reducing toxicity: unfit, elderly and renal-impaired patients

One major problem in urothelial tumors is that ‘unfit’ or ‘poor performance status’ patients are often mixed or confused with ‘elderly’ and ‘renal-impaired patients.’ Clinical trials should be designed to clearly distinguish among these three groups of patients. Efficacy data about the use of chemotherapeutic combinations in clearly defined ‘unfit’ patients as effective and safe palliative therapy are still scant and the results of EORTC30986 trial are awaited.

In a mixture of fit/unfit patients several carboplatin-based regimens have been evaluated. The EOCG reported on a 20.6% response rate with the combination of paclitaxel/carboplatin [38]. With gemcitabine-based regimens the response rates are the following: gemcitabine/epirubicin - 46%, gemcitabine/vinorelbine - 47.6% and gemcitabine/carboplatin - 44% [38, 39].

With the aim of diminishing cisplatin toxicity, the platinum-free combination of gemcitabine and paclitaxel combination chemotherapy has been evaluated in also a mixture of fit/unfit...
patients with favorable results, even in pretreated patients [40–45]. Of concern was the pulmonary toxicity observed in the Hoosier group study in which a weekly regimen of this combination (gemcitabine 1000 mg/m² and paclitaxel 110 mg/m² on days 1, 8, and 15 every four weeks) was utilized in unpretreated patients. Overall 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.

Outside of a clinical trial, M-CAVI, carboplatin-gemcitabine, CBDCA-paclitaxel, gemcitabine-taxane, or monotherapy with gemcitabine, CBDCA, or a taxane can be considered for ‘unfit’ patients on an individual basis.

**future directions**

The next logical question to address is how to further optimize therapy. In addition to incorporating the new active agents in two, three or multiple drug combinations, dose intensification of conventional agents, dose-dense sequential administration of new agents or cisplatin-free combinations, several other new approaches are being defined as: chemotherapy optimization using molecular markers predicting chemosensitivity, improvement of delivery/activity of chemotherapy agents like gemcitabine, and the use of the new biologics.

**chemotherapy response predictive factors**

**molecular predictive factors**

Little has been done to date to address the genetic/molecular and growth factor alterations in patients with advanced disease. This represents a major obstacle to therapeutic progress for both metastatic disease and the adjuvant setting [46].

Studies on P-glycoprotein [47], glutathione [48] and metalloproteinase [49] expression in tumor specimens of metastatic urothelial disease have indicated that these parameters could predict resistance and toxicity to chemotherapy.

Alterations in p53 and pRb occur in approximately 50% and 35% respectively of bladder cancers and have been reported to correlate with high grade and stage [50–52]. There are conflicting reports regarding the relationship between chemosensitivity and p53 and several authors suggest that altered expression of p53 may be associated with resistance to M-VAC although others suggest the contrary [53]. Paclitaxel seems to act independently to the presence of p53 mutations [54]. The identification of prognostic and predictive markers has guided the way for a series of ‘first-generation’, biologically-driven trials. One of the lead trials involves the study of M-VAC in patients with organ-condensed bladder cancer based on p53 status. The results of the currently ongoing studies are eagerly awaited. In addition, some studies have shown that the metastatic potential of bladder cancer correlates with the expression of several genes that regulate proliferation (EGF-R) and angiogenesis (bFGF, VEGF, MMP-9 and interleukin-8, some of them being predictors of response. Adding paclitaxel to EGFr directed therapy has produced a synergistic biologic effect on xenographs [55, 56]. It is suggested that advances in molecular research may help to develop reliable tumor markers that enable the clinician a more accurately selection of appropriate therapy for each individual patient based on predicted response. At the moment, none of these molecular markers has been yet widely accepted in routine clinical practice.

**molecular pharmacology predicting response to chemotherapy**

In addition to what is known about the variability of expression of intratumoral determinants of cytotoxic response, there is also an emerging understanding of the role of molecular pharmacology in the prediction of response to chemotherapy. Paradigms developed from the treatment of colorectal malignancy and lung cancer, in which the metabolism of cytotoxic agents is affected by genetic factors, specially the nucleotide repair system, are now being applied to the management of bladder cancer. Some data is emerging in the adjuvant setting [57]. It is clear that the future design of clinical trials that assess novel anticancer treatments will have to take into account the significant differences in drug metabolism systems among individuals and also among population groups [57].

The SOGUG is presently conducting a retrospective analysis on patients treated with either CG or TCG. The study objective is to test the hypotheses of whether the relative mRNA expression of the excision cross-complementing (ERCC1), Ribonucleotide reductase subunit M1 (RRM1), BRCA1, and Caveolin 1 genes (all potentially related to Cisplatin sensitivity) are associated with response and survival in advanced bladder cancer patients treated with cisplatin-based chemotherapy.

**improving chemo delivery/activity**

Phosphorylation of gemcitabine by deoxycytidine kinase is saturable and the optimal infusion dose rate that maximizes amount of gemcitabine triphosphate is 10 mg/m²/min. In a study phase I [58], biweekly constant rate infusion (CRI) of gemcitabine has been feasible and can be given safely up to a dose of 5400 mg/m² in 9 h infusion every 15 days without growth factor support. Activity has been seen in patients pretreated with gemcitabine including one patient with metastatic bladder cancer who received prior standard 30-min gemcitabine treatment and in one prostate cancer patient. Minor response with prolonged disease stabilization has been observed in a renal cancer patient.

**targeted treatments**

Advances in the molecular biology of urothelial malignancies may allow identification of specific genetic lesions and biochemical pathways upon which future therapeutic approaches can be focused.

Her-2/neu is over-expressed in several advanced bladder tumors [59]. Recently, Hussain et al. [60] have reported the activity of the combination of carboplatin, paclitaxel, gemcitabine and trastuzumab, a monoclonal antibody against Her-2/neu, in metastatic Her-2 over-expressing bladder cancer
patients. There were 32 responses (5 complete and 27 partial) with an overall response rate of 72.7%. Time to progression and median survival were 8.5 and 15.2 months, respectively.

Epidermal growth factor receptors (EGFRs), are overexpressed in high-grade invasive tumors. Gefitinib (Iressa®) is a selective orally-active EGFR tyrosine kinase inhibitor, which in preclinical and clinical studies has demonstrated activity in tumors expressing EGFR. Philips et al. [61] have reported the activity of the combination of cisplatin, gemcitabine administered at a fixed dose rate of 10 mg/m²/min and gefitinib in 27 patients with chemo-naïve advanced bladder cancer. Of 24 evaluable patients there were 12 responses for an overall response rate of 50% (95% CI = 29–71%). Median time to progression was 6.9 months (95% CI: 3.8–8.9). Unfortunately this regimen was associated with excessive toxicity, precluding further development.

conclusions
With reduced toxicity, improved quality of life and similar survival to MVAC, gemcitabine/cisplatin is a new standard of care for patients with advanced bladder cancer. Whether or not the activity of the new triplet TCG is superior to the existing care for patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract (TCC) who have received prior chemotherapy. Proc Am Soc Clin Oncol 2003; 22: 408 (abstr 1638).

disclosures
Dr Bellmunt has indicated that he has been an invited speaker of Eli Lilly.

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