Adjuvant chemotherapy of bladder cancer

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Background: Bladder cancer is one of the most common genitourinary cancer. 1/3 of patients present with invasive disease. Radical cystectomy is the standard treatment for patients with muscle invasive disease: although local treatment can be curative, about 50% of patients will develop distant metastases. Optimal treatment for high risk patients includes local and perioperative systemic therapy (adjuvant or neoadjuvant chemotherapy).

Patients and methods: We performed a review of clinical trials and metaanalysis of adjuvant treatment for muscle-invasive bladder cancer.

Results: Data from single published trials of adjuvant chemotherapy (CT) are not univocal, and several methodological problems were found. A recent meta-analysis of individual patient data (IPD) from all eligible published and unpublished trials, found that adjuvant chemotherapy administration provides a significant survival and disease-free survival advantage. Two large, multi-center, randomized trials are on-going to clarify the role of post-operative CT.

Conclusions: A trend in favour of adjuvant chemotherapy comes out from some of the trials reviewed by us and by the metaanalysis performed by the ABC collaborative group. However it is not clear yet which patients might derive the maximum benefit from such an approach and which ones might be safety candidate to deferred treatment, on relapse.

The incoming results of the EORTC trial and of the Italian trial which are currently comparing the value of early vs. deferred treatment of patients at higher risk of relapse will probably provide an adequate answer to this question. Outside clinical trials, the potential benefit of adjuvant chemotherapy should be appropriately weighted versus the putative hazards and decision making appropriately tailored in the individual patients according to the aggressiveness of his/her disease and the presence of comorbidities.

Key words: adjuvant therapy, bladder cancer, muscle-invasive

Urothelial cancer is one of the most common cancer in developed countries: transitional cells carcinoma (TCC) of the bladder accounts for the 90–95% of urothelial tract cancer. About 70% of patients present without lamina propria or muscle invasion, but, on the other hand, 1/3 of patients present with de novo muscle invasive disease. Moreover, the natural history of superficial bladder cancer is not easily predictable.

Local management includes total cystectomy or radical radiotherapy. Radical cystectomy remains the standard of care for the invasive disease and in association with pelvic lymph node dissection provides fundamental prognostic informations through a complete pathological staging: the overall 5-year survival ranging from 60–75% for pT2 tumors to 4–35% for pT4 or node positive tumors (Stein et al. [1]). Despite adequate surgical or radiation treatment, 10–15% of locally-treated patients recur within 6–12 months developing invasive or metastatic disease. Therefore micrometastases are probably present at the time of the local treatment: this support the perioperative use of systemic treatment strategies.

To date, the most commonly chemotherapy combination used both for the treatment of locally advanced and metastatic TCC has been the M-VAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin), which was introduced about 15 years ago since three randomized trials demonstrated the superiority of this regimen in metastatic urothelial cancer compared with single agent cisplatin (Loehrer et al. [2]; Saxman et al. [3]) or with cisplatin, cyclophosphamide and doxorubicin regimen (Logothesis et al. [4]). However the M-VAC regimen is quite toxic, because it is often associated with severe neutropenia, significant mucositis, nausea and vomiting, renal, cardiac, and neurologic toxicities, with a toxic death rate of 3% to 4% (Loehrer et al. [2]; Sternberg et al. [5]). Nevertheless, the results achieved with M-VAC combination chemotherapy in the metastatic disease encouraged the use of this therapeutic regimen in the adjuvant setting as well.

Since a large phase III trial by von der Maase et al., comparing the use of M-VAC versus gemcitabine and cisplatin (GC) in the metastatic disease, found comparable response rates between the two arms but a lower toxicity for GC, the use of this latter combination has been introduced among the treatment options for the treatment of both of metastatic and early bladder cancer (von der Maase et al. [6]).

Adjuvant chemotherapy

Adjuvant chemotherapy approach for TCC has been studied since the late 1980s. Randomized and non-randomized trials
have compared appropriate adjuvant chemotherapy versus observation after local treatment. Overall results are not univocal and only few trials did show a survival benefit for adjuvant chemotherapy (Table 1).

One of the first investigations was conducted by Logothesis et al. [7]. They retrospectively analyzed a population of 71 high-risk patients treated with adjuvant cyclophosphamide, doxorubicin, and cisplatin reporting a significant survival advantage in comparison with a comparable population of patients treated with cystectomy alone. Superimposable results were achieved by Michael et al. in another early non-randomized study [8].

One of the first randomized trials evaluating in a randomized fashion the impact of chemotherapy on disease-free survival (DFS) and survival of completely resected non metastatic bladder cancer patients was reported by Skinner et al. in 1991 [9]. Adjuvant treatment significantly prolonged the DFS (51% vs. 34%). Nodal status at the time of cystectomy was found to be the most important prognostic factor for patients with muscle invasive bladder cancer. Five years OS was also prolonged (44% vs. 39%), but the difference was not statistically significant. Moreover this trial raises several methodological problems: small sample size; variability in treatment regimens and number of cycles; 25% of patients assigned to CT never actually received it; the use of Wilcoxon statistics gives more weight to early differences in survival; drawing conclusion from a subgroup analysis (indeed the advantage in favour of adjuvant CT was evident only in patients with one positive node).

Similar methodological problems are present in the most part of the studies published in the 1990s. In 1992, Stockle et al. published the results of a small trial including 49 patients of whom 26 had been randomized to receive M-VAC/M-VEC (methotrexate, vinblastine, (CMV) and 25 to the control arm. This trial was stopped early because an interim analysis demonstrated a significant advantage for the adjuvant treatment. However, only 18/26 patients randomized to receive CT, actually received it (Stockle et al. [10]). The authors updated their data a few years later, adding 117 non-randomized patients (Stockle et al. [11]). On the intent to treat analysis (ITT) at a median 3.5-year follow-up time 63% of CT-receiving patients were disease-free, compared with 13% of the control arm, with a stronger advantage for node positive patients.

Two of the studies that failed to show a benefit for the adjuvant treatment did not use a platinum-based combination in the experimental arm in comparison with the observation arm, leaving the doubt that the chemotherapy regimen was not appropriate (Richards et al. [12]; Studer et al. [13]). Moreover, the trial by Studer et al. was stopped early because an interim analysis showed a ‘too small’ advantage for the chemotherapy arm. A possible explanation for this result can be found in the small number of patients enrolled (77), thus supporting the hypothesis that the study was underpowered to detect small differences in survival. Another point of criticism may be found also in the selection criteria, given that more than 50% of patients had organ-confined disease (node-positive patients were excluded from the study).

Similarly, in the trial by Bono et al. no advantage was found for the adjuvant cisplatin-based arm but again the size of this trial was too small (83 patients) to disclose an advantage in terms of survival (Bono et al. [14]). Comparable results come from a more recent trial by Otto et al. in which no benefit was showed for the adjuvant treatment (Otto et al. [15]). This trial was comparable in the design to the trial previously reported by Stockle et al. [10] but with M-VEC in place of M-VAC. However, the two trials differed substantially in that all patients originally allocated to control arm in the Otto’s study were scheduled to receive at least 4 cycles of the M-VEC regimen at relapse. This probably accounts for the lack of a survival benefit for the patients assigned to adjuvant chemotherapy.

Another small trial was conducted by Freiha et al. They assigned 25 patients to receive a combination of cisplatin, methotrexate, vinblastine, (CMV) and 25 to observation only. The trial was stopped early because the advantage (freedom from progression) for the chemotherapy arm was too great (median time to progression: 37 months for CMV vs. 12 for

**Table 1. Randomized trials of adjuvant chemotherapy for TCC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Stages</th>
<th>No &amp; treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner et al. (1991)</td>
<td>pT3-4 or N+; M0</td>
<td>91 (44 CISCA; 47 cystectomy alone)</td>
<td>Significant increase in TTP for adjuvant therapy; no significant differences in OS except for subgroups</td>
</tr>
<tr>
<td>Stockle et al. (1992)</td>
<td>pT3b-4a or N+</td>
<td>49 (26 M-VAC/M-VEC; 23 observation)</td>
<td>Stopped early due to a significant increase in DFS for adjuvant therapy</td>
</tr>
<tr>
<td>Studer et al. (1994)</td>
<td>T1 (G2) – T4</td>
<td>77 (37 cisplatin; 40 observation)</td>
<td>No advantage for adjuvant therapy</td>
</tr>
<tr>
<td>Freiha et al. (1996)</td>
<td>pT3b-4, any N; M0</td>
<td>50 (25 CMV immediately after cystectomy; 25 CMV at relapse)</td>
<td>Stopped early because of a significant increase in TTP for adjuvant therapy; not significant differences in OS</td>
</tr>
<tr>
<td>Bono et al. (1997)</td>
<td>T2-T4a, N0, M0</td>
<td>83 (48 CM; 35 cystectomy only)</td>
<td>No benefit for adjuvant therapy</td>
</tr>
<tr>
<td>Otto et al. (2001)</td>
<td>T3, N1-2, M0</td>
<td>108 (55 M-VEC; 53 observation)</td>
<td>No advantage for adjuvant therapy in terms of survival</td>
</tr>
<tr>
<td>Lehmann et al. (2005)</td>
<td>pT3-4a and/or N+</td>
<td>327 (163 CM; 164 M-VEC)</td>
<td>No inferiority of CM; better tolerability for CM</td>
</tr>
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controls). However, no difference in OS was reported between the two arms (Freiha et al. [16]). This was again probably due to the fact that at relapse those patients assigned to the control arm, received salvage chemotherapy, thus influencing the tumor-specific survival difference between the two groups.

More recently a randomized, multicenter, phase III trial has been conducted by Lehmann et al. (Lehmann et al. [17]). These investigators have compared cisplatin plus methotrexate (CM) versus M-VEC achieving similar results in the two arms in terms of TTP (median time to progression: CM 43.4 months vs. M-VEC 49.7 months) and OS (CM 47.1 months; M-VEC 51.8 months). However, also a significant reduction in the incidence of side effects was recorded in the CM, thus encouraging the use of chemotherapy regimens alternative to M-VEC in the adjuvant setting.

In absence of conclusive results, in the last 3 years many systematic reviews have been conducted in the attempt of clarify this specific topic. But the lack of adequate data, did not allow the authors to reach their scope (Sternberg [18]; Juffs et al. [19]; Pectasides et al. [20]; Boyar and Petrylak [21]; Rosenberg et al. [22]).

Data from the first meta-analysis on adjuvant treatment have become recently available (The Advanced Bladder Cancer Meta-Analysis Collaboration [23]). These investigators identified 11 trials, but only 6 could be included, for a total of 498 patients (66% of all patients randomised in all adjuvant chemotherapy trials and 90% of all patients randomised in cisplatin-based adjuvant chemotherapy trials) (Otto et al. [15]; Stockle et al. a [11]; Studer et al. [13]; Freiha et al. [16]; Skinner et al. [9]; Bono et al. [14]). For all of the included trials local treatment was cystectomy and the adjuvant chemotherapy was cisplatin-based (one as a single agent, 5 in combination regimen). Four out of the 6 trials were stopped early: 3 because an interim analysis had favoured chemotherapy (Stockle et al. a [11]; Freiha et al. [16]; Skinner et al. [9]), one because of the opposite reason (Studer et al. [13]). In order to reduce potential bias, data about patients excluded from the original investigators’ analysis were also collected: a meta-analysis of individual patient data (IPD) was thus possible for 493/498 patients.

Survival analysis was based on data from 491 patients: an overall hazard ratio (HR) of 0.75 (95% CI 0.60–0.96) was found, representing a 25% relative decrease in the risk of death for chemotherapy as compared to the control arm (P = 0.003).

Data on DFS were available for 383 patients (trial by Otto et al. could not provide data about recurrence and metastases): an overall HR of 0.68 (95% CI 0.53–0.89), representing a 32% relative decrease in the risk of recurrence for chemotherapy compared with controls, was found (P < 0.0001).

The IPD analysis has allowed the authors to by-pass some of the previous bias of the original trials, such as inappropriate or non-standard statistical analysis, but many others flaws could not be avoided.

Because none of the published studies has been able to show a clear-cut survival benefit in favour of the adjuvant treatment and because the role of chemotherapy administered at the time of first relapse is not clear yet, the EORTC-GU group is conducting a trial designed with the aim of comparing the efficacy of early vs. delayed CT.

This on-going trial is recruiting pT3-4a pN0-1 or pN1 patients who have received radical cystectomy. Patients are randomized to receive chemotherapy immediately after cystectomy or at relapse. The chemotherapy program consists of either 4 cycles of conventional M-VAC, or 4 cycles of accelerated (every 2 weeks) M-VAC, or of 4 cycles of the combination of gemcitabine and cisplatin (GC).

Another trial, sharing the same design, but including also pT2 G3 patients, is similarly underway in Italy under the sponsorship of the National Research Council and the Minister of Health. In this trial the chemotherapy program consists of 4 cycles of cisplatin plus gemcitabine (CG), and includes a further randomization for cisplatin to be administered at day 2 or 15 of each cycle.

conclusions

Bladder cancer is chemosensitive and using chemotherapy perioperatively (neoadjuvant and/or adjuvant) is likely to improve the outcome of local treatment and to decrease the rates of distant metastases.

Although individual trials, published reviews and the meta-analysis show a trend in favour of adjuvant chemotherapy, serious methodological problems overstay: small sample sizes, early stopping of patient entry, variability in chemotherapy regimen, number of cycles and doses, suboptimal therapy, so that current evidence is strongly limited with too few data on which to base reliable treatment decision.

Results from additional appropriately-sized randomized studies are required before a definitive answer can be obtained and patients should be encouraged to participate.

Results from the EORTC and Italian trials will probably clarify whether or not a survival benefit can derive from early treatment of patients at higher risk and which is the most effective and/or less toxic regimen.

Outside clinical trials, on the basis of available data, it seems reasonable to suggest reserving the adjuvant treatment for patients with clinical confined disease that are found intraoperatively to have an extended disease.

In this case, putative benefits should be carefully weighted against putative risks (including chemotherapy lethality) and patients appropriately informed.

disclosures

The authors have indicated no financial relationships with companies whose products are mentioned in this article.

references

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