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Neo-adjuvant and adjuvant chemotherapy in bladder cancer

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introduction

Transitional cell carcinoma of the bladder represents the second most common genitourinary malignancy [1]; the clinical approach to muscle-invasive disease has been modified in the last decade, considering the important role of multidisciplinary team, including surgeon, oncologist and radiotherapist.

In fact, despite relevant progress in surgical management of these patients, the global prognosis remains poor, with about 50% of patients developing metastatic disease.

Moving from these issues, in the two last decades, a big effort has been made in order to evaluate an ameliorating strategy for muscle-invasive bladder cancer [2].

In metastatic setting, chemotherapy obtains about 50% of objective response, with a median progression-free survival of about 8 months and a median overall survival of about 14 months [3, 4]. Given the chemosensitivity of transitional cell carcinoma, chemotherapy has been investigated in preoperative setting.

neo-adjuvant chemotherapy

In the treatment of muscle-invasive disease, preoperatory chemotherapy offers several advantages:

1. no delay in initiating treatment with potential sooner activity on microscopic metastases in patients with chemosensitive disease
2. greater tolerability and compliance in administrating chemotherapy before cystectomy in patients with better performance status
3. an *in vivo* evaluation of chemotherapy activity
4. prognostic information obtained from response to chemotherapy [5].

In the past 20 years many trials concerning the role of neo-adjuvant chemotherapy and the hypothetical improvement in patients outcome have been conducted; most of these studies used platinum-based combination chemotherapy. Unfortunately, all of these trials suffered from a small sample size and a statistical under-powered design and were not able to demonstrate the potential benefit of neo-adjuvant chemotherapy in terms of overall survival.

In 2003, the Advanced Bladder Cancer Meta-analysis Collaboration Group (ABC) published the first report of a meta-analysis on 2688 individual patients' data from 10 randomised trials comparing the addition of a platinum-based chemotherapy with local treatment in invasive transitional cell carcinoma [6]. The ABC meta-analysis showed a beneficial effect of neo-adjuvant chemotherapy; with a median follow-up of 13 years, a 5% absolute survival benefit at 5 years was demonstrated, improving the overall survival from 45% to 50%, for patients who received chemotherapy; moreover, the results concerning disease-free survival, locoregional disease-free survival and metastases-free survival gave support to the evidence of survival benefit; this beneficial effect was observed irrespectively by the type of local treatment and did not vary between patients' subgroups. This benefit was most clear for those trials that used platinum-based combination chemotherapy.

These data were confirmed by subsequent abstracted-data meta-analysis published in 2004, demonstrating an absolute overall survival benefit of 6.5% (from 50% to 56.5%) in favour of neo-adjuvant chemotherapy [7].

In 2005, the ABC published an updated report based on 3005 individual patients' data from 11 randomised trials; these more recent results confirmed the significant benefit in terms of overall survival and progression-free survival favouring neo-adjuvant chemotherapy, providing the best available evidence in support of the use of preoperative chemotherapy in invasive bladder cancer [8].

The benefit of neo-adjuvant chemotherapy was supported by another trial published in 2003. This trial, conducted by the Southwest Oncology Group, randomly assigned 317 patients with locally advanced bladder cancer (cT2 to cT4a) to receive three cycles of neo-adjuvant MVAC (methotexate-vinblastine-doxorubucun-cisplatin) followed by surgery versus radical cystectomy alone. Patients were accrued over a 11-year period. At a median follow-up of 8.7 years, neo-adjuvant chemotherapy showed an advantage in median survival (77 versus 46 months). At 5 years, 57% of the patients in the combination group were alive versus 43% in the cystectomy group ($P = 0.06$). The survival benefit was related to down-staging of the tumour to pT0: 38% of patients in neo-adjuvant group were pathologically free of cancer at the time of surgery, compared with 15% of patients in the cystectomy group ($P < 0.001$) [9].

adjuvant chemotherapy

In the multidisciplinary approach of transistional bladder cancer, adjuvant chemotherapy provides several advantages:

1. pathological staging offering a most accurate prognostic indicator
2. no delay in surgery
3. maximising chance of cure for patients with chemoresistant disease
4. sparing low-risk patients unnecessary toxicity.

As for neo-adjuvant chemotherapy, the same methodological limits regarding the trials conducted in the past two decades exist; in fact; the available results of trials on adjuvant chemotherapy are limited for both number and size of studies.

In 2005, the ABC reported the results of a meta-analysis based on 491 individual patients' data from six randomised trials comparing local treatment followed by adjuvant chemotherapy with local treatment alone in patients with invasive bladder cancer [10]. Chemotherapy consisted in a platinum-based combination chemotherapy, most frequently associated with anthracyclines and methotrexate. Whereas this meta-analysis has a clear methodological limit due to the small number of patients included, the overall hazard ratio for survival of 0.75 indicates a 25% relative reduction in the risk of death for chemotherapy compared with control, showing an absolute improvement in survival of 9% at 3 years. Data on overall disease-free survival indicates an absolute improvement of 12% at 3 years.

A pooled analysis from phase III studies published in 2006 included five trials comparing cystectomy alone with cystectomy followed by chemotherapy; the results of this analysis based on a total of 350 patients, with 36 patients as a median number of patients per arm, favoured the adjuvant approach; in fact, a significant benefit from postoperative chemotherapy was noted both in overall survival and disease-free survival [11].

conclusion

The analysis of data available on perioperative chemotherapy, both in neo-adjuvant and adjuvant setting, in muscle-invasive transitional cell carcinoma, even with the methodological limit discussed above, supports the use of an integrated approach including radical surgery and a platinum-based treatment.

More consistent evidence supports the use of neo-adjuvant chemotherapy; based on these findings, this strategy should be proposed to the patients eligible.

More limited data support the use of adjuvant chemotherapy after local treatment of bladder cancer; although, if inclusion in ongoing clinical trials is not possible, adjuvant chemotherapy represents an option to be discussed with high-risk radically resected patients.

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