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Review—Bladder Cancer

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

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Abstract

Objectives: To update a systematic review and meta-analysis that assesses the effect of neoadjuvant chemotherapy in the treatment of patients with invasive bladder cancer.

Methods: Following a prespecified protocol, we analysed updated individual patient data from all eligible randomised controlled trials that compared neoadjuvant chemotherapy plus local treatment with the same local treatment alone.

Results: Updated results are based on 11 trials, 3005 patients; comprising 98% of all patients from known eligible randomised controlled trials. We found a significant survival benefit associated with platinum-based combination chemotherapy (HR = 0.86, 95% CI 0.77–0.95, $p = 0.003$). This is equivalent to a 5% absolute improvement in survival at 5 years. There was also a significant disease-free survival benefit associated with platinum-based combination chemotherapy (HR = 0.78 95% CI 0.71–0.86, $p < 0.0001$), equivalent to a 9% absolute improvement at 5 years.

Conclusions: These results provide the best available evidence in support of the use of neoadjuvant platinum-based combination chemotherapy.

Keywords: Systematic review; Meta-analysis; Randomised controlled trials; Cancer; Bladder; Chemotherapy

1. Introduction

In 2003, an individual patient data (IPD) meta-analysis of neoadjuvant chemotherapy plus local treatment versus the same local treatment alone in invasive bladder cancer [1] was carried out on behalf of the Advanced Bladder Cancer (ABC) Meta-analysis Collaboration.

This meta-analysis was based on 10 randomised controlled trials (Cortesi E, unpublished and [2–8]) including 2688 patients. This comprised 88% of patients from all known eligible randomised controlled trials, all of which had used platinum either as a single agent or in combination with other drugs. It concluded that neoadjuvant chemotherapy had a beneficial effect, with a 9% relative reduction in the risk of death on chemotherapy compared to that on control. This benefit was most clear for those trials that used platinum-based combination chemotherapy. For these trials, the 13% relative reduction in the risk of death on chemotherapy compared to that on control ($p = 0.016$) was equivalent to a 5% absolute survival benefit at 5 years. Further information about the trials, methods and results can be found in the original paper.

At the time of the original publication, the authors of one unpublished trial [9] felt unable to contribute their data for inclusion in the meta-analysis since at that time it had not been published independently. This trial randomised 317 patients between 1987–1998 to receive neoadjuvant chemotherapy and cystectomy

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or cystectomy alone. The trial used cisplatin (70 mg/m^2) in combination with methotrexate (30 mg/m^2), vinblastine (3 mg/m^2) and doxorubicin (30 mg/m^2) given in three cycles every four weeks. Following publication of the trial, the investigators were able to provide data for inclusion in the meta-analysis. Therefore this meta-analysis is now based on 11 randomised controlled trials and 3005 individuals.

2. Methods

The systematic review and meta-analysis followed a detailed pre-specified protocol (available on request). This included a comprehensive search strategy, trial inclusion criteria, information on data collection and all pre-planned analyses. Further details of inclusion criteria, search strategy, data requested and statistical analysis are available in the original publication [1]. We sought and analysed updated individual patient data from all eligible randomised controlled trials that compared neoadjuvant chemotherapy plus local treatment with the same local treatment alone.

3. Results

We analysed updated individual patient data on 3005 patients from 11 randomised controlled trials, comprising 98% of patients from all known eligible trials. As with the previous analysis, when we grouped the trials according to whether they had used single agent platinum or platinum-based combination chemotherapy, we noted a difference in the effect of chemotherapy between the groups (interaction $p = 0.029$) (Table 1). For overall survival (Fig. 1), there is a significant benefit of platinum-based combination chemotherapy. The combined hazard ratio of 0.86 has changed little from the original analysis and represents a 14% reduction in the risk of death with chemotherapy compared to that on control. However the 95% confidence intervals have narrowed (95% CI 0.77 to 0.95, $p = 0.003$). This is equivalent to an absolute survival benefit of 5%, improving overall survival from 45% to 50% at 5 years. There was no clear evidence of statistical heterogeneity ($p = 0.83$) or inconsistency ($I^2 = 0\%$) between the trial results. However there was not sufficient evidence to reliably determine the effect of single-agent cisplatin on survival. The survival curve for the platinum-based combination chemotherapy trials is given in Fig. 2. We noted no evidence of a difference in the effect of platinum-based combination chemotherapy when the trials were grouped according to whether they had used cystectomy alone, radiotherapy alone or in combination with cystectomy as the local treatment (interaction $p = 0.656$).

Data on overall disease free-survival were available for 10 trials, 2846 patients (1847 events). Again, there was a significant benefit of platinum-based combination chemotherapy (HR = 0.78 95% CI 0.71–0.86, $p < 0.0001$) with a difference in the effect of chemotherapy between groups of trials using single-agent and platinum-based combination chemotherapy (interaction $p = 0.024$) (Table 1). Data on locoregional disease-free survival and metastases-free survival were not provided for the additional trial and so these analyses could not be updated from the original publication.

The inclusion of the additional trial has confirmed that there is no strong evidence of a differential effect of neoadjuvant chemotherapy in any of the patient subgroups defined by age, sex, clinical T or N category or performance status. Analyses of grade, tumour diameter or renal function could not be updated. Further details are available on request.

4. Discussion

Inclusion of the additional trial means that we have been able to include 98% of patients from all known randomised trials. The results of this additional trial are consistent with those in the original meta-analysis. Its inclusion here strengthens the original results, increasing the power in the analysis and our confidence in the

Table 1
Results for survival and disease-free survival overall and for trials grouped by chemotherapy type

Endpoint	Chemotherapy type	Number of patients/events	HR (95% CI)	Effect *p*-value	Absolute benefit at 5 yrs (95% CI)	Interaction *p*-value
Overall survival	Single agent platinum	261/376	1.15 (0.90–1.47)	0.26	−5% (−14% to 4%)	
	Platinum based combinations	1430/2433	0.86 (0.77–0.95)	0.003	5% (2% to 9%)	0.029
	All trials	1691/2890	0.89 (0.81–0.98)	0.022	4% (0% to 7%)	
Disease-free survival	Single agent platinum	166/217	1.14 (0.83–1.55)	0.42	−5% (−16% to 7%)	
	Platinum based combinations	1681/2629	0.78 (0.71–0.86)	<0.0001	9% (5% to 12%)	0.024
	All trials	1847/2846	0.81 (0.74–0.89)	<0.0001	8% (4% to 11%)	

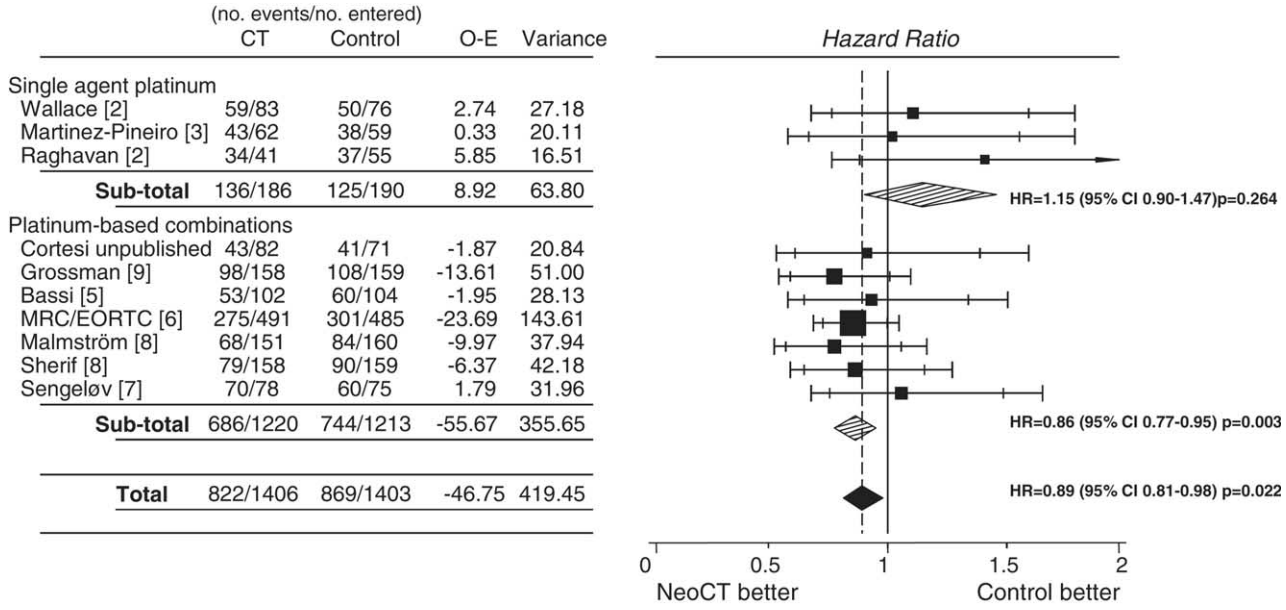

Fig. 1. Hazard ratio plot for overall survival CT = chemotherapy. O-E = observed minus expected events. Each trial is represented by a square, the centre of which gives the hazard ratio for that trial. Size of the square is proportional to the information in that trial. Ends of horizontal bars denote the 99% CI and inner bars mark the 95% CI. Trials are ordered chronologically by start date (oldest first). The black diamond gives the overall hazard ratio for the combined results of all trials; the centre denotes the hazard ratio, the extremities the 95% CI. The shaded diamonds denote the hazard ratios for the trial groups; the centre denotes the hazard ratio, the extremities the 95% CI. Single-agent platinum: Heterogeneity $Chi^2 = 1.11$ ($p = 0.57$); Inconsistency $I^2 = 0\%$ Platinum-based combinations: Heterogeneity $Chi^2 = 2.81$ ($p = 0.83$); Inconsistency $I^2 = 0\%$ All trials: Heterogeneity $Chi^2 = 8.67$ ($p = 0.57$); Inconsistency $I^2 - 0\%$.

results. We therefore report a more precise estimate of the effect of neoadjuvant chemotherapy in the treatment of patients with invasive bladder cancer. This benefit remains clearer for those trials that used platinum-based combination chemotherapy, with an absolute benefit in survival of 5% at 5 years, consistent across all patient subgroups.

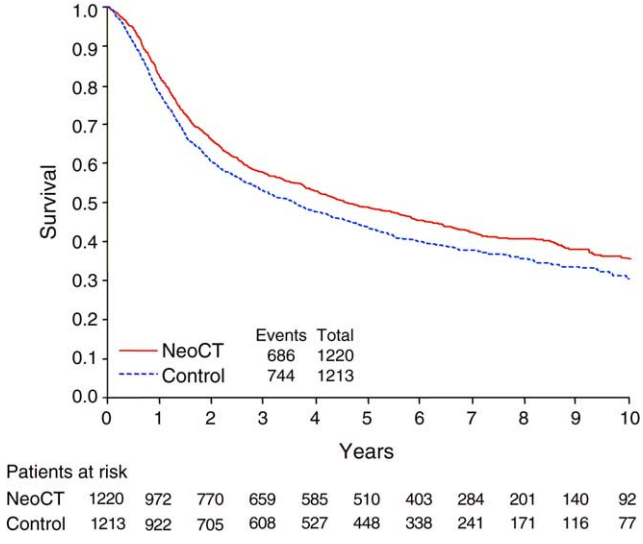

Fig. 2. Overall survival curve (platinum based combination chemotherapy trials only).

5. Conclusions

This meta-analysis provides the best available evidence on which to base treatment decisions in patients with invasive bladder cancer. Platinum-based combination chemotherapy continues to show a clear and modest benefit for survival and disease-free survival. Neoadjuvant platinum-based combination chemotherapy therefore remains the treatment against which all new treatments for invasive bladder cancer should be judged.

Contributors: All aspects of the meta-analysis were carried out under the auspices of the ABC group. H. Abol-Enein, P. Bassi, M. Boyer, C.M.L. Coppin, E. Cortesi, H.B. Grossman, R.R. Hall, A. Horwich, P.-U. Malmström, J.A. Martinez-Piñeiro, L. Sengeløv, A. Sherif, D.M.A. Wallace, collated and supplied the individual patients' data, contributed to the discussions of the results and commented on the drafts of the report. A.V. Bono, P.J. Goebell, S. Groshen, F.M. Torti, contributed to the discussions of the results and commented on the drafts of the report. The project was organised by the Advisory Group, N.W. Clarke, J.T. Roberts, R. Sylvester, the Secretariat, M.K.B. Parmar, L.A. Stewart, J.F. Tierney, C.L. Vale, who were responsible for formulating the questions, developing the protocol and discussing the preliminary results.

The secretariat, M.K.B. Parmar, L.A. Stewart, J.F. Tierney, C.L. Vale, were responsible for receiving, checking and analysing data. C.L. Vale, managed the project and drafted the report, with detailed input from J.F. Tierney, L.A. Stewart, M.K.B. Parmar, None of these authors have declared any conflict of interest in connection with this research.

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Editorial Comment

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Investigators from the Medical Research Council Trials Units have published in this issue of European Urology the results of a very important meta-analysis of neoadjuvant chemotherapy in localised bladder cancer [1]. They conclude that the results of this study provide the best evidence to support the use of cisplatin-based neoadjuvant chemotherapy before local treatment, either radical cystectomy or curative radiotherapy, in T2–4a N0 urothelial cancer of the bladder. This conclusion is based on a well conducted meta-analysis on 3005 updated individual patients data issued from 11 randomised controlled clinical trials. The clinical benefit is a 5% absolute improvement in 5-year survival. The results are convincing, but one may ask if they may be generalised to the whole patients population in the routine treatment of invasive bladder cancer. For this purpose a review of inclusion criteria and patients characteristics has been made in the three major trials of this study [2–4] which represent 1913 out of 3005 patients (64%). It has been focused on age, Performance Status (PS) and renal function evaluation and compared to data from the Surveillance, Epidemiology and End Results (SEER) data base of the National Cancer Institute [5] and to a large series of patients who were treated by cystectomy [6]. In the SEER patients population, age groups are: <55 years: 12.7%, 55–64: 16.5%, 65–74: 29.8%, 75–84: 31.4% and >84: 10.9% of the patients with bladder cancer [5]. It is noteworthy that median age in SEER bladder cancer patients population is 68 years, 66 in the cystectomy series [6], 65 in the Nordic trials [4], 64 in the International trial [2] and 63 in the US trial [3]. Furthermore patients older than 80 are not represented in the chemotherapy trials, while they represent at least 5% of patient in the cystectomy group and more than 10% of patients in the SEER data base. The majority of patients who were enrolled in the neoadjuvant chemotherapy trials had a PS of 0 or 1. Patients with PS 2 or 3 represent 4%, 0% and is unknown in the international [2], US [3] and the Nordic [4] trials respectively. In order to made a parallel it is noteworthy that in a population of elderly patients (age >70 years) with

different stages prostate cancer, the proportion of patients with PS of 0/1 is only 37%, and the proportion of patients who are fully independant is 13% [7]. Eligibility criteria concerning renal function before chemotherapy are not described in the Nordic trials [4], but they are detailled in the International [2] and US [3] trials: creatinine clearance had to be $>$ 50 ml/mn in both trials. A prospective study in a healthy persons population has shown that creatinine clearance is $<$50 ml/mn in 12.6% and 47.3% of patients aged 60 to 69 and $>$70 years respectively [8]. It is thus very unlikely that patients older than 70 years may receive neoadjuvant chemotherapy when PS and renal function are taken into account. Furthermore this elderly patients population is under-represented in the trials, then no firm conclusions may be drawn from the meta-analysis in this setting.

In conclusion this meta-analysis demonstrates very clearly a 5% survival advantage of neoadjuvant cisplatin-based chemotherapy in T2–4a N0 bladder cancer patients before local curative therapy. Nevertheless these results are valid in a selected patients population who have a PS 0/1, a creatinine clearance $>$50 ml/mn and who are less than 70 years old. The 30 to 40% proportion of patients who are actually older than 70 years, those with PS 3/4 or impaired renal function are unlikely to benefit from this treatment strategy. As they represent more than a third of patients with localised bladder cancer, their treatment requires further specific studies.

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