Annals of Oncology 25: 1930–1934, 2014
doi:10.1093/annonc/mdu092
Published online 25 February 2014

Adjuvant chemotherapy for bladder cancer—why does level 1 evidence not support it?

D. Raghavan*, A. Bawtinhimer, J. Mahoney, S. Eckrich & S. Riggs

Carolinas HealthCare System, Levine Cancer Institute, Charlotte, USA

Received 23 December 2013; revised 23 January 2014; accepted 10 February 2014

Neoadjuvant cisplatin-based combination chemotherapy provides a 5% increase in cure rate, an increase in median survival of about 3 years, and statistically significant and clinically relevant increments in overall survival for patients with invasive bladder cancer. Despite compelling level 1 data, it has become quite clear that facts that are similar to those that changed the paradigm of treatment of breast cancer in the 1970s have not had a similar influence on patterns of practice in bladder cancer care. Instead of using this proven approach, cystectomy alone or surgery followed by adjuvant chemotherapy is often used as a functional alternative for patients with deeply invasive and/or node-metastatic disease discovered at radical cystectomy. However, there is no well-powered level 1 evidence to support routine adjuvant chemotherapy for invasive bladder cancer, and some randomized trials have shown inferior outcomes. There is a clear need for a well-designed, randomized trial that tests the utility of adjuvant chemotherapy for invasive bladder cancer, but until that has been completed, neoadjuvant chemotherapy followed by definitive local treatment should be the standard of care for invasive bladder cancer.

Key words: adjuvant, bladder cancer, meta-analysis, neoadjuvant, randomized trials, chemotherapy

introduction

More than 30 years ago, the concept of neoadjuvant chemotherapy was applied to invasive bladder cancer in phase II trials [1–3], and was then tested in randomized studies [4]. Despite encouraging early data that were confounded by stage migration from the introduction of the CT scan into urological practice, it became obvious that single-agent cisplatin was not sufficiently effective to provide a clinically useful survival benefit. In view of the objective evidence of tumor downstaging, the concept was not abandoned, and multiagent neoadjuvant regimens (drawn from the metastatic setting) were assessed in phase II trials, using cisplatin, methotrexate and vinblastine, with or without doxorubicin [5–7]. High response rates in phase II trials led to large randomized trials, and two major studies demonstrated a clinically relevant survival benefit [8–10]. There was an absolute survival increase of 5%–7% and, in one study [10], the increase in median survival was about 3 years. A meta-analysis of all published and unpublished data also showed a 5% absolute improvement in overall survival from neoadjuvant chemotherapy [11].

Despite these compelling level 1 data, many patients with invasive bladder cancer are not treated with neoadjuvant chemotherapy, despite the fact that the survival benefit is similar to that which changed the paradigm of treatment of breast cancer in the 1970s. Many clinicians continue to avoid the use of any chemotherapy for invasive bladder cancer or alternatively deliver adjuvant chemotherapy as a functional alternative for patients with deeply invasive and/or node-metastatic disease discovered at radical cystectomy [12–15]. It thus seems timely to consider whether there is any real basis for the routine use of adjuvant cytotoxic chemotherapy for invasive bladder cancer in clinical practice.

randomized adjuvant studies

Based on extensive data from the treatment of locally invasive cancers of breast, colon, prostate and lung, it has seemed likely that classical adjuvant chemotherapy, in which systemic treatment is delivered after completion of tumor resection, *should* improve overall survival for patients with muscle invasive bladder cancer. Nonrandomized, phase I–II studies indicated the feasibility of delivering adjuvant chemotherapy after definitive local treatment, but had little value in defining whether adjuvant chemotherapy actually works, due to problems of case selection bias, duration of follow-up, and the heterogeneity of patient populations.

However, starting more than 20 years ago, investigators at the University of Southern California [16], University of Mainz [17, 18] and Stanford University [19] attempted to conduct

*Correspondence to: Dr Derek Raghavan, Carolinas HealthCare System, Levine Cancer Institute, Suite 3100, 1021 Morehead Medical Drive, Charlotte, NC 28204, USA. Tel: +1-980-442-3112; Fax: +1-980-442-3101; E-mail: derek.raghavan@carolinashealthcare.org

randomized trials that tested the hypothesis that adjuvant chemotherapy is of benefit for patients with invasive bladder cancer. An important point to emphasize is that any adjuvant therapy that has significant anticancer effect is likely to produce a *disease-free* survival increment, when compared with no-treatment or placebo. Explained simply, an active agent will reduce the extant residual population of tumor cells by some logs of cell kill, but this does not necessarily translate into an *overall* survival benefit, particularly if there are innately resistant cells present. Although many different tumor types have been exposed to a range of adjuvant therapies, there is surprisingly little evidence to support an increment in overall survival or cure rates beyond the setting of adults with breast and colon cancers.

The early trials were somewhat flawed in design and execution [16–19]. Skinner et al. [16] planned a study to test the use of adjuvant cisplatin, doxorubicin and cyclophosphamide after radical cystectomy, and reported a significant delay in time to progression ($P = 0.001$) and a median survival increment from 2.4 years in the control group to 4.3 years in the treated group. However, although this study was visionary in concept and design, there were major flaws in execution, including failure to obey randomization, and the modification of chemotherapy regimens employed, rendering it a much less useful test of true utility of adjuvant chemotherapy [20]. Nonetheless, this study proved to be very important as it provided clinical material for a series of *post hoc* studies of P53 mutation and its impact on prognosis and cytotoxic response [21, 22]. That noted, subsequent studies did not confirm the initial observations of the USC group (see below).

The seminal and oft-quoted German study that reported a survival benefit from adjuvant methotrexate, vinblastine, epibubicin and cisplatin (MVEC) actually compared adjuvant chemotherapy after radical cystectomy to a randomization in which salvage chemotherapy was not routinely used [17]. As a result, it actually tested the utility of chemotherapy *per se*, rather than focusing on adjuvant use [17, 18]. The interpretation was further confounded by the compilation of a set of nonrandomized trial patients into the initial series in order to increase clinical numbers and follow-up [18], a fundamental flaw of design and interpretation.

Torti's team at Stanford executed a well-structured trial that tested the utility of adjuvant MVAC chemotherapy after cystectomy [19]. However, as disease-free survival was the primary end point, a design flaw as noted above, the Data and Safety Monitoring Committee closed the study early, with only 55 randomized cases, when that end point had been met. Unfortunately, no statistically significant impact on *overall* survival was identified (median survival 63 versus 36 months, $P = 0.32$), and the authors concluded that salvage of relapsed patients may have explained this outcome. While this may also have been because of the size of the study at the time of closure, this study still did not prove the utility of adjuvant therapy in delivering an overall statistically significant increment in survival. An unexplained feature was that the mean and median durations of follow-up, respectively, were longer for the control group, allowing more time for the occurrence of events.

We recently reported a randomized, international trial [23] which tested the hypotheses that P53 mutation connotes for worse prognosis, and that bladder cancers expressing mutant P53 are more likely to be responsive to adjuvant chemotherapy [22]. This study may be relevant to the conceptual issue under discussion as it failed to confirm the prognostic significance of mutant P53, but also showed no evidence at all to support the concept that adjuvant MVAC chemotherapy has any impact on overall survival [23]. Of importance, this trial recruited patients with pT1-2 disease, and thus does not reflect fully the biology of T3-4 bladder cancer extending beyond the bladder. However, while this relates only to P53 mutant, organ-confined disease, the absence of survival benefit in a contemporary and well-powered study should not be ignored.

In a randomized, controlled study of adjuvant gemcitabine–cisplatin after radical cystectomy, Cognetti et al. [24] were unable to demonstrate any impact on survival from the cytotoxic regimen for patients with pT2-4, N0-1 disease, again a somewhat different population from some of the other trials listed above. Although the study was underpowered, with only 194 cases, it is important to note that overall survival was *inferior*, in absolute terms, for the chemotherapy arm [hazard ratio (HR) for mortality 1.29; 95% confidence interval (CI) 0.84–1.99; $P = 0.24$] [24]; this may have been influenced by the larger number of N+ cases in the control arm, although this was not statistically significant.

Although still not published in peer-reviewed form, Paz-Ares and the SOGUG investigators reported a randomized trial assessing the utility of their adjuvant regimen of gemcitabine–cisplatin–paclitaxel at the Annual Scientific Meeting of the American Society of Clinical Oncology in June 2010 [25]. Although the study result favored adjuvant chemotherapy, it was relatively underpowered, and without a peer-reviewed final report, it is premature to view the results as definitive. Of note, early results reported in abstract form from this group, regarding the utility of this regimen for metastatic disease, was considerably softened in final peer-reviewed form after the data had matured.

When one considers a collection of randomized trials without statistical *post hoc* manipulation (Table 1), it is difficult to become excited about the utility of adjuvant chemotherapy.

Adding confusion to the debate, there has been an increasing general trend toward mining of large databases, with the attempt to extract useful data by comparison against large historical datasets instead of using randomized trial design. While this strategy has some merit, volume of cases does not necessarily overcome case selection and treatment selection biases. Recently, Svatek et al. [26] collected 932 patients who received adjuvant chemotherapy, which was claimed to achieve 'improved survival', with a HR of 0.83 (95% CI 0.72–0.97). They noted that the impact was significantly modified by individual risk of disease progression, with the most benefit derived by patients with T3-4 and node-positive disease. Once again, the level of case selection bias was not addressed, and there was no central pathology or staging review.

Another issue has been the misapplication of the meta-analytic statistical tool to this subject. Initially, Vale [27] presented a meta-analysis of extant studies, which was heavily influenced by the German study which compared cystectomy (and no chemotherapy at any time) versus cystectomy followed by elective, planned adjuvant chemotherapy. This study design biased the outcome heavily in favor of adjuvant chemotherapy. This error

Table 1. Randomized adjuvant trials in bladder cancer

Series	Control (number)	Adjuvant (number)	Regimen	Problems
Skinner et al. [16]	52	50	CAP	Low power, poor protocol adherence
Stockle et al. [17, 18]	23	26	MVEC	Many control patients with no chemo ever; addition of nonrandomized cases in one paper
Freiha et al. [19]	28	27	MVAC	Early closure, end point DFI
Stadler et al. [23]	56	58	MVAC	P53 mutant; inadequate numbers; early closure; control arm superior (NS)
Cognetti et al. [24]	92	102	GC	Underpowered, control arm superior (NS)

CAP, cyclophosphamide, doxorubicin, cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; MVEC, methotrexate, vinblastine, epirubicin, cisplatin; DFI, disease-free interval; GC, gemcitabine, cisplatin; NS, nonsignificant.

has been compounded subsequently by others [28], who have made similar errors, adding *post hoc* analysis of unplanned stratifications of node-positive patients (further biasing interpretation) and including series that have only appeared in abstract format. While meta-analysis of large datasets can sometimes be useful, it is a tool that can easily be confounded by inclusion of nonrandomized datasets, patients who have not been managed per protocol, or with small, noncomparable series with widely overlapping CIs, which do not actually represent patients from the broad population. Meta-analysis is useful for hypothesis generation, but often confounds the ability of clinicians to effect well-constructed, randomized trials because of poor clinical and statistical construction leading to severe misinterpretation of data.

cystectomy without chemotherapy

An important consideration that appears to have been neglected in the assessment of the utility of adjuvant chemotherapy is that there are well delineated 10-year survival rates as high as 40% and 30%, respectively, for patients with pT3-4 disease [29–31] and even for proven lymph node metastases [29–31]. Added factors, such as lympho-vascular invasion, grade, presence of hydronephrosis, anemia and gene expression, may allow further refinement of prognostication [32]. This serves to underscore the importance of randomized comparison in the accurate assessment of the utility of adjunctive therapies for this disease, and the potential impact of case selection biases in interpretation of nonrandomized, historically controlled studies, irrespective of their size.

cost considerations

More than 50 000 men and 18 000 women are diagnosed with bladder cancer in the United States each year [32], and thus one can assume that there are more than 12 000 new cases of invasive bladder cancer present annually, with perhaps another 2000–3000 representing progression from nonmuscle invasive disease. These figures can lead to very high overall treatment costs for the community, considering the costs of the employed drug regimens, drug administration, inpatient services and potential hospitalization due to treatment complications, such as febrile neutropenia [33].

If one considers only drug costs, three 28-day cycles of the standard MVAC regimen cost ~$11 000, and the actual levied charge is influenced by many factors, including contractual obligations with payers, demographic of patients (including proportion of patients with no insurance at all) and many other factors. If one constructs a conservative, theoretical algorithm based on three cycles of adjuvant MVAC chemotherapy delivered to 12 000 cases per year (representing less than the number of new cases plus relapsed noninvasive disease), and includes the costs of drugs, drug delivery, whether in hospital or an office setting, and compounds this by the potential for 10%–20% of patients to require inpatient admission for complications of care, it is clear that adjuvant chemotherapy could potentially cost the United States healthcare system more than $140 000 000 per year, or more, depending on the neutropenia management regimens employed [33]. Although unproven in randomized trials, it appears that gemcitabine–cisplatin is often used as an alternative to MVAC in this setting; while the use of four cycles is somewhat less expensive, the potential for myelosuppression and/or febrile neutropenia is higher, and the difference in cost is likely to be small.

Thus, it would seem rational to require unequivocal, level 1 evidence of an overall survival benefit, rather than resorting to rhetoric and statistical gamesmanship, before expending such a large sum each year. It is not clear that such a randomized trial can be completed, in view of the current perceptions in the medical community about adjuvant chemotherapy for bladder cancer. The courageous attempt by the European Organization for the Research and Treatment of Cancer to test this hypothesis in a well-designed, randomized clinical trial (NCT00028756) was confounded by poor accrual, and the study was eventually terminated early and before any definitive conclusions could be drawn.

conclusions

Despite the rhetoric and some invalid comparisons that have been published, there is still no level 1 evidence to demonstrate an overall survival benefit from adjuvant chemotherapy for invasive bladder cancer after cystectomy. It seems that the practice

community has been heavily influenced by nonrandomized or historically controlled studies, or flawed meta-analyses, that imply improved outcome, but which are heavily influenced by case or treatment selection bias, stage migration and changes in patterns of supportive and salvage therapy.

In contrast, there is unequivocal evidence that neoadjuvant chemotherapy improves overall survival, with studies showing quite clearly that the proportion of patients with long-term overall survival after radical cystectomy, with or without node dissection, can be increased, and that median survival is increased by around 3 years. Patients with locally advanced cancers of breast, colo-rectum and prostate have received adjuvant chemotherapy for decades, based on similar outcomes, and more recently, adjuvant therapy has found a role in lung cancer. In the setting of bladder cancer, it is neoadjuvant chemotherapy that has been proven to improve survival, and yet this approach has not become the standard of care. Surely, our patients are entitled to the benefits of 30 years of meticulous clinical research instead of a series of anecdotal reports, confounded by hype, rhetoric and misinterpretation of data.

The final important issue is to consider how progress should be made. The field of biomarker research, while interesting and replete with early-phase studies, has not yet identified reliable prognostic markers that identify candidates for more aggressive therapy. This clearly is an area that requires additional focus. In addition, the past two decades have been quite disappointing with respect to the introduction of novel therapies that actually have an impact on survival in bladder cancer. Thus, for the time being, we suggest that it behooves the cooperative cancer trial groups to collaborate in a definitive, randomized clinical trial that tests the utility of adjuvant treatment of high-risk disease, perhaps adding important prognostic and biomarker studies, and that clinicians should accept the realities discussed above and refer their patients for treatment in these studies.

disclosure

The authors have declared no conflicts of interest.

references

1. Raghavan D, Pearson B, Coorey G et al. Intravenous cisplatinum for invasive bladder cancer: safety and feasibility of a new approach. Med J Aust 1984; 140: 276–278.
2. Raghavan D, Pearson B, Duval P et al. Initial intravenous cis-platinum therapy: improved management for invasive high risk bladder cancer? J Urol 1985; 133: 399–402.
3. Soloway MS, Ikard M, Scheinberg M et al. Concurrent radiation and cisplatin in the treatment of advanced bladder cancer: a preliminary report. J Urol 1982; 128: 1031–1033.
4. Wallace DMA, Raghavan D, Kelly KA et al. Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. Br J Urol 1991; 67: 608–615.
5. Scher HI, Yagoda A, Herr HW et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. J Urol 1988; 139: 470.
6. Schultz P, Herr HW, Zhang ZF et al. Neoadjuvant chemotherapy for invasive bladder cancer: prognostic factors for survival of patients treated with M-VAC with 5-year follow-up. J Clin Oncol 1994; 12: 1394.
7. Fossa SD, Harland SJ, Kaye SB et al. Initial combination chemotherapy with cisplatin, methotrexate and vinblastine in locally advanced transitional cell carcinoma —response rate and pitfalls. MRC Subgroup in Advanced Bladder Cancer (on behalf of the MRC Urological Working Party). Br J Urol 1992; 70: 161–168.
8. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International Collaboration of trialists. Lancet 1999; 354: 533.
9. Griffiths G, Sylvester R, Hall RR et al. for International Collaboration of Triallists. International phase III trial assessing neoadjuvant cisplatin, methotrexate, vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011; 29: 2171–2177.
10. Grossman HB, Natale RB, Tangen CM et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003; 349: 859–866.
11. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003; 361: 1927–1934.
12. David KA, Milowsky MI, Ritchey J et al. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. J Urol 2007; 178: 451–455.
13. Porter MP, Kerrigan MC, Donato BM et al. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. Urol Oncol 2011; 29: 252–258.
14. Miles BJW, Fairey AS, Eliasziw M et al. Referral and treatment rates of neoadjvuant chemotherapy in muscle-invasive bladder cancer before and after publication of a clinical practice guideline. Can Urol Assoc J 2010; 4: 263–267.
15. Raj GV, Karavadia S, Schlomer B et al. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. Cancer 2011; 117: 276–282.
16. Skinner DG, Daniels JR, Russell CA et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 1991; 145: 459–464.
17. Stockle M, Meyenburg W, Wellek S et al. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy: results of a controlled prospective study. J Urol 1992; 148: 302–307.
18. Stockle M, Wellek S, Meyenburg W et al. Radical cystectomy with or without adjuvant polychemotherapy for non-organ-confined transitional cell carcinoma of the urinary bladder: Prognostic impact of lymph node involvement. J Urol 1996; 48: 868–875.
19. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996; 155: 495–500.
20. Raghavan D. Editorial comment: the role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 1991; 145: 459–467.
21. Esrig D, Elmajian D, Groshen S et al. Accumulation of nuclear p53 and tumor progression in bladder cancer. N Engl J Med 1994; 331: 1259.
22. Cote R, Esrig D, Groshen S et al. p53 and the treatment of bladder cancer. Nature 1997; 385: 123.
23. Stadler WM, Lerner SP, Groshen S et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on P53 status. J Clin Oncol 2011; 29: 3443–3449.
24. Cognetti F, Ruggeri EM, Felici A et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian multicenter, randomized phase III trial. Ann Oncol 2012; 23: 695–700.
25. Paz-Ares L, Solsona E, Esteban E et al. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: results of the SOGUG (Spanish Oncology Genito-Urinary Group) 99/01 study. J Clin Oncol 2010; 28 (Suppl): 7s (Abstr LBA4518).
26. Svatek RS, Shariat SF, Lasky RE et al. The effectiveness of off-protocol adjuvant chemotherapy for patients with urothelial carcinoma of the bladder. Clin Cancer Res 2010; 16: 4461–4467.
27. Vale CL. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboratoin. Eur Urol 2005; 48: 189–201.

28. Leow JJ, Martin-Doyle W, Rajogopal PS et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 2013; pii: S0203-2838(13)00861-0, Epub Ahead of Print.
29. Stein JP, Lieskovsky G, Cote R et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001; 19: 666.
30. Vieweg J, Gschwend JE, Herr HW et al. Pelvic lymph node dissection can be curative in patients with node positive bladder cancer. J Urol 1999; 161: 449.
31. Power NE, Kassouf W, Bell D et al. Natural history of pT3-T4 or node positive bladder cancer treated with radical cystectomy and no neoadjuvant chemotherapy in a contemporary North-American multi-institutional cohort. Can Urol Assoc J 2112; 6: E217–E223.
32. Raghavan D, Shipley WU, Garnick MB et al. Biology and management of bladder cancer. New Engl J Med 1990; 322: 1129–1138.
33. Michels SL, Barron RL, Reynolds MW et al. Costs associated with febrile neutropenia in the US. Pharmacoeconomics 2012; 30: 809–823.