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Muscle Invasive Bladder Cancer: To Cystectomise or Not? The Role of Neoadjuvant Chemotherapy

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Abstract

Background: Bladder cancer is one of the most common cancers in the western world with associated significant mortality. Once proven to be muscle invasive, radical therapy is required. Neoadjuvant chemotherapy prior to radical treatment has been present for at least three decades.

Objective: We review the literature associated with clinical and cost effectiveness related to neoadjuvant chemotherapy for muscle invasive bladder cancer.

Design: literature review

Setting/ Participants/ Intervention: none applicable.

Outcomes Measures: papers related to search terms of neoadjuvant chemotherapy, muscle invasive bladder cancer, clinical and cost effectiveness.

Results: From the literature review, the benefits of neoadjuvant chemotherapy for muscle invasive bladder cancer are wide ranging. This includes a greatly improved response rate including compete response and improved survival rate. Potential disadvantages of NAC include less accurate staging, delay in curative surgery (risk greater if delay > 12 weeks) in none-responders and a well-known fact that none responders will fare worse later on.

Conclusions: In conclusion neoadjuvant chemotherapy followed by radical therapy is the gold standard for muscle invasive bladder tumours for patients sufficiently fit despite cost effectiveness. As yet, this intervention has not been examined by NICE. However, there are many unanswered questions. Patient summary: Whilst neoadjuvant chemotherapy remains the gold standard therapy for muscle invasive bladder cancer, it has not yet been approved by NICE, and a number of questions are raised.

Keywords: Muscle invasive bladder cancer; Neoadjuvant chemotherapy; Clinical effectiveness; Cost effectiveness

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Introduction

Bladder cancer is the fifth most common cancer in the Western world, yet only seventh in the ranking of cancer related mortality [1]. Transitional cell carcinoma represents more than 90%. The majority are superficial disease but 40% will become muscle invasive [1]. This has different biological behaviour to superficial disease and is prognostically important due to the metastatic potential [2,3]. Despite local therapy with cystectomy and/or radical radiotherapy, the 5-year survival rate of patients with muscle invasive transitional cell carcinoma, is approximately 50% [4-6]. 10–25% will occur in association with relapsed superficial bladder cancer [7]. Due to the unsatisfactory 5 year survival rates post cystectomy for muscle invasive urothelial tumours (5 year survival 60% for patients with T2, 50% with T3a, and 15% with T3b tumours) require strategies to improve prognostic outcomes [8]. Neoadjuvant chemotherapy has been used in management of muscle invasive bladder cancer. We aim to review management of bladder cancer, EAU and NICE guidance, with clinical and cost effectiveness of neoadjuvant treatment.

The Rationale for Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy treats subclinical disease and improves survival [9]. It uses systemic drugs prior to the radical traetment. Advantages of neoadjuvant chemotherapy include early treatment of micrometastatic disease, assessment of chemo-sensitivity of tumour response *in vivo* [7,8], more effective delivery of chemotherapy before surgical disturbance, to allow bladder

preservation, tumour down staging, to prevent tumour cells from settling, to reduce tumour size and to increase survival duration [8]. Criteria for neoadjuvant chemotherapy include, having a T2–T4a N0 tumour, in good general health (PS 0–1), with good renal function (creatinine clearance >50 ml/min) [10]. Radical cystectomy and pelvic lymphadenectomy have been the cornerstone treatment for muscle-invasive bladder cancer [11]. Despite negative preoperative staging, pelvic lymphadenectomy and cystectomy for bladder cancer reveal a high percentage of unsuspected nodal metastases (24%) that have a 25% chance for long-term survival [11]. Lymphadenectomy ensures a low pelvic recurrence rate even in lymph node-positive patients, and patients with locally advanced cancer have a 56% probability of 5-year recurrence-free survival [11].

Neoadjuvant chemotherapy: clinical effectiveness

Initially cisplatin based therapy was used in the 1980s. This demonstrated a 60% response rate including 10% with a complete response [12]. This has also been shown in metastatic disease with up to 60% demonstrating clinically complete response [13]. The MVAC combination, (methotrexate, vinblastine, doxorubicin and cisplatin) demonstrated an overall and progression free survival benefit over cisplatin alone [14,15]. In the 90s, a randomized trial comparing standard MVAC to GC (gemcitabine plus cisplatin). Both regimens showed nearly identical response rates and median survival rates [16].

Several phase III trials and meta-analyses have been published. In Europe combination chemotherapy, CMV (cisplatin, methotrexate and vinblastine) or no chemotherapy before local treatment, surgery or radiotherapy alone was examined. 428 patients underwent cystectomy, the complete response rate (pT0) was higher in the chemotherapy arm (32% versus 12%). With a median follow-up of 8 years, there was a statistically significant 16% reduction in the risk of death corresponding to an increase in 10-y-ear survival from 30% to 36% with CMV [17].

European Organisation for Research and Treatment of Cancer (EORTC) examined CMV [18]. Loco-regional treatment included cystectomy or radiotherapy. A survival increase of 5.5% for the chemotherapy group was demonstrated. The pT0 rate was 32% for patients who received a cystectomy (57%).

The South West Oncology Group (SWOG) study examined methotrexate-vinblastine-cisplatin plus doxorubicin (MVAC) vs. no chemotherapy before radical cystectomy. The pT0 response rate was higher in the chemotherapy arm (38% versus 15%). An overall survival improvement was reported (77 months versus 46 months). These results correspond to a 33% greater risk of death in the cystectomy alone group. Survival benefit was related to complete pathological response. The 5-year survival of patients with pT0 at cystectomy (with or without MVAC) was 85% [19]. In the first Nordic cystectomy trial (NCT1) examined cisplatin-doxorubicin, plus 40 Gray irradiation and cystectomy vs. irradiation and cystectomy. The trial reported a small difference in a subgroup analysis of patients with T3-T4 disease. In a second Nordic cystectomy trial (NCT2), patients randomly received three cycles of cisplatin-methotrexate and leucovorin prior to cystectomy, or cystectomy alone [20]. The combined analysis of both demonstrated overall survival in favour of neoadjuvant treatment. Efficacy of neoadjuvant chemotherapy is shown by the pT0 rate on cystectomy increasing from 15% to 35%-45% [21]. Significant clinical effects including complete response are demonstrated in 50-60% with single agent cisplatin [22,23]. During this time, tumour progression or metastases nearly never occur. It does not contribute to the morbidity or mortality outcomes. Combination chemotherapies also been tested as part of phase 2 trials [24]. MVAC demonstrated complete remission in 20-30%. The lower the stage, the better the outcome. Tumour downstaging occurred in 40-60%.

Seven small series examined gemcitabine-based regimens (gemcitabine and cisplatin) reported pT0 response rates ranging from 7% to 50% [24]. The literature review clearly supports the use of neoadjuvant chemotherapy by level I evidence demonstrating a survival benefit compared with surgery alone.

Meta-analyses

Two main meta-analyses have been performed. The first used cisplatin-based chemotherapy. The overall survival improvement was 5.7 % and risk reduction of death was 10% with neoadjuvant chemotherapy [25]. In the second, the 5-year survival rate improved from 45% to 50% in patients receiving cisplatin-based combination neoadjuvant chemotherapy [26]. The risk of death was reduced by 14% with an increase in specific survival of 9% [27].

The BC2001 trial looked at outcomes of chemo-radiotherapy vs. radiotherapy alone [28]. At 2 years, rates of locoregional disease–free survival were 67% in the chemo radiotherapy group and 54% in the radiotherapy group. Five-year rates of overall survival were 48% (95% CI, 40 to 55) in the chemo-radiotherapy group and 35% in the radiotherapy group. However, Grade 3 or 4 adverse events were slightly more common in the chemo radiotherapy group than in the radiotherapy group during treatment. Results of this trial have led some to surmise that chemoradiotherapy is equivalent to cystectomy with neoadjuvant chemotherapy but no head to head comparison has been completed. A randomised controlled trial between surgery and chemoradiotherapy is unlikely largely because urologists still regard cystectomy as a gold standard and select fitter patients for surgery. The SPARE Trial attempted to examine bladder preservation vs. cystectomy. However, after months, only a few patients were recruited, not enough for a phase 3 trial [29]. This was thought to be for a number of reasons. Patients having a number of treatment options available, having a complex care requiring a range of healthcare professionals. In addition it took an excessively long period of time for patients to be recruited.

Disadvantages of neoadjuvant chemotherapy

Potential disadvantages of NAC include less accurate staging, delay in curative surgery (risk greater if delay > 12 weeks) if patient does not respond, toxicity from chemotherapy. Patients with disease progression on chemotherapy may have their benefit from surgery compromised. It is difficult to identify patients who would benefit from neoadjuvant chemotherapy. There has been very little research into this region. Although T2 and T3a patients, have an almost complete response, bladder preservation remains controversial. Absence of residual tumour does not mean the patient has been cured. Patient survival after resection has not yet been compared in a randomised trial with survival after cystectomy. Several factors are favourable indications for bladder preservation: clinical stage, tumour size (<3 cm), absence of a palpable mass, and a single lesion [5].

Controversies in Clinical Effectiveness

Data from randomized trials did not show any morbidity difference after neoadjuvant treatment [29,30]. Even randomized trials did not demonstrate statistical survival benefit despite the prolongation of disease free interval [31-33]. These early reports

were criticized due to single agent chemotherapy regimen used, and insufficient number of patients enrolled. A randomised trial [34] has compared outcomes after cystectomy plus adjuvant MVAC with pre- and postoperative MVAC. No differences were found between the groups. In intention-to-treat analyses, 81 patients (58%) were in remission with a median follow-up of 6.8 yr. Again, the study design and small number of inclusions prevent us from concluding the differences in outcome. Other combinations e.g. cyclophosphamide, fluorouracil and methotrexate for T3 disease, did not demonstrated any significant effect [29]. Methotrexate has been used as part of a clinical trial [30]. No survival benefit was observed. Single agent cisplatin has also been trialled followed by radical radiotherapy. However, trials closed prematurely, due to poor patient recruitment. Separate and meta-analysis have failed to show any benefit [35]. Another study, similar to the SWOG one, is the Italian GUONE trial [35]. Patients were randomized to M-VAC before cystectomy, or cystectomy alone. The trial was closed early because failed to achieve any difference in survival. This is a small trial in which no difference in survival was observed (62% vs. 68%). Another Italian trial substituted doxorubicin with epirubicin and studied the neoadjuvant M-VEC regimen plus cystectomy versus cystectomy alone [36,37]. Again, no difference in survival was observed. Several other published randomized trials of neoadjuvant chemotherapy [38-40] have failed to show survival difference, mostly because in order to detect a 10% survival benefit of investigational chemotherapy arm over standard therapy, a randomized trial requires approximately 1000 patients. A single-centre randomized trial of five cycles of MVAC chemotherapy, given either as two neoadjuvant and three post-operative cycles, or five cycles of adjuvant therapy has recently been published [21]. 140 patients with T3b or T4a were enrolled. Significant difference in overall survival was not observed between the two arms. A disadvantage of this trial was that no observation-only arm was included.

Targeted Therapies and Bladder Preservation

Preliminary data with anti-angiogenic agents such as bevacizumab or sunitinib combined with chemotherapy suggest an absence of improvement in pT0 response rates as compared to historical data with chemotherapy alone [41]. However, further results are required. Futhermore, predictive biomarkers are urgently needed in order to determine responses from neoadjuvant chemotherapy. Interestingly, several trials [42-45] evaluated neoadjuvant chemotherapy associated with radiotherapy alone or combined with chemotherapy, dose-dense MVAC, or gemcitabine and cisplatin (GC). Survival varied from 48% to 63% at 5 years [42-44]. The proportion of bladders left in place at 5 yr is >40% [45,46]. A bladder sparing option could use neoadjuvant chemotherapy in combination with a high-quality transurethral bladder resection in complete responders.

Cost Effectiveness

Even though neoadjuvant chemotherapy for this cohort has become the gold standard, it has never been evaluated by the National Institute for Clinical Excellence (NICE).

Evaluation of 'QUALYs.'

NICE use a standard and internationally recognised method to compare different drugs and measure their clinical effectiveness: the quality-adjusted life years measurement (the 'QALY') [48]. A QALY gives an idea of how many extra months or years of life of a reasonable quality a person might gain as a result of treatment and show much the drug or treatment costs per QALY. This is the cost of using the drugs to provide a year of the best quality of life available Cost effectiveness is expressed as '£ per QALY, [48]. Generally, however, if a treatment costs more than £20,000-30,000 per QALY, then it would not be considered cost effective. Few studies, if any have been conducted into cost effectiveness of neoadjuvant chemotherapy. One American study examined mean total cost of treatment during follow-up for radical cystectomy vs. cost of neoadjuvant chemotherapy and cystectomy [47]. These were £26,317 and £32111, respectively. The absolute increase in cost of therapy for patients receiving NAC compared to RC alone was £5959. The increased cost per additional QALY gained for patients receiving NAC was £6,330. In addition NAC has a significant number of side effects, which would contribute further to the cost.

Benefits *vs.* Risks of Neoadjuvant Chemotherapy

From the literature review, the benefits of neoadjuvant chemotherapy for muscle invasive bladder cancer are wide ranging. This includes a greatly improved response rate including compete response and improved survival rate. Potential disadvantages of NAC include less accurate staging, delay in curative surgery (risk greater if delay > 12 weeks) in none-responders and a well-known fact that none responders will fare worse later on.

Conclusions

In conclusion neoadjuvant chemotherapy followed by radical therapy is the gold standard for muscle invasive bladder tumours for patients sufficiently fit despite cost effectiveness. As yet, this intervention has not been examined by NICE. However, there are many unanswered questions. The choice of neoadjuvant chemotherapy, whether MVAC, CMV or GC needs to be decided. However both its' cost effectiveness and clinical effectiveness remains to be evaluated in a prospective trial. Translational genomic and proteomic research needs to predict treatment response to different neoadjuvant chemotherapies needs to continue, to separate patients into responders or none responders based on genetic profile.

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