Original Article

Singapore Cancer Network (SCAN) Guidelines for Neoadjuvant and Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer

The Singapore Cancer Network (SCAN) Genitourinary Cancer Workgroup

Abstract

Introduction: The SCAN genitourinary cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer (MIBC). Materials and Methods: The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. Results: Three international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), the European Society of Medical Oncology (2011) and the European Association of Urology (2013). Recommendations on the use of neoadjuvant and adjuvant chemotherapy in MIBC were developed. Conclusion: These adapted guidelines form the SCAN Guidelines 2015 for neoadjuvant and adjuvant chemotherapy in MIBC.

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Key words: Perioperative, Recommendations, Survival benefit

Introduction

In Singapore, bladder cancer is the ninth most common cancer in men. It is less frequent among women. A total of 675 new cases of bladder cancer were diagnosed between 2003 and 2007, with an estimated male to female ratio of 3:1.[1]

At initial diagnosis, about 30% of patients present with muscle-invasive bladder cancer (MIBC). MIBC may be locally controlled with cystectomy or radiotherapy but up to 50% of patients ultimately die of distant metastases. These systemic relapses are due to occult micrometastases which may be eliminated by the use of chemotherapy in the perioperative or periradiotherapy period.

There is consistent Level I evidence demonstrating the efficacy of neoadjuvant chemotherapy (NACT) in MIBC. As for adjuvant chemotherapy (ACT) in MIBC, there is convergence of evidence of benefit, but not Level I data. Despite the demonstration of efficacy, the use of NACT and ACT is surprisingly low in the clinical setting.[2] Thus, there is a need to review the evidence for NACT and ACT for MIBC before or after cystectomy or radiotherapy in order to make recommendations for clinical practice.

The SCAN Guidelines for the Use of NACT or ACT for MIBC

The SCAN Guidelines are clinical practice guidelines for the use of NACT or ACT for MIBC.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of MIBC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, urologists, allied health workers and general practitioners involved in the management of patients with MIBC.

Guideline Recommendations/Development

The SCAN Genitourinary Cancer Working Group comprises a panel of 7 medical oncologists from Singapore

Address for Correspondence: Dr Chee-Keong Toh, Department of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
Email: toh.chee.keong@nccs.com.sg

with special interests in the management of genitourinary cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICJME) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework[3] was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 2 main management issues which were selected for this topic:

1. Use of NACT for MIBC
2. Use of ACT for MIBC

Three international guidelines were selected for review (Supplementary Table 1):

- "NCCN Clinical Practice Guidelines in Oncology for Bladder Cancer Version 2.2014" by the National Cancer Comprehensive Network (NCCN, USA)[4]
- "Bladder Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up" by the European Society for Medical Oncology (ESMO), October 2011[5]
- "Guidelines on Muscle-Invasive and Metastatic Bladder Cancer: EAU Guideline" by the European Association of Urology (EAU), March 2013[6]

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of MIBC, it will be reviewed earlier.

1. Use of NACT for MIBC

The use of NACT has several advantages, including better tolerability of chemotherapy prior to surgery, assessment of chemosensitivity of primary tumour prior to resection, and chemotherapy is given when the burden of metastases is low. However, there are disadvantages and these include delayed surgery, which might compromise outcome in patients who do not respond to chemotherapy and overtreatment, which is a possibility as clinical staging has an accuracy of only 70%. Another problem with regard to the use of NACT is that its uptake is low as surgeons and urologists do not consistently refer to medical oncologists for NACT to be given.

Randomised controlled trials[7-10] and meta-analyses[11,12] have demonstrated the efficacy of NACT in MIBC. The MRC/EORTC randomised trial of neoadjuvant cisplatin/methotrexate/vinblastine (CMV) chemotherapy showed a survival benefit, with a reduction of risk of death by 16% (HR = 0.84; 95% CI, 0.72 to 0.99; $P = 0.037$, corresponding to an increase in 10-year survival from 30% to 36%) from CMV.[9,10] The SWOG/Intergroup trial also showed improved survival for patients given NACT.[7] After approximately 8.5 years of follow-up, there was a 25% reduction in the risk of death for patients treated with methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) prior to cystectomy (HR = 0.75; 95% CI, 0.57 to 1.00; $P = 0.06$). Another randomised trial, the Nordic Cystectomy 1 trial, using NACT with doxorubicin and cisplatin, found a statistically significant effect of chemotherapy in patients with stages T3-T4a (5-year survival, 52% vs 37% for chemotherapy and control, $P = 0.03$).[8]

In the most recent meta-analysis with updated independent patient data published in 2005, there was a significant survival benefit associated with platinum-based combination chemotherapy (HR = 0.86; 95% CI, 0.77 to 0.95; $P = 0.003$), equivalent to a 5% absolute improvement in survival at 5 years. There was also a significant disease-free survival (DFS) benefit associated with platinum-based combination chemotherapy (HR = 0.78; 95% CI, 0.71 to 0.86; $P < 0.0001$), equivalent to a 9% absolute improvement at 5 years.[13]

The randomised trials that have shown survival benefit utilise cisplatin-based combination chemotherapy which mainly included CMV or MVAC for 3 cycles. Thus, the regimens of CMV or MVAC should be considered standards. Newer less toxic regimens (gemcitabine/cisplatin or dose-dense MVAC) have been shown to be equivalent in the more advanced metastatic setting[14,15] but further

data on them are still unavailable and are unlikely to be available in the neoadjuvant setting. Although it is unlikely that there will be Level I data on the use of gemcitabine/cisplatin in the neoadjuvant setting, the ease of use and the better tolerability of this regimen make it a suitable alternative chemotherapy combination. In addition, the use of carboplatin in substitution for cisplatin is not advocated.

There is no data on cost-effectiveness of these recommendations, but an unsystematic estimate has suggested that NACT is associated with an increased cost of USD $6000/quality-adjusted life year (QALY) gained.[16]

Recommendations for NACT in MIBC

The SCAN workgroup has voted 5 to 2 in support of the adoption of the EAU guidelines (Supplementary Table 1). Two of the workgroup members support the use of the ESMO guidelines.

There is unanimous agreement among the working group members that cisplatin-based chemotherapy is the standard of care for NACT. The EAU guidelines recommend cisplatin-based combination chemotherapy, without specifying specific regimens. Although there is no evidence to suggest that the newer chemotherapy regimens are as effective as the older ones in the neoadjuvant setting, the workgroup members do not exclude the use of the newer chemotherapy regimens due to better toxicity profiles.

The majority of the workgroup members agree with the EAU guidelines that NACT is not recommended for patients with poor performance status and/or impaired renal function.

2. Use of ACT for MIBC

Despite the fact that there is not enough evidence in favour of ACT, it is still much in use as some clinicians prefer the adjuvant approach. The advantages of ACT include more accurate pathological staging postsurgery, avoidance of overtreatment in patients with earlier stage disease and no delay in surgery, especially for patients who do not respond well to chemotherapy. The disadvantages include delay of chemotherapy due to prolonged postoperative recovery and difficulty in monitoring chemosensitivity of primary tumour as there is no measurable disease. As such, the panel feels the need to review the data and make recommendations.

To date, few published randomised trials have been performed comparing ACT and observation.[17-20] In addition, these trials had a small sample size and methodological limitations including early termination of trials, poor patient accrual and lack of recommendations regarding salvage chemotherapy for relapse or metastases. Chemotherapy regimens also differed among the trials and a substantial number of patients randomised to the chemotherapy arm did not receive chemotherapy or had less than 2 courses of chemotherapy.

There was no statistically significant improvement in overall survival (OS) in the trials that reported statistical comparisons between trial arms.[17-20] DFS defined as the time from cystectomy until evidence of disease recurrence, was significantly prolonged in the ACT groups compared with controls.[17,18,20] Results of the trials found that patients with more involved nodes were at higher risk of recurrence or death.[17,19] Only one of the trials found, on subgroup analysis, that chemotherapy has benefit in time to progression and survival in patients with 1 lymph node involved.[17] A meta-analysis based on 491 patients from 6 trials found an overall hazard ratio (HR) for survival of 0.75 (95% CI, 0.60 to 0.96; $P = 0.019$), suggesting a 25% relative reduction in the risk of death for chemotherapy compared to that of control.[21] However, the impact of trials that stopped early, of patients not receiving allocated treatments or not receiving salvage chemotherapy on the results of this meta-analysis is not clear. Although there is unlikely to be any Level I evidence supporting the use of ACT, there is other evidence of benefit in health outcomes.[22]

It is unclear, at the moment, whether immediate ACT is superior to chemotherapy at the time of relapse. Although there are a few long-term survivors with chemotherapy at relapse, this is very rare. In the largest trial to date, which involved 284 patients but was unfortunately stopped early due to poor accrual, immediate adjuvant cisplatin-based combination chemotherapy led to a statistically significant improvement in the secondary endpoint of progression-free survival (PFS) but a non-significant decrease in the primary endpoint of death.[23] The estimated absolute difference in 5-year PFS and OS was 17.3% (46.8% vs 29.5%) and 5.9% (53.6% vs 47.7%) between the 2 arms respectively.

Although there is no Level I evidence to support the routine use of ACT in patients with MIBC, there is data that suggests consistent benefit, including large community-based health outcome research studies.[2] In addition, as there is some evidence of a statistically significant benefit with regard to DFS, it is reasonable to discuss with patients for whom an improvement of DFS is important, especially for patients with extravesical extension and/or nodal involvement. Patients should be well informed of the scarce data available and the possible benefits and risks of chemotherapy must be discussed.

There is also no evidence that more modern or carboplatin-containing chemotherapy combinations are as effective in the adjuvant setting and that patients ineligible for cisplatin should not receive adjuvant chemotherapy.

There is no data on cost-effectiveness of these recommendations.

Table 1. Singapore Cancer Network (SCAN) Guidelines for NACT and ACT Chemotherapy for MIBC

	Guideline Recommendations
Use of NACT for MIBC	EAU Guidelines: Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (Level Ia, Grade A). Neoadjuvant chemotherapy is not recommended in patients with PS >2 and/or impaired renal function (Grade B). Although there is no evidence to suggest that the newer chemotherapy regimens are as effective as the older ones in the neoadjuvant setting, the SCAN workgroup members do not exclude the use of the newer chemotherapy regimens due to better toxicity profiles.
Use of ACT for MIBC	ESMO Guidelines: Platinum-based combination not recommended for routine use (Level Ia, Grade A) but can be considered for node positive patients. There is unanimous agreement among the workgroup members that cisplatin-based chemotherapy is not recommended for routine use due to its limited clinical data and evidence. However, as many patients are referred only after surgery, ACT should be considered in patients with high risk of relapse, namely, those with extravesical extension and/or node positive disease due to the possible improvement in DFS.

ACT: Adjuvant chemotherapy; DFS: Disease-free survival; EAU: European Association of Urology; ESMO: European Society for Medical Oncology; MIBC: Muscle-invasive bladder cancer; NACT: Neoadjuvant chemotherapy; PS: Performance status

Recommendations for ACT in MIBC

The SCAN Workgroup voted 4 to 3 in support of the adoption of the ESMO guidelines[5] (Supplementary Table 1). Two workgroup members support the use of EAU guidelines while 1 member preferred case by case individualised discussion for high risk patients.

There is unanimous agreement among the workgroup members that cisplatin-based chemotherapy is not recommended for routine use due to its limited clinical data and evidence. However, as many patients are referred only after surgery, ACT should be considered in patients with high risk of relapse, namely, those with extravesical extension and/or node positive disease due to the possible improvement in DFS (Table 1).

Conflicts of Interest

Dr Kanesvaran reports receiving advisory board fees from Pfizer, GSK and Bayer and speaker bureau fees from Pfizer and GSK; Dr Ng, receiving advisory board fees from Bayer and Astra Zeneca; Dr Tan, receiving grant support from Pfizer and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients That Identifies Distinct Biological Subtypes", "Method for predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody Specific for Parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Dr Tan, Ms Tan, Dr Tay, Dr Toh and Dr Wong have nothing to disclose.

Workgroup Members

The Members of the SCAN Genitourinary Cancer Workgroup are Section Lead: Chee-Keong Toh, MBBS, MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Chairperson: Ravindran Kanesvaran, MD, MRCP, FAMS, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Quan Sing Ng, MBBS, MD, MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Min-Han Tan, MBBS, FRCP, PhD, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Yew Oo Tan, MBBS, FAMS, Singapore Oncology Consultants, Singapore; Miah Hiang Tay, MBBS, MRCP, FAMS, Onco-Care Cancer Centre, Gleneagles Hospital, Singapore; Alvin Wong, MBBS, MRCP, Department of Haematology-Oncology, National University Health System, Singapore; Workgroup Members (Non-voting): Hui Shan Tan, BSc, MPH, Department of Medical Oncology, National Cancer Centre Singapore, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Daniel YC Heng, MD, MPH, FRCPC, Department of Oncology, University of Calgary, Canada; Brian Rini, MD, Taussig Cancer Institute, USA. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines for the Treatment of Metastatic Bladder Cancer

Guideline Title	**NCCN Clinical Practice Guidelines in Oncology Bladder Cancer Version 2.2014**	**Bladder Cancer: ESMO Clinical Practice Guidelines**	**Guidelines on Muscle-invasive and Metastatic Bladder Cancer: EAU Guidelines**
Date Released	May 2014	October 2011	March 2013
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	European Association of Urology (EAU)
Description of Method of Guideline Validation	Guidelines are statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. All recommendations are Category IIA unless specified.	Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO).	Specialist multidisciplinary team. Comprehensive literature searches in the Cochrane Database of Systematic Reviews, Cochrane Database of Controlled Clinical Trials, and Medline and Embase on the Dialog/DataStar platform.
Target Population	Muscle-invasive bladder cancer, cT2 to T4.	Clinical stage II to III	T2-T4A muscle-invasive bladder cancer.
Neoadjuvant Chemotherapy	Cisplatin-based chemotherapy (Category I) • Dose-dense methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) • Gemcitabine/cisplatin • Cisplatin, methotrexate, and vinblastine (CMV)	Platinum-based combination chemotherapy (Level I, Grade A)	Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (Level Ia, Grade A). Neoadjuvant chemotherapy is not recommended in patients with PS >2 and/or impaired renal function (Grade B).
Member Votes	NIL	2 of 7 votes	5 of 7 votes
Adjuvant Chemotherapy	Cisplatin-based combination chemotherapy (Category IIB) based on pathologic risk (pT3-4 or positive nodes) if neoadjuvant chemotherapy was not given.	Platinum-based combination not recommended for routine use (Level I, Grade A) but can be considered for node-positive patients.	Adjuvant chemotherapy is under debate. Neither randomised trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy (Level Ia). Adjuvant chemotherapy is advised within clinical trials, but not as a routine therapeutic option (Grade A).
Member Votes	NIL	4 of 7 votes	2 of 7 votes

PS: Performance status