Clinical outlook

Clinical trial design for non-muscle invasive bladder cancer

Wei Shen Tan[1,2]*
Emma Hall[3]
Ashish M Kamat[1]
John D Kelly[2,4]

1. Department of Urology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston 77030, TX, USA
2. Division of Surgery & Interventional Science, University College London, Charles Bell House, 43-45 Foley St, London W1W 7TY, UK
3. Clinical Trials and Statistics Unit, The Institute of Cancer Research, Sir Richard Doll Building, 15 Cotswold Road, Sutton, SM2 5NG London, UK
4. Department of Urology, University College London Hospital at Westmoreland Street, 16-18 Westmoreland St, London W1G 8PH, UK

*Corresponding author

Emails:
Wei Shen Tan (Wstan@mdanderson.org)
Emma Hall (emma.hall@icr.ac.uk)
Ashish M Kamat (akamat@mdanderson.org)
Kohn D Kelly (j.d.kelly@ucl.ac.uk)

Word count: 999/1000

The heterogenous nature of non-muscle invasive bladder cancer is a challenge when designing clinical trials. Careful consideration in clinical trial design, endpoints and adequate patient characterization are important when evaluating new therapies.

Non-muscle invasive bladder cancer (NMIBC) represents a heterogenous disease reflected by the differing risk of recurrence and progression. Historically, a limited number of intravesical treatments have been the mainstay of treatment (Figure 1). A desire to reduce the need for radical cystectomy in BCG unresponsive disease and, in recent years, BCG supply shortages, have driven efforts to develop bladder sparing treatments. Given the different aims of treatment and subsets of NMIBC, careful consideration in clinical trial design, endpoints and adequate patient characterization is important when evaluating new therapies.

Adoption of new treatments

Despite challenges in evaluating new technologies in surgery, it is important to adopt new treatments based on high-quality evidence. This has not always happened. An example is the use of conductive chemohyperthermia for NMIBC which was adopted in Europe based on retrospective data. Two subsequent randomized-controlled trials (RCT), HIVEC-I and HIVEC-II, found no evidence of benefit for chemohyperthermia when compared to room temperature intravesical chemotherapy in intermediate-risk NMIBC.[1,2]

In high-risk NMIBC and despite the lack of randomized data, BCG shortages led to the use of conductive hyperthermia in the UK and intravesical gemcitabine and docetaxel in North America as alternatives. Fortunately, there are ongoing efforts to evaluate gemcitabine-docetaxel in a phase III RCT (BRIDGE [NCT05538663])(Figure 1), although it maybe >5 years before the trial will report outcomes.

Patient characterization

Another consideration is the importance of adequately characterizing patients. This continues to remain a challenge for intermediate-risk NMIBC which is often described as the patient cohort who falls between the low- and high-risk cohorts.[3] The International

Bladder Cancer Group (IBCG) has proposed sub-classifying intermediate risk NMIBC based on clinical risk factors (multifocal tumor (>1), early recurrence (<1 year), frequent recurrence (>1/year), tumor size (≥3 cm), and failure of prior intravesical treatment) and recommended treatment approaches to personalize management.[3] Five-year risk of recurrence (39% versus 78%) and progression (3% versus 17%) can vary significantly between the lowest risk to the highest risk intermediate-risk NMIBC patients. Acknowledging such variation in recurrence and progression risk can have significant implication in clinical trial power calculations and expected study duration.

Endpoints

Recurrence- (RFS) or disease-free survival (DFS) are often used as primary outcome measures in RCTs however, these may be clinically less meaningful particularly in intermediate-risk NMIBC where low grade Ta recurrence has little consequence to a patients' life.[4] A more patient-centric endpoint may be number of invasive procedures a patient is subject to over a 24-month period. Newer management approaches such as the role of active surveillance and chemoablation may also be attractive. Chemoablation in particular has gained interest with complete response rates of up to 65%, and may provide an early readout at 3 months as an intermediate or surrogate endpoint for efficacy acknowledging that this may not translate directly to the adjuvant setting.[5]

In designing deliverable clinical trials, it is important to balance the needs of an ideal versus pragmatic endpoint. The ideal endpoint for NMIBC trials would be progression to muscle invasive bladder cancer (MIBC). However, even in high-risk NMIBC, contemporary data would suggest a progression-free survival (PFS) rate of 90% at 3 years, meaning that trials powered to detect plausible treatment effects would require large numbers (>1000) of patients rendering them infeasible.[6] High-grade RFS may be an attainable and clinically relevant endpoint since low grade recurrences should not suggest treatment failure and a change in management is not indicated.

Trial design

The evaluation of novel therapies intended to replace the standard of care should usually be powered for superiority. Superiority in efficacy of a new treatment is not required for adoption if there are benefits relating to reduced toxicity or convenience. In such cases, a non-inferiority design would be appropriate but there is a need to show no detriment in

terms of efficacy. An example would be RCTs of alternative treatments for BCG (driven by BCG shortages) in BCG-naive NMIBC. Equally important is the effect size for superiority studies and the non-inferiority margin (the magnitude of detriment deemed acceptable) for non-inferiority studies. A small margin would require a considerable number of patients, in the thousands, leading to a trial with unrealistic recruitment targets. On the contrary, a trial with a wide non-inferiority margin would not be clinically meaningful even if the null hypothesis is rejected. A Bayesian approach to trial design could overcome some of the challenges of a large sample size and although, to our knowledge, this approach has not been previously used in NMIBC trials. The concept of platform trials is also attractive in NMIBC, where numerous promising new agents exist. Whilst such an approach would add complexity to trial design it has the advantage of efficiently testing multiple agents with predefined futility and success criteria.

Importance of randomized control trials

In the case of BCG unresponsive disease, the Food and Drug Administration (FDA) has recommended that single arm studies are appropriate where a RCT is not ethical or feasible.[7] Hence, because no effective bladder sparing treatment previously existed and radical cystectomy was the recommended treatment, single arm studies were allowed for this patient cohort. However, this had led to the approvals of drugs with limited efficacy and poor cost-benefit ratio. We would argue equipoise does exist today and randomization is feasible and should be mandated when evaluating new agents prior to regulatory approval. A variety of both systemic and intravesical treatments have reported 12-month complete response rates of between 19-45% in prospective single arm studies (Figure 1).[8,9] Twenty-four month PFS rates were low (5-15% PFS -≥T2/ metastasis, median: 20-36 months) suggesting that it is not unreasonable to consider a bladder sparing treatment.[8,9] The HYMN trial, evaluated radiofrequency chemohyperthermia against institutional standard in patients with disease recurrence following BCG treatment and reported no significant differences efficacy.[4,10] However, based on single arm results alone, the interventional arm would have been deemed 'clinically meaningful' highlighting the importance of a control arm.[4,10]

In conclusion, patient characteristics, endpoints and trial design are important considerations in designing NMIBC clinical trials. RCTs are essential when evaluating novel agents prior to clinical adoption.

Competing interest

Wei Shen Tan was a consultant to Combat Medical and research fellow for HYMN and HIVEC-II trials. Emma Hall reports grants paid to their institution from Merck Sharpe & Dohme, Bayer, AstraZeneca, Accuray, Aventis Pharma, Varian Medical Systems, Janssen-Cilag, Roche. Ashish M Kamat received grants from Adolor, BMS, FKD Industries, Heat Biologics, Janssen, Merck, Photocure, Seattle Genetics, Taris, and SWOG; is on the board of and recieves consulting fees from Asieris, Astellas, Biological Dynamics, BMS, CG Oncology, H3 Biomedicine, Eisai, Engene, FerGene, Imagin Medical, Incyte DSMB, Janssen, Medac, Merck, Photocure, ProTara, Roche, Seattle Genetics, Sessen Bio, Theralase, TMC Innovation, US Biotest, and Urogen; has a joint patent for CyPRIT (Cytokine Predictors of Response to Intravesical Therapy) with UT MD Anderson Cancer Center; and is the President of IBCG. John D Kelly was chief investigator for HYMN and HIVEC-II trials, consultant to Combat Medical and is funded by the University College London Hospitals Biomedical Research Center, Intuitive Surgical and The Urology Foundation

References

1 Tan, W. S. *et al.* Adjuvant Intravesical Chemohyperthermia Versus Passive Chemotherapy in Patients with Intermediate-risk Non–muscle-invasive Bladder Cancer (HIVEC-II): A Phase 2, Open-label, Randomised Controlled Trial. *European Urology* (2022).

2 Angulo, J. C. *et al.* Hyperthermic Mitomycin C in Intermediate-risk Non–muscle-invasive Bladder Cancer: Results of the HIVEC-1 Trial. *European Urology Oncology* (2022).

3 Tan, W. S. *et al.* Intermediate-risk Non-muscle-invasive Bladder Cancer: Updated Consensus Definition and Management Recommendations from the International Bladder Cancer Group. *Eur Urol Oncol*, doi:10.1016/j.euo.2022.05.005 (2022).

4 Kamat, A. M. *et al.* Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. *J Clin Oncol* **34**, 1935-1944, doi:10.1200/jco.2015.64.4070 (2016).

5 Lindgren, M. S. *et al.* DaBlaCa-13 Study: Oncological Outcome of Short-Term, Intensive Chemoresection With Mitomycin in Nonmuscle Invasive Bladder Cancer: Primary Outcome of a Randomized Controlled Trial. *Journal of Clinical Oncology* **0**, JCO.22.00470, doi:10.1200/jco.22.00470.

6 Kelly, J. D. *et al.* BOXIT—A Randomised Phase III Placebo-controlled Trial Evaluating the Addition of Celecoxib to Standard Treatment of Transitional Cell Carcinoma of the Bladder (CRUK/07/004). *European Urology* **75**, 593-601, doi:https://doi.org/10.1016/j.eururo.2018.09.020 (2019).

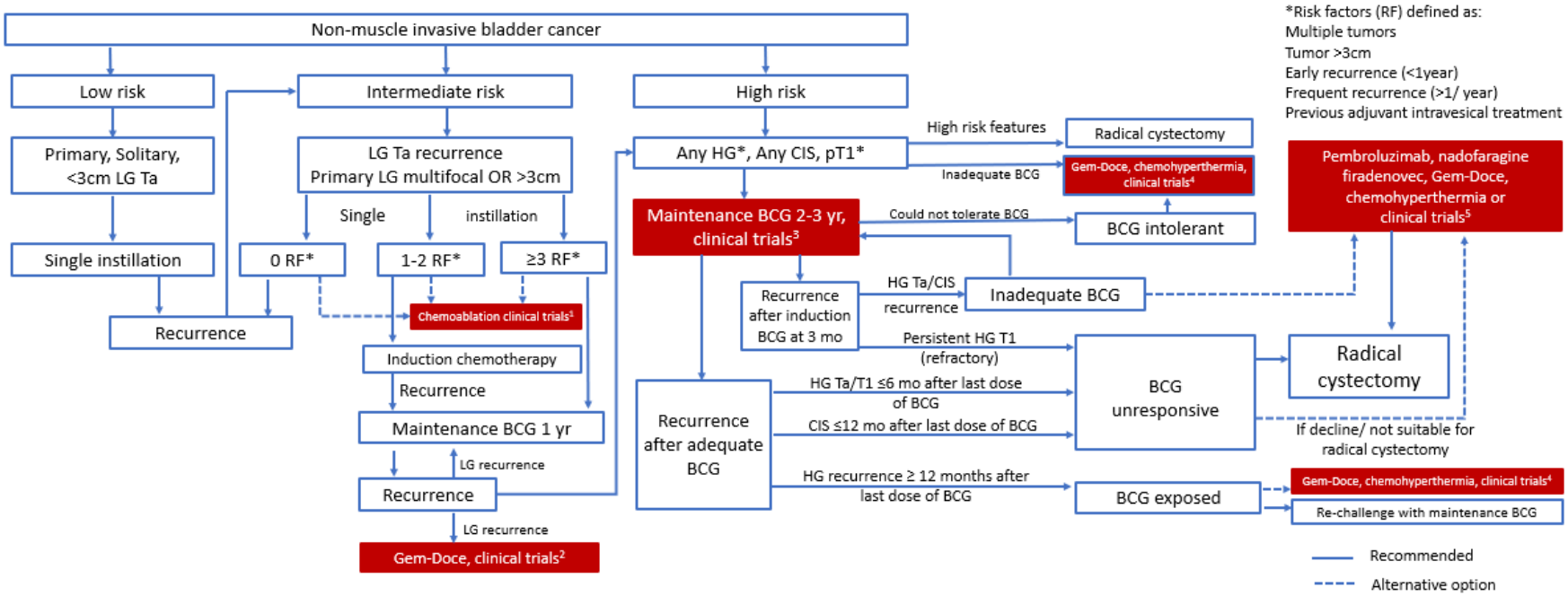
7 Food, U. & Administration, D. BCG-unresponsive nonmuscle invasive bladder cancer: developing drugs and biologics for treatment guidance for industry. *Rockville, MD2018* (2018).

8 Balar, A. V. *et al.* Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. *Lancet Oncol* **22**, 919-930, doi:10.1016/s1470-2045(21)00147-9 (2021).

9 Boorjian, S. A. *et al.* Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol* **22**, 107-117, doi:10.1016/s1470-2045(20)30540-4 (2021).

10 Tan, W. S. *et al.* Radiofrequency-induced thermo-chemotherapy effect versus a second course of bacillus Calmette-Guérin or institutional standard in patients with recurrence of non–muscle-invasive bladder cancer following induction or maintenance bacillus Calmette-Guérin therapy (HYMN): a phase III, open-label, randomised controlled trial. *European urology* **75**, 63-71 (2019).

Figure 1: Non-muscle invasive bladder cancer management and current ongoing clinical trials based on cancer risk classification.



Ongoing/ recruiting trials:
1 ENVISION (NCT05243550)
2 NCT03914794, ASCERTAIN (NCT04736394)
3 POTOMAC (NCT03528694), BRIDGE (NCT05538663), RIDEAU (NCT05120622), SunRISe 3, NCT03759496, TACBIN-01 (NCT04922047), NCT04730232, CREST (NCT04165317), ALBAN (NCT03799835), MK-3475-676/KEYNOTE-676 (NCT03711032), NCT01731652, NCT02138734, NCT03664869, NCT04134000, NCT03091660
4 NCT04917809, NCT04799847, NCT04498702, NCT04172675, NCT02371447
5 SunRISE 1 (NCT04640623), CORE-001 (NCT04387461), QUILT-3.032 (NCT03022825), NCT04738630, NCT04706598, NCT04164082, NCT03759496, CheckMate 9UT (NCT03519256), CheckMate 7G8 (NCT04149574), DURANCE (NCT04106115), NCT03892642, NCT05014139, BOND-003 (NCT04452591), NCT04172675, NCT02009332