Original Article

Contemporary Cost-Effectiveness Analysis Comparing Sequential Bacillus Calmette-Guerin and Electromotive Mitomycin Versus Bacillus Calmette-Guerin Alone for Patients With High-Risk Non–Muscle-Invasive Bladder Cancer

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BACKGROUND: Sequential bacillus Calmette-Guerin (BCG) and electromotive mitomycin (sequential therapy) have been shown in a randomized prospective trial to be superior to therapy with BCG alone in patients with high-risk non–muscle-invasive bladder cancer. The objective of the current study was to compare the costs and benefits of these 2 treatment strategies by performing a 5-year and 10-year cost-effectiveness study. **METHODS:** A Markov model was developed to estimate the incremental cost-effectiveness ratio over a 5-year and 10-year period. Estimates of disease progression, death, and treatment efficacy were obtained from what to the authors' knowledge is the only randomized trial comparing the 2 therapies. Costs included: 1) medical costs (physician fees); 2) drug costs (preparation and instillation); and 3) hospital costs (procedure fees, admission fees, and tests and procedures done during surveillance). Patients were allowed a second course of induction therapy. **RESULTS:** Sequential therapy was found to be associated with a higher initial material cost for induction and maintenance. The average effectiveness for the patients treated with therapy with BCG alone was 4.39 years with a mean cost of $9236 (95% confidence interval, $9118-$9345) per patient. The sequential group resulted in an average effectiveness of 4.65 years, with a mean cost of $16,468 (95% confidence interval, $16,371-$16,527). The 5-year incremental cost-effectiveness ratio of sequential versus BCG-alone therapy was $27,815 per life-year gained. The corresponding figure over a 10-year period was $8618 per life-year gained. **CONCLUSIONS:** The results of the current study suggest that sequential therapy is a cost-effective treatment for patients with high-risk non–muscle-invasive bladder cancer. ***Cancer* 2014;000:000-000.** © *2014 American Cancer Society.*

KEYWORDS: cost-effectiveness, bacillus Calmette-Guerin (BCG), electromotive mitomycin, sequential therapy, non-muscle invasive bladder cancer.

INTRODUCTION

Intravesical chemotherapy and immunotherapy have become essential components in the treatment paradigm of patients with non–muscle-invasive urothelial carcinoma of the bladder (NMIBC).[1] Although intravesical chemotherapy with agents such as mitomycin (MMC) has been shown to reduce disease recurrence, maintenance therapy with bacillus Calmette-Guerin (BCG) was for a long time the only treatment that had been shown to reduce both disease recurrence and progression.[1] Because failures to both types of treatments remain common, urologists continue to search for better therapies. Although several drugs and treatment combinations continue to be investigated, to the best of our knowledge only 1 therapy to date has been shown in a randomized controlled trial to be superior to BCG alone in the treatment of patients with high-risk NMIBC.[2] In 2006, Di Stasi et al published the results of their trial demonstrating the superiority of sequential therapy with BCG and electromotive MMC (EMDA) versus BCG alone in patients with high-risk NMIBC, with all study endpoints significantly in favor of sequential therapy (Table 1).[2] This study indicated that over a median follow-up of 88 months (interquartile range [IQR] 63 months-110 months), patients assigned to treatment with

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sequential BCG and EMDA had a higher disease-free interval than those assigned to BCG alone (absolute difference between groups of 48 months [IQR, 42 months-54 months]; log-rank $P = .0012$). In addition, patients assigned to receive sequential BCG and EMDA also had lower rates of disease recurrence (absolute difference of 16.0% [IQR, 2.7%-29.3%]), disease progression (difference of 12.6% [IQR, 3.0%-22.2%]), overall mortality (absolute difference of 10.9% [IQR, 0.6%-21.2%]), and disease-specific mortality (absolute difference of 10.6% [IQR, 2.5%-18.7%]). The interest in this study stemmed from the rationale of combining chemotherapeutic agents to increase efficacy, and the theory behind this improved efficacy is that BCG-induced inflammation of the bladder urothelium potentially results in better penetration of MMC via EMDA into the bladder wall. Although this trial clearly identified a superior treatment, to the best of our knowledge no study to date has investigated the economic impact of incorporating sequential therapy from a payer's perspective. This is important because current economic conditions and cost constraints continue to play a vital role in all aspects of the medical decision-making process. Due to the superiority of this new treatment among patients with high-risk NMIBC and our interest in incorporating it into the hospital budget as a therapeutic option, we decided to perform an economic evaluation to determine the incremental cost-effectiveness of these 2 treatment strategies in light of the recent approval by Health Canada (in addition to approval from health agencies from several other countries) for the EMDA technology and delivery approach of intravesical MMC.

TABLE 1. Comparison of Outcomes After Treatment With Sequential Therapy Versus BCG Alone

	Sequential Therapy	BCG Alone	Δ	*P*
Recurrence	41.9%	57.9%	16%	.0012
Progression	9.3%	25.0%[a]	15.7%	.004
Overall mortality	21.5%	32.4%	10.9%	.045
Disease-specific mortality	5.6%	16.2%	10.6%	.01

Abbreviation: BCG, bacillus Calmette-Guerin; Δ, difference between the two values.
Adapted from Di Stasi SM, Giannantoni A, Giurioli A, et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol*. 2006;7:43-51.[2]
[a] As per the Kaplan-Maier curve shown in Di Stasi et al.[2] Please note that this value differs from 21.9%, as mentioned in article text.

MATERIALS AND METHODS

Modeling Assumptions

A Markov model with Monte Carlo microsimulations[3] was constructed to determine the incremental cost-effectiveness ratio (ICER) and health economic impact of incorporating sequential therapy (Fig. 1) as a treatment alternative for patients with high-risk NMIBC. Patient

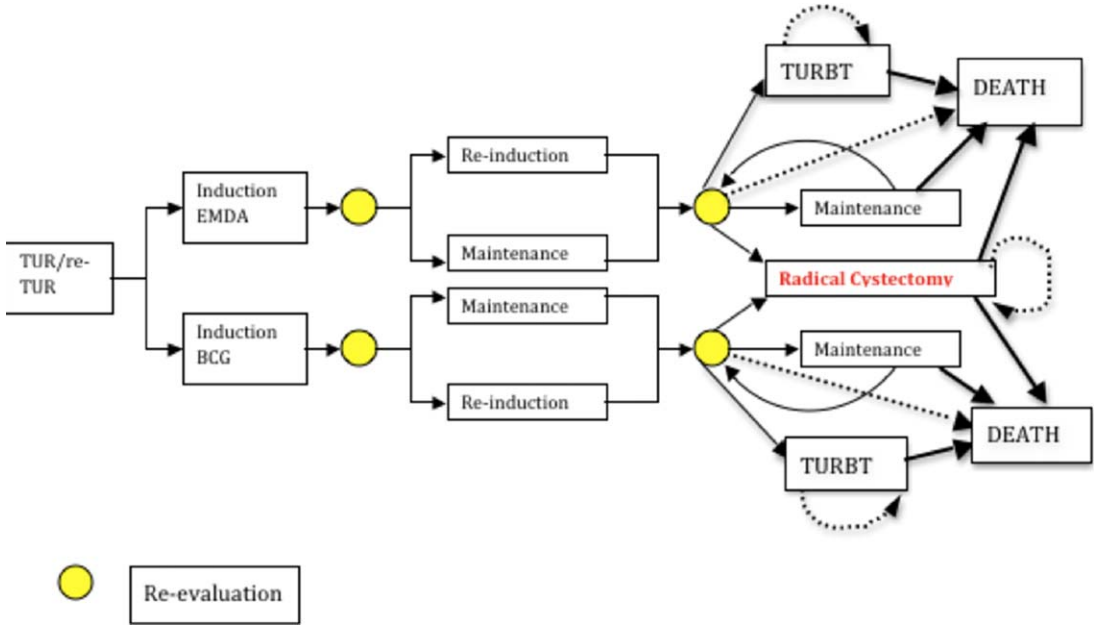

Figure 1. .The Markov model structure is shown. BCG indicates bacillus Calmette-Guerin; EMDA, electromotive mitomycin; TUR/re-TUR indicates initial transurethral resection of bladder tumor (TURBT) before treatment; TURBT, TURBT performed in case of disease recurrence.

characteristics were assumed to be similar to those in the study by Di Stasi et al,[2] with 18.7% of the patients being women and a median age among patients of 67 years. Because no difference was observed between the patients treated with BCG alone and those receiving sequential therapy in terms of adverse events, the cost-effectiveness analysis was considered more appropriate than a cost-utility analysis. The general accepted threshold of ICER is a range of $50,000 to $100,000 per life-year gained.[4] Estimates for annual rates of disease progression and death as well as treatment efficacy were obtained using the data from the single randomized trial by Di Stasi et al comparing both treatment strategies.[2] Our model was built with a 5-year and 10-year time horizon. Induction and maintenance therapy followed the same protocol used in the study by Di Stasi et al,[2] differing from the maintenance schedule of the Southwest Oncology Group protocol.[5] Patients receiving therapy with BCG alone received weekly instillations of BCG as an induction course for 6 weeks, followed by 1 monthly instillation of BCG as maintenance for a total of 10 months. Patients receiving sequential therapy received weekly instillations of BCG for 2 weeks followed by 1 weekly instillation of EMDA as 1 cycle for 3 cycles as an induction course (9 weeks total). This was followed by monthly instillations of EMDA for 2 months and 1 monthly instillation of BCG for 1 month as 1 cycle for 3 cycles as maintenance thereafter (9 months total). Patients were allowed to receive a second course of induction therapy. Reevaluation was performed every 3 months for the first 3 years, and then every 6 months for the following 2 years. Patients who developed disease recurrence at a similar or lower stage were assumed to undergo transurethral resection. Patients from both groups who failed therapy and developed disease progression and were still alive were assumed to receive a radical cystectomy. A death state was integrated into our model.

The Markov model[3] is a health state transition model that started at the initiation of treatment as described above. A cycle length of 3 months was used. The model measured disease recurrences, disease progression, and death within the 5-year and 10-year periods for all patients, and it comprised the following health states: 1) reinduction; 2) radical cystectomy (disease progression requiring radical cystectomy); 3) transurethral resection of bladder tumor (TURBT) (disease recurrence without disease progression); 4) maintenance (patients without disease recurrence or progression); and 5) death. Death is an absorbing state. Patients could remain in the same state for >1 Markov cycle. The effectiveness measure (outcome) considered in the analysis was the life-years gained, which is equivalent to the overall survival. Results of the clinical trial (disease-free survival, progression-free survival, overall survival, and disease-specific survival) were used to derive the 3-month probabilities of undergoing reinduction, of undergoing radical cystectomy, of undergoing TURBT, of remaining in a maintenance state (free of disease progression or recurrence), and of death. As per the study by Di Stasi et al,[2] patients were withdrawn from the trial at the time of a second disease recurrence, if there was persistent carcinoma in situ, if carcinoma developed in the upper urinary tract or prostatic urethra, if disease progressed to muscle-invasive disease (ie, pT2 or more advanced disease), or if metastasis developed; further treatment was left to the discretion of the local investigator. Therefore, only the first TURBT or radical cystectomy event after the maintenance state was accounted for by the model. The derived probabilities are presented in Table 2. In addition, because no distinction was made between mortality from different health states, the probability of death from TURBT and radical cystectomy was derived from the probability of mortality after cystectomy as reported by Kulkarni et al.[6] The models were built using TreeAge Pro 2013 statistical software (Release 13.1.1.0, TreeAge Software Inc, Williamstown, Mass).

TABLE 2. Probabilities of Transition Based on a 3-Month Cycle

	Sequential Therapy	BCG Alone
Recurrence	0.0183	0.0198
Progression	0.0032	0.0143
Death from maintenance state	0.0075	0.0127
Remain in maintenance state	0.9710	0.9532
Death after recurrence	0.02	0.02

Abbreviation: BCG, bacillus Calmette-Guerin.

Cost Assignments

Calculated costs included: 1) medical costs (physician fees); 2) drug costs (cost of drug, its preparation, and instillation); and 3) hospital costs (procedure and admission fees and cost of tests and procedures performed during surveillance). All cost assignments were in Canadian dollars and were estimated from the 2013 Quebec public health system perspective. Medical and hospital costs were estimated from the Regie de l"Assurance Maladie du Quebec (RAMQ) and Ministere de la Santé et des Services Sociaux (MSSS) lists.[7-9] Drug costs were obtained from pharmacy records at the Montreal General Hospital in

TABLE 3. Initial Costs of Induction and Maintenance of Sequential Therapy and Therapy With BCG Alone: Cost Components, Unit and Total Costs[a]

Procedure	Unit Cost	Total Cost	Source
Induction (BCG for 6 cycles)		$770.9	
Catheter	$3.1		MUHC pharmacy list
Bladder instillation (physician fee)	$32.4		RAMQ list
BCG (50 mg)	$93.0		MUHC pharmacy list
Induction: sequential therapy (EMDA for 3 cycles plus BCG for 6 cycles)		$3883.1	
EMDA-related cost		$3112.2	
EMDA catheter plus grounding pads	$280.0		MUHC pharmacy list
Bladder instillation (physician fee)	$32.4		RAMQ list
Mitomycin (40 mg)	$725.0		MUHC pharmacy list
BCG-related cost		$770.9	
Catheter	$3.1		MUHC pharmacy list
Bladder instillation (physician fee)	$32.4		RAMQ list
BCG (50 mg)	$93.0		MUHC pharmacy list
Maintenance (BCG for 10 cycles)		$1284.8	
Catheter	$3.1		MUHC pharmacy list
Bladder instillation (physician fee)	$32.4		RAMQ list
BCG (50 mg)	$93.0		MUHC pharmacy list
Maintenance: sequential therapy(BCG for 3 cycles plus EMDA for 6 cycles)		$6609.8	
EMDA-related cost		$6224.4	
EMDA catheter plus grounding pads	$280.0		MUHC pharmacy list
Bladder instillation (physician fee)	$32.4		RAMQ list
Mitomycin (40 mg)	$725.0		MUHC pharmacy list
BCG-related cost		$385.4	
Catheter	$3.1		MUHC pharmacy list
Bladder instillation (physician fee)	$32.4		RAMQ list
BCG (50 mg)	$93.0		MUHC pharmacy list
Reevaluation (every 3 mo)		$330.2	
Cystoscopy		$243.2	
Physician fees	$50.9		RAMQ list
Procedure fees (same-d surgery with partial anesthesia)	$192.3		Quebec MSSS
Urinary cytology	$87.0	$87.0	MUHC administration
TURBT/re-TURBT		$1729.0	
Physician fees	$208.0		RAMQ list
Anesthesia physician fees	$150.0		
Hospitalization cost (1 d)	$1371.0		Quebec MSSS
Radical cystoprostatectomy/anterior exenteration with PLND (no continent pouch)		$17,894.0	
Physician fees	$1880.0		RAMQ list
Anesthesia physician fees	$1160.0		
Hospitalization cost	$14,854.0		Quebec MSSS

Abbreviation: BCG, bacillus Calmette-Guerin; EMDA, electromotive mitomycin; MSSS, Ministère de Santé et de Services Sociaux (Department of Health and Welfare); MUHC, McGill University Health Center; PLND, pelvic lymph node dissection; RAMQ, Régie de l'Assurance Maladie du Québec; TURBT, transurethral resection of bladder tumor.

Adapted from Ministere de la Sante et des Services Sociaux. Banque de Donnees APR-DRG 2010-2011 et Contour Financier de Sante Physique. informa.msss.gouv.qc.ca/Details.aspx?Id=OLgRnU5HvPw=2010-2011[7]; Regie de l'Assurance Maladie du Quebec. Manuel des Medecins Specialistes. Quebec: Regie de l'Assurance Maladie du Quebec; 2012[8]; and Regie de l'Assurance Maladie du Quebec. Liste de Medicaments Assures. Quebec: Regie de l'Assurance Maladie du Quebec; 2012.[9]

[a] Costs are shown in 2013 Canadian dollars.

Montreal, Quebec, Canada. The unit costs and sources are presented in Table 3.[7-9]

Statistical Analysis

Cost analyses

Patients' outcomes and associated costs of 10,000 incident subjects who were assigned to receive sequential therapy or BCG alone were simulated over the first year and 5 years and 10 years of follow-up by applying the corresponding Markov models. The mean cost per patient is the average of individual cost estimations obtained with Monte Carlo microsimulations. The 95% confidence interval (95% CI) for the mean cost was obtained through simulation of 1000 samples of equal sample size of 10,000 simulated cases. To reflect the time value, a standard discount rate of 5% was used on both the outcomes and costs.[10]

Sensitivity analysis

Several sensitivity analyses were conducted to test the robustness of the results with regard to variations in key parameters considered in our model, specifically a discount rate of 3%, a 5% and 10%, reinduction rate in the sequential therapy group (increased probability by 25%),

TABLE 4. ICER Summary Table[a]

Variable and Variations	ICER (5-Year)	ICER (10-Year)
Base case	$27,815	$8618
Base case (with 5% discount rate)	$32,494	$9643
Base case (with 3% discount rate)	$29,994	$9323
Base case (with 10% discount rate)	$33,142	$10,874
Variation of transition probabilities		
Reinduction rate: Increased probability of reinduction by 25% in sequential therapy group	$29,918	$8869
Progression rate: Increased probability of progression by 25% in sequential therapy group	$30,228	$8608
Decreased probability of progression by 25% in sequential therapy group	$29,840	$8275
Variation of costs		
Base case model with Ontario costs[b]	$22,211	$6887
Base case model with US costs[c]	$5419	$594
Base case model with UK costs[c]	$13,892	$6278
Base case model with British Columbia costs[d]	$29,656	$9862

Abbreviation: ICER, incremental cost-effectiveness ratio.
[a] Costs are shown in 2013 Canadian dollars.
[b] Ontario Health Insurance Plan Schedule of Benefits (October 2013), The Ottawa Hospital Cost Centre (February 2014).
[c] Derived from Svatek RS, Hollenbeck BK, Holmang S, et al. The economics of bladder cancer: costs and considerations of caring for this disease [published online ahead of print January 21, 2014]. *Eur Urol*. doi: 10.1016/j.eururo.2014.01.006.[11]
[d] British Columbia Cancer Agency Pharmacy. Note that these are generic prices and could be lowered if purchased in bulk/on contract. Medical Services Plan British Columbia Payment Schedule, April 2013, Vancouver Coastal Health Authority (quote from Red Leaf Medical, December 2012).

and a disease progression rate in the sequential therapy group (increased or decreased probability by 25%). In addition, costs specific to other health care systems (namely Ontario and British Columbia, Canada; the United States; and the United Kingdom) were used to test the generalizability of this study. Specific analyses are presented in Table 4.[11]

RESULTS

After a 5-year period, 13.5% of the patients in the group receiving sequential therapy died, 5.5% underwent radical cystectomy, and 17.8% of patients underwent TURBT. The corresponding values in the patients treated with BCG alone were 20.6% of patients died, 18.8% underwent radical cystectomy, and 25.62% of patients underwent TURBT. Results of the analysis performed over the 10-year period demonstrated that 32.5% and 22.1% of patients in the BCG-alone and sequential therapy groups, respectively, had died. In addition, the corresponding disease progression rates were 25.8% and 7.0%, respectively, among the patients in the BCG-alone and sequential therapy groups, with a total recurrence rate (with or without disease progression) of 58.0% and 39.5%, respectively. The initial costs of induction and maintenance for both groups are presented in Table 3. Sequential therapy is associated with an increased initial cost of both induction and maintenance, and this does not include the $7000 cost of purchasing the EMDA delivery machine. When these initial costs and other costs were integrated into our Markov model and simulated over a 5-year period, it resulted in an average effectiveness for the BCG group of 4.39 years (95% CI, 4.36 years-4.42 years), with a mean cost of $9236 (95% CI, $9118-$9345). With regard to the sequential therapy group, this resulted in an average effectiveness of 4.65 years (95% CI, 4.62 years-4.66 years), with a mean cost of $16,468 (95% CI, $16,371-$16,527). When one treatment strategy was deemed more effective yet was also more expensive, the ICER was calculated to determine the benefit of using one treatment over the other. The ICER was the difference in cost divided by the difference in effectiveness. In the current study, the 5-year ICER was calculated at $27,815 per life-year gained for the sequential therapy group versus the BCG-alone group.

Over the 10-year period, the average effectiveness was 7.58 years (95% CI, 7.53 years-7.66 years) in the BCG-alone group and 8.40 years (95% CI, 8.35 years-8.47 years) in the sequential therapy group, with a mean cost of $11,588 (95% CI, $11,428-$11,661) and $18,655 (95% CI, $18,599-$18,803), respectively. Consequently, the 10-year ICER was estimated at $8618 per life-year gained.

Sensitivity Analysis

The results of the sensitivity analysis are presented in Table 4. The 5-year ICER varied from $5419 to $33,142 per life-year gained, whereas the 10-year ICER varied from $594 to $10,874 per life-year gained.

DISCUSSION

Sequential therapy is associated with a higher cost of treatment compared with BCG therapy, but is more effective.

The incremental cost-effectiveness ratio of incorporating this treatment is calculated at $27,815 per life-year gained, which is well below the accepted threshold of $50,000 to $100,000 per life-year gained[4] that was initially defined in 1992, but that may currently be accepted as even higher as reported by Eichler et al in 2004,[12] allowing for the possible integration of sequential therapy into treatment options for patients with high-risk NMIBC. Our models simulate outcomes that are very similar to those reported in the clinical trial by Di Stasi et al,[2] thus demonstrating the validation of the model. Over the 10-year period, the simulated rates of death were 32.5% and 22.1%, respectively, in the BCG-alone and sequential therapy groups compared with rates of 32.4% and 21.5%, respectively, reported in the clinical trial.[2] Furthermore, the simulated disease progression rates were 25.8% and 7.0%, respectively, in BCG-alone and sequential therapy groups compared with 25.0% and 6.3%, respectively, as reported in the clinical trial.[2] In addition, the results of the sensitivity analysis were similar to the base case results, thereby demonstrating the stability of the results obtained with these models.

Budget limitations will continue to dictate which types of treatments receive government funding. With a trend toward cost containment in all aspects of medicine, this will invariably affect the treatment of patients with bladder cancer because research into this disease is already one of the most underfunded.[13] For this reason, it is of utmost importance for urologists to perform cost-effectiveness studies on new and emerging therapies in bladder cancer to convince health officials to fund these various treatments. Ultimately however, despite cost analysis studies and supporting evidence, it is the responsibility of the treating physicians to integrate these novel therapies into their daily armamentarium. One example of a novel urologic therapy that, although it has been shown to be effective in randomized trials and has also proven to be cost-effective, continues to be underused, is the immediate post-TURBT intravesical chemotherapy instillation.[14,15] Although a recent meta-analysis reconfirmed the efficacy of this therapy in reducing disease recurrence among patients with NIMBC,[16] and despite its endorsement by the American, Canadian, and European guidelines alike,[1,17,18] recent evidence points to the continued worldwide underuse of a post-TURBT administration of chemotherapy.[19-21] In addition to cost and the urologist's perception of the added value in the absence of disease progression/survival benefit, there may be other barriers to the adoption of a postoperative dose of chemotherapy. In some hospitals, logistic restrictions may make it impossible to administer a postoperative chemotherapeutic medication in the recovery room. Furthermore, nursing staff in the recovery room are often not trained in the administration of chemotherapy, and this may further restrict the use of a post-TURBT dose of chemotherapy. Therefore, despite its proven efficacy, it may rest with urologists to incorporate sequential therapy into their regular practice to avoid the underuse of yet another effective treatment. With recent approval from Health Canada, this trend may change in Canada, yet with no approval for use in the United States, it will likely remain difficult for sequential therapy to be used in American institutions. However, it is important to keep in mind that because the randomized trial was published nearly 8 years ago, cost is most likely not the only reason why more centers have still not adopted sequential therapy. The finding that no further trials validating the efficacy of sequential therapy have been published to date may have made it difficult for this treatment to gain wider acceptance.

To our knowledge, the current study is the first cost-effectiveness study comparing these 2 treatment strategies, with the results revealing a 5-year ICER of $27,815 and a 10-year ICER of $8618 per life-year gained for sequential therapy versus therapy with BCG alone. It is interesting to note that this is significantly less than the ICER for other more established oncologic treatments in urology, including sunitinib for metastatic renal cell carcinoma, which has a reported ICER of $67,215 per life-year gained versus interferon-α,[22] as well as abiraterone for metastatic castration-resistant prostate cancer, with an ICER of $91,200 per life-year gained versus mitoxantrone.[23] Moreover, the 10-year ICER of $8618 is also well below the lower limit of $50,000 that society is willing to reimburse for therapy. As such, this strongly supports the case (from an economic standpoint) for adopting sequential therapy as a standard of care for patients with high-risk NMIBC. Furthermore, the maintenance strategy of the patients receiving BCG alone in the study by Di Stasi et al was found to result in a lower number of BCG instillations being used compared with the Southwest Oncology Group protocol (11 fewer therapies administered per patient)[2] and as such, this would translate into an even lower cost-effectiveness ratio in favor of sequential therapy. However, the opposite may also be true in that a longer BCG maintenance schedule may make the BCG-only arm more effective (lower rates of disease progression/recurrence) and the sequential therapy arm therefore less cost-effective. Nevertheless, the 5-year outcomes reported by Lamm et al for BCG maintenance[5] among a lower-risk patient population (considered as such because it included

a mixture of patients with Ta and T1 disease, unlike the population in the study by Di Stasi et al,[2] which included only patients with high-risk T1 disease) indicated a disease recurrence rate of 40%, a disease progression rate of 24%, and overall mortality rate of 17%, which are similar to those observed at 5 years by Di Stasi et al (33%, 25%, and 22%, respectively).[2]

It is well known that the cost of individual drugs varies significantly from one country to another, and this depends on several factors including manufacturing and importing costs as well as the presence of generic medications. In the current study, there was a substantial discrepancy in cost noted between BCG and MMC, making sequential therapy significantly more expensive. Furthermore, the cost of MMC within the model was based on Canadian prices, which are also significantly higher than those in several other countries, including the United States and Italy. In 2 separate studies from the United States, the cost of a single dose of MMC was reported as $241 and $312, respectively.[24,25] In a study from Italy, the cost of a single instillation of MMC was calculated at €178.[26] These costs demonstrate the significant additional expense of MMC in Canada, and there is no doubt that substantial cost savings can be further incurred in countries such as the United States, in which MMC is much less expensive.

There are several limitations to the current study, the majority of which are inherent to cost analysis studies. First, the costs were derived from RAMQ lists and our own hospital pharmacy records and as such, it is unclear whether the results can be accurately extrapolated to other countries or even other provinces within Canada. Furthermore, medical costs such as physician fees do vary between provinces and countries, and this may further limit the generalizability of the results of the current study. Second, this model did not account for costs associated with side effects or complications nor quality of life as related to treatments. Indirect costs such as time off work and lost productivity were also not considered. The principal limitation of the current study, as well as others using modeling, is the reliance on estimates from a single randomized trial and therefore it is unclear how valid these results can be expected to be in reality.

Conclusions

Based on our cost analysis, the 10-year ICER of adopting sequential therapy over therapy with BCG alone for patients with high-risk NMIBC is estimated at $8618 per life-year gained. These data suggest that sequential therapy can be potentially integrated into hospital and health systems as a standard of care, with the cost-effectiveness ratio well below the threshold of $50,000 to $100,000 that is deemed acceptable to society.

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CONFLICT OF INTEREST DISCLOSURES

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