

Paper Alert

Implementing a New Standard of Care

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It should probably be considered shameless self-advertising for the author of Paper Alert to highlight a clinical trial and subsequent articles related to it that he was study chair and senior author on, but there is some justification for doing this (for the first time since I've written Paper Alert), and I have received the “green light” from one of the editors (SPL) of Bladder Cancer.

In May 2017, I presented the results of the SWOG randomized trial, S0337, at the “Late Breaking Abstract” podium session of the American Urological Association (AUA) annual meeting. In that multicenter randomized study, a single immediate post transurethral resection (TURBT) intravesical instillation of gemcitabine (Gem) significantly reduced the likelihood of recurrence of non-muscle invading (NMI) bladder cancer (BC) compared with an instillation of saline—particularly for the target lesion of low grade (LG) NMI BC.

After the presentation there was an opportunity for the audience to ask questions—and one came from an attendee I didn't know, who asked: “Why present the study? American urologists are still not going to do this, since they have not taken up post TURBT intravesical chemotherapy with other agents, which also had been shown to reduce recurrence,” (I paraphrase his comment). I didn't have much of a reply, mum-

bling something about Gem being better tolerated and less costly than the agent that had been, up until then, the standard in the US, mitomycin C (MMC). However, his words stayed with me, although I hoped he'd be proven wrong when the study was published a year later [1]. Unfortunately, as confirmed in a recent paper [2], the commentator was correct, and he remains so almost five years after making his remark.

Lewicki and colleagues used the premier healthcare database, “a large, all-payer sample”, capturing 84,994 index TURBTs between January 2015 and March 2020, across all US census regions. The population was representative of BC in the US, with a median age of 72, 75% being male, 83% Caucasian, and 68% having a Charlson Comorbidity Index of < 2. Almost 18% received immediate post TURBT intravesical chemotherapy, but that proportion did not change after publication of the article (17.9% before publication, and 17.2% after—odds ratio 0.97:95% CI, 0.93-1.01, $P=0.11$). Perhaps the only impact on clinical care made by the publication of S0337 in a prestigious journal (JAMA), was that the use of Gem rose from 0.1% in patients undergoing TURBT before the article's publication to 5.3% by March 2020 (and the use of MMC fell by this amount over the same period).

The authors acknowledge that they did not have access to histopathologic information, and since the use of immediate post TURBT chemotherapy is beneficial only for LG NMI BC, it is possible that instillation was not planned or administered if the

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tumor appeared high grade (HG), or if pre-TURBT cytology was positive for HG cancer [1,2]. Similarly, contraindications to administering immediate post-TURBT intravesical therapy (e.g. too much hematuria or too deep a resection to safely clamp a catheter post-operatively), which occur in about 10-15% of TURBTs, were also unknown [1]. Even so, since LG NMI urothelial cancer (UC) represents roughly 55% of the newly diagnosed BC cases (and index TURBTs), even if 30% of patients received this therapy—a number far higher than reported in previous publications[3, 4], it means that at least 70% of patients who are eligible do not receive this treatment.

Why not? The University of Rochester Medical Center (URMC) was one of the largest accruing sites to S0337 [1]; however, within 4 months after the publication of the study's results, an audit was performed which indicated that fewer than 21% of eligible patients were receiving such therapy at URMC, despite all urology attendings (many of whom participated in S0337) being aware of the results of the study [5].

Why did utilization fail? It was primarily because, during the conduct of S0337, a study nurse (supported by SWOG) made sure all surgeons, pharmacists, and operating room (OR) personnel were aware of the study, checked subject eligibility, made sure that consent was signed by patients, then came to the OR with the medication, followed the patient to the recovery room where the study drug (Gem or saline) was administered, made sure of the one hour dwell time, and worked with recovery room nurses to facilitate safe medication disposal. After accrual to S0337 closed, the study coordinator was assigned to other projects and the infrastructure supported by the study was lost. To correct this, each step in the Gem delivery chain had to be investigated, stakeholders (Cancer Center pharmacists who prepare Gem, OR pharmacists who dispense it, OR and recovery room nurses who oversee patient care, and of course, attendings and resident physicians who order and administer it) had to be coached and reminded of each person's role. "Order sets", which were unnecessary for S0337, were established to initiate these steps. Educational and update meetings were held with all stakeholders. Within 4 months, appropriate use had increased to 76% of cases, and this continued to rise, so that at the 12-month audit, 91% of appropriate patients received post TURBT Gem. This rate has been maintained in audits over the two subsequent years, despite the addition of new faculty and turnover of residents. However, the effort that went

into this process was considerable and required several champions to identify and overcome barriers to implementation [5].

To significantly raise the utilization nationally, this effort has to be duplicated at every location where TURBTs are performed, because, in the words of the former Speaker of the US House of Representatives, "Tip" O'Neill, "All politics is local". For successful implementation, knowledge of the local Gem supply chain (I certainly did not know it at URMC, despite being study chair of S0337, Chairman of the Urology Department, and a very busy BC surgeon), and having a local champion who can inspire/ cajole buy-in from urologists and other stakeholders is critical. However, our patients deserve the effort to experience a 20% reduction in recurrences with very little morbidity and cost [1, 6]. Perhaps SWOG, which is dedicated to testing new treatments that change the standard of care (SOC) for the diseases they study, can assist in the education and implementation of this, so that this new SOC is widely embraced well before the 17 years it usually takes to successfully incorporate new medical information into standard practices [5, 7].

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CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

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