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Academy of Medical Royal Colleges

Evidence-based Interventions

Proposed clinical guidance

Transurethral resection of bladder tumour (TURBT) single post instillation of mitomycin C (SPI-MMC)

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Transurethral resection of bladder tumour (TURBT) single post instillation of mitomycin C (SPI-MMC)

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Introduction

The Evidence-based Interventions (EBI) programme is an initiative led by the Academy of Medical Royal Colleges to improve the quality of care. Since its inception in 2018, the programme has been supported by four partners: NHS England, NHS Confederation, the Patients Association and the National Institute for Health and Care Excellence (NICE).

Backed by both doctors and patients, the programme is designed to maximise the value patients get from healthcare. This might mean carrying out fewer interventions — where the benefit of certain tests, treatments and procedures is no longer supported by the evidence — but might also mean increasing activity, where the positive impact of a particular intervention for patients is compelling. And finally, it might mean changing the way a particular condition is diagnosed and then treated.

As well as improving outcomes and reducing patient harm, prioritising evidence-based care means we can improve outcomes, reduce patient harm and minimise unwarranted variation in service provision, as well as freeing up valuable resources for use elsewhere in the NHS This is more important than ever as the NHS recovers from the impact of COVID-19 and restores services.

These recommendations target improvements in how care is delivered to patients with bladder cancer, aiming to reduce cancer recurrence, improve patient experience and reduce unwarranted variation by setting out best practice.

The recommendations have been drafted by a panel of senior specialist clinicians. The panel is overseen by an Expert Advisory Committee (EAC) which evaluates the evidence and ensures only those proposals which meet strict criteria are progressed. This committee in turn reports to a Programme Board which makes the ultimate decision on whether a change to the clinical guidance can be made. Their decision is based on feedback from all key stakeholders including patient groups, clinical commissioners, and clinicians. You can find out more about EBI on our website.

We are keen to hear from individuals and organisations with views on this proposal. The engagement period closes on 1 September 2023. These proposals and any views received will be considered by the Programme Board who will reach a conclusion on the practicality and appropriateness of the proposed changes to clinical guidance in Winter 2023.

Summary of current practice

These recommendations outline how mitomycin C (SPI-MMC) is best administered post-transurethral resection of bladder tumour (TURBT). The need for prompt administration is guided by best evidence as well as a drive to deliver more TURBTs as day cases where this is clinically appropriate, improving patient experience and optimising the use of resources.

Mitomycin C (MMC), a chemotherapy agent, has been in use in urology practice for over a decade and is recommended as part of the treatment of non-muscle invasive bladder cancer (NMIBC) to reduce recurrence. It is theorised that MMC kills cancer cells floating in the bladder, cells at the resection site and any missed tumours[1]. This reduces recurrence and the need for further invasive and expensive interventions. MMC is instilled into the bladder after transurethral resection of bladder tumour (TURBT), a process which is termed 'single post TURBT instillation of mitomycin C' (SPI-MMC).

There is a wide variation in clinical practice relating to SPI-MMC. The Getting It Right First Time (GIRFT) urology programme[2] identified variation in the proportion of patients being offered SPI-MMC, and when offered, variation in the timing and clinical setting in which it was administered. Exemplar units had functioning pathways that allowed installation of MMC in the operating theatre or recovery area, maximising the chance of a day case pathway for the patient. Where MMC was not given in theatre, patients were often reliant on administration on the ward and this could lead to delays or, in some cases, missed doses. The most common reason cited for not being able to perform SPI-MMC in theatre related to local pharmacy guidelines on chemotherapy. Training was occasionally an issue, though this was usually easier to overcome.

Single dose MMC is used after the first TURBT to reduce the likelihood of tumour recurrence. Some patients having subsequent TURBTs are also prescribed SPI-MMC but those patients are outside the scope of this guidance. It is important that patients have consented for the administration of MMC prior to their first TURBT procedure and those with known intolerance or allergy to MMC do not receive it. At the time of the procedure, SPI-MMC should be administered where the operating surgeon identifies a bladder tumour that does not invade the muscle layer and there are no contraindications (perforation of the bladder, need for deep resection or need for irrigation due to ongoing gross haematuria). Histological examination of the tumour specimen is used to assess whether further intravesical chemotherapy may be required, but these subsequent procedures are not covered in this guideline.

Single dose MMC works best when delivered soon after TURBT. Best practice is for the operating surgeon to administer the dose of chemotherapeutic agent in theatre as it reduces the risk of MMC being missed, minimises the need for patients to stay overnight and likely increases clinical efficacy. MMC is also administered in other locations including the recovery unit and the inpatient ward. In the 'non-theatre' setting, any appropriately trained medical practitioner can administer single dose MMC; in practice, this is normally a urology nurse specialist or a ward nurse with urology experience.

Recommendations

Scope

This recommendation applies to all patients undergoing their initial TURBT for a new non-muscle invasive bladder cancer, who meet the clinical criteria for single dose mitomycin-C administration as outlined in NICE guideline NG2[3].

It excludes patients with contraindications, such as allergies/intolerance to MMC, bladder perforation/deep resection or significant post-operative bleeding.

Recommendations

1. Single dose mitomycin-C should be administered within the theatre or theatre recovery setting for all eligible patients following TURBT.
2. Where this is not possible, single dose mitomycin-C should be administered within 6 hours of the TURBT procedure being completed.
3. Mitomycin-C should only be administered by appropriately trained practitioners.
4. The use of closed systems (e.g. Mito-In or similar) are preferable for the delivery of mitomycin-C.

These recommendations are in line with the GIRFT best practice day case TURBT pathway[2].

Rationale for recommendations

The panel considered the evidence supporting the use of intra-vesical chemotherapy, including mitomycin-C, in reducing the recurrence of NMIBC after TURBT. The panel discussed the findings of three systematic reviews[4,5,6] relevant to the clinical question that provided data on recurrence rates and adverse effects. The key conclusions considered by the panel are summarised in the table below.

Study	Number of Randomised controlled trials	Total Patients	Median follow up (years)	NMIBC recurrence Rates	Adverse Effects
Title Sylvester et al. (2004)[5]	7	1,476	3.4	267 of 728 patients (36.7%) receiving 1 postoperative instillation of epirubicin, mitomycin C, thiotepa or (2'R)-4'-O-tetrahydropyranyl-doxorubicin (pirarubicin) had recurrence compared to 362 of 748 patients (48.4%) with trans-urethral resection alone, a decrease of 39% in the odds of recurrence with chemotherapy (OR 0.61, p <0.0001).	Mild storage symptoms (10%) Allergic skin reaction (1-3%) Systemic toxicity was extremely rare

Study	Number of Randomised controlled trials	Total Patients	Median follow up (years)	NMIBC recurrence Rates	Adverse Effects
Sylvester et al. (2015)[6]	13 IPD from 11 trials	2,384 IPD=2,278	6	A single instillation reduced the risk of recurrence by 35% (hazard ratio [HR]: 0.65; 95% confidence interval [CI], 0.58-0.74; p<0.001) and the 5-yr recurrence rate from 58.8% to 44.8%. A single instillation did not reduce recurrences in patients with a prior recurrence rate of more than one recurrence per year or in patients with an European Organization for Research and Treatment of Cancer (EORTC) recurrence score ≥5.	Not reported
Perlis et al. (2013)[4]	13	2,548	Not reported	Intra-vesical chemotherapy prolonged recurrence-free interval by 38% (HR: 0.62; 95% confidence interval [CI], 0.50-0.77; p<0.001; I(2): 69%), and early recurrences (recurrence within 12 months) were 12% less likely in the intervention population (ARR: 0.12; 95% CI, -0.18 to -0.06; p<0.001, I(2): 0%). The number needed to treat to prevent one early recurrence was 9 (95% CI, 6-17 patients).	No documented serious adverse events in any study (9 studies)

Regarding the timing of mitomycin-C instillation the panel considered the recommendations from international guidelines. Recently updated guidance from the European Association of Urology states[7]:

'Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by the extracellular matrix'.

'To maximise the efficacy of SI, one should devise flexible practices that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre.'

Similarly, guidelines from the American Urological Association/Society of Urologic Oncology state[8]:

'In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g. gemcitabine, mitomycin C) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative intravesical chemotherapy.'

Scotland's Quality Performance Indicators Programme also recommends administration within 24 hours following the initial TURBT[9].

The panel discussed the differences between recommendations, especially the EUA guidelines, which advise MMC is delivered 'within the first few hours after TURBT' (as opposed to within 24 hours). The panel noted that most clinical trials evaluating MMC used a 24-hour limit as this was more pragmatic in terms of trial design. However, the panel discussed how the EUA guidelines reflect a belief among the urological community that early delivery is preferable as tumour cells become firmly implanted and covered by the extracellular matrix in the first few hours after TURBT.

The panel also considered qualitative feedback from GIRFT site visits (one panel member was the GIRFT urology lead) and its relevance to when and where MMC is delivered. Not administering MMC in theatre or recovery was identified as important driver of missed chemotherapy doses following TURBT by GIRFT. It was also flagged as a key contributor to delayed discharge and unnecessary overnight admissions. Units with optimal practice were discussed, including how barriers limiting the use of chemotherapy in theatre were overcome.

Taking the clinical and operational evidence together, the panel considered there was a clear rationale for delivering MMC as soon as possible after TURBT and that exemplar units had demonstrated that this was feasible. The panel was therefore of the opinion that mitomycin-C should be delivered in theatre or recovery, or within a six hour period of completing TURBT where this was not possible.

Evidence demonstrating the cost effectiveness of immediate (within 24 hours) vs delayed (within two weeks) MMC instillation was noted by the panel[10] with one study demonstrating a mean saving of 1,350 euros per patient over a three year period. The panel agreed that further cost savings were achievable by maximising the day case rate, and that this would also help to improve patient experience (where wasn't another clinical reason for admission). This was considered to further justify the recommendation that MMC should be administered as soon as possible after TURBT, rather than simply within 24 hours.

Patient information

A trans urethral resection of bladder tumour (TURBT) is the usual treatment for bladder cancer when it is diagnosed early. It enables a doctor to remove a cancer by inserting a thin tube called a cystoscope through the patient's urethra and up into their bladder. As well as optic fibres which provide pictures of the bladder the cystoscope also has minute tools attached to the end which enable the doctor to cut out any tumours they may find.

Cancerous tumours can sometimes recur and to reduce the chances of tumours coming back, chemotherapy drugs, such as Mitomycin C, can be administered into the bladder as part of the TURBT procedure. These drugs kill tumours cells very effectively because they are targeted at the site of the cancer. It also means they are not associated with any of the adverse effects of conventional chemotherapy such as hair loss or nausea. The only notable ill effects are a mild skin in reaction in 1-3% and the temporary sensation of needing to pass urine in around 10%.

Evidence shows that patients who received chemotherapy into the bladder immediately after a TURBT have an estimated 12-14% less chance of bladder cancer recurrence at five years. Guidelines from reputed global organisations such as the European Association of Urology and American Urological Association (AUA)/ Society of Urologic Oncology (SUO) recommend that patients who undergo a TURBT for suspected superficial bladder cancer must have bladder chemotherapy within hours provided they do not have any bleeding or a tear in the bladder wall.

This guidance recommends that Mitomycin-C is routinely administered after a patient undergoes their first TURBT procedure where clinical criteria are met. It recommends that this is done as close to the surgical procedure as possible to maximise the clinical benefit and minimise the chance that a patient must stay unnecessarily in hospital when there are no other reasons for doing so.

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