The BCG shortage – what isn't the fuss about?

VAIBHAV MODGIL, SOPHIA CASHMAN AND LYNDON GOMMERSALL

A recent widespread shortage of BCG supplies in the UK has resulted in many patients receiving suboptimal doses of BCG or alternative treatment regimens that may not be as effective. The authors consider the lack of media interest in the issue and look at the potential solutions to the problem.

Bladder cancer is common – it remains the fourth most common cancer in males in the UK. Bacillus Calmette-Guérin (BCG) remains a crucial bladder preserving treatment in the management of high-risk non-muscle-invasive bladder cancer (NMIBC). While the optimal induction and maintenance schedule may be debated, its use and ability to delay progression of high-risk bladder cancer in selected patients is not. In areas where BCG has not been available, patients have been offered primary cystectomy to avoid progression of this life-threatening cancer. Almost as concerning as the lack of BCG supplies has been the relative lack of media interest and public outcry regarding the issue.

THE ROLE OF BCG

BCG has been used in the treatment of high-risk NMIBC since the 1970s. Although the exact mechanism of action has yet to be fully elucidated, the process centres around the adherence to and internalisation of BCG by urothelial cells, with subsequent cytokine secretion and immune system activation, resulting in cancer cell destruction. As a therapy, there have been controversies over the role of BCG; however, it has been extensively researched in terms of both the risk reduction of recurrence and progression it provides to patients. A review article published in 2010 recommended BCG as the standard of care for high-risk disease. There is robust evidence suggesting its usefulness in reducing both progression and recurrence of high-risk NMIBC when combined with maintenance therapy. The role it plays in intermediate-risk disease is less clear-cut. Treatment guidelines, including those issued by the European Association of Urology, NICE and the American Urological Association.
Association, continue to advocate BCG as the non-operative therapy of choice for high-risk NMIBC.

**THE BCG SHORTAGE**

The use of BCG in bladder cancer has been made difficult in recent years by ongoing supply issues. Sanofi ceased production of its Connaught strain of BCG in 2012, following an FDA inspection visit to its Toronto manufacturing facility. In a warning letter from the FDA, a number of failings were highlighted in the production process, including the isolation of mould in the processing areas. The other strain licensed for use in the UK is OncoTICE, supplied by Merck Sharp and Dohme (MSD), which has struggled to keep up with demand, only recently announcing its return to full supply.

**CURRENT RECOMMENDATIONS**

In 2012 the Department of Health estimated that 6000 patients a year would be affected by the shortage of BCG. A joint statement from the British Association of Urological Surgeons, British Association of Urological Nurses, Fight Bladder Cancer and Action on Bladder Cancer released in November 2014 outlined the following treatment strategies as options to deal with the shortage:

- 1/3 dose BCG induction, followed by maintenance for up to one year
- Reduced frequency instillations if 1/3 dose not available
- Stopping maintenance therapy after one year
- Intravesical chemotherapy if BCG has either run out or is in insufficient supply to allow for a reduced dose or frequency

These recommendations are based on a limited evidence base. A number of studies have shown little difference between standard and reduced-dose regimens and there may also be an improvement in toxicity rates. However, logistical problems may exist in obtaining and reconstituting reduced-dose instillations.

Secondly, the optimum maintenance schedule remains a subject of some debate. The standard South West Oncology Group (SWOG) regimen, involving an initial induction period followed by a three-year maintenance schedule, was adopted as common practice following the results of its study, which demonstrate a significant improvement in recurrence and progression-free survival when compared with induction therapy alone. The European Association of Urology guidelines currently recommend between one and three years’ full-dose maintenance BCG, with the minimum time period based on a meta-analysis by Böhle et al, which demonstrates that at least one year’s maintenance therapy is needed to gain superiority over mitomycin C. The guidelines accept that the optimum maintenance strategy remains unknown.

Perhaps it is time to review the optimum BCG regimen. In a study published in European Urology, maintenance therapy was found not to be superior to induction alone; however, the regimen used differed to the SWOG regimen and some caution is therefore needed in applying the findings to UK practice. Nonetheless, the paper was featured as the topic for an International Urology Journal Club (@iurojc) Twitter debate in April, sparking a healthy discussion on the optimal strategy in view of the supply crisis. A summary of the debate is available online.

**MANAGING FUTURE SHORTAGES**

Device-assisted therapy (DAT), involving either electromotive drug administration or chemohyperthermia, has shown some promising results, although further work is needed. A systematic review of chemohyperthermia indicated lower recurrence rate in NMIBC when combined with mitomycin C alone; however, again, it highlighted the lack of conclusive data from randomised trials. The current uptake of DAT in the UK is unknown, but the authors believe it to be low. If the BCG shortage recurs, optimising the current available treatments may be a way forward. There is therefore a need to formalise the evidence behind DAT and, if proven to be effective, invest in the availability of this nationally, together with training, to incorporate its use into current practice. The HIVEC I and II trials, currently underway in Spain and the UK, looking into the role of hyperthermia and mitomycin C in intermediate-risk bladder cancer, will help to provide an evidence base for the therapy.

Would the media have been more interested in a breast cancer drug shortage?

A further avenue to explore is the use of alternative BCG strains. There are currently two strains licensed for use in the UK, with a number of other strains available. Evidence has indicated little difference in efficacy between the different strains. A group in Japan has demonstrated no significant difference in terms of recurrence-free survival and adverse events between the Japanese strain Tokyo 172 and Connaught. More recently, there are some data to suggest a difference in five-year recurrence-free survival between Connaught and OncoTICE, with Connaught appearing superior, albeit following induction therapy only.

**BCG AND THE MEDIA**

While all of these strategies may help provide solutions to the shortfall in BCG in the future, patients affected by the recent shortage had limited options available to them – a significant concern for both patient and clinician alike. Despite this concern, media coverage of the shortage has been limited. A simple search of the term ‘bladder cancer drug shortage’ brings up a number of professional articles, but relatively few articles from the national media over the past 12 months. The Daily Mail ran an article outlining the issue in December 2012. This leads us to question whether the media coverage would be similarly lacking if drug treatments for other cancers, such as Zoladex in prostate cancer or Herceptin in breast cancer, were in short supply.

Other articles identified in the search include a recent article from the New York Post.
If the BCG shortage recurs, optimising the current available treatments may be a way forward

which asked whether the shortage might be due to the lack of profit to be made from the vaccine. The manufacturer, MSD, denies this as a factor, claiming that it simply cannot keep up with demand.

CONCLUSIONS
Where does this leave us as clinicians? And, more importantly, where does it leave our bladder cancer patients? Regardless of supply issues and media disinterest, we as clinicians have a responsibility to minimise the harmful effect a BCG shortage will have on our patients – both physically and psychologically – and to ensure there is no recurrence of this crisis in the future. In the authors’ experience, there is considerable variation across the UK in the communication between trusts and patients in sharing updates on the issue, ranging from letters in the post to formally organised meetings, to explain the shortfall and discuss options.

Whilst optimal information sharing may not change the clinical outcome, it may help to alleviate some of the psychological stress the shortage will inevitably have on patients. It may also help to increase national interest in this issue. Supportive charities, such as Action on Bladder Cancer and Fight Bladder Cancer, who continue to lobby for support for our bladder cancer patients, have an important role to play.

As BCG is a live attenuated vaccine, there can never be a guarantee on drug availability. The recent crisis has highlighted the difficulty in relying on a limited number of manufacturers for such a vital drug, and this review has identified a number of areas for further work. Licensing other strains may provide an immediate solution, while investing in DAT and in trials to clarify the most effective optimal intravesical chemotherapy regimen may provide us with more robust long-term plans. We hope that by reviewing the topic it will continue to keep the BCG shortfall at the forefront of readers’ minds.

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REFERENCES