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Platinum Opinion

Therapeutic Options in High-risk Non-muscle-invasive Bladder Cancer During the Current Worldwide Shortage of Bacille Calmette-Guérin

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In July 2012, Sanofi Pasteur (Lyon, France) announced that it was halting production of ImmuCyst, the Connaught strain of bacille Calmette-Guérin (BCG), after inspectors found mould in the sterile manufacturing area of the Toronto, Canada, plant following a flood [1]. The Toronto facility was the only one in the world manufacturing ImmuCyst, the market leader in many countries including the United Kingdom and the United States. This halt led to a severe worldwide shortage of BCG as other manufacturers struggled to keep up with demand.

Although the problem appeared to be improving slowly, Merck Sharp & Dohme Limited (Hertfordshire, UK)—the manufacturer of OncoTICE (TICE strain of BCG), which had become the market leader in many countries—announced that it expected severely reduced OncoTICE supplies throughout 2015 due to a combination of increased demand and a manufacturing issue. In the meantime, Sanofi Pasteur indicated that ImmuCyst should be available from the second quarter of 2015. Finally, the production of the RIVM BCG strain by Medac (Wedel, Germany) has been on hold for some time during the fourth quarter of 2014.

The ongoing manufacturing problems reflect the great difficulties in producing BCG. The fermentation process has not changed in nearly 100 yr, since it was first described by Calmette and Guérin in 1921, and is highly unreliable [2]. Furthermore, the doses used in bladder cancer are vast compared with BCG vaccine doses. It has been estimated that one induction course of six BCG instillations would be sufficient to vaccinate 10 000–100 000 people, far more than the total UK BCG vaccine requirement for 1 yr (pers. comm.,

D. Lewis, Guildford, UK). Consequently, the current shortage for bladder cancer treatment is not surprising and might remain an issue in the future.

1. Therapeutic options

What are the consequences for patients with high-risk non-muscle-invasive bladder cancer (NMIBC)? Because management with transurethral resection of bladder tumour and cystoscopic surveillance alone is not appropriate even if local BCG supplies have run out, patients should be offered an alternative (see recommendations). They should be made aware that suboptimal courses of BCG may result in higher recurrence rates and, for the very highest risk cases, higher progression rates. Such very high-risk patients should be considered for immediate radical cystectomy (RC). For all other high-risk patients, an initial bladder-sparing approach would seem reasonable using one of the therapeutic options outlined below. Finally, all patients with high-risk NMIBC should be discussed at a bladder cancer multidisciplinary team meeting, as ideally should already be the case.

2. Clinical recommendations

Local availability of some of these options, such as device-assisted therapy (DAT), will vary from country to country and by hospital. The current recommendations take this into account and are presented as a series of *descending* options, with the most evidence-based option listed first.

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First, BCG maintenance can be stopped after 1 yr. Patients in years 2 and 3 of maintenance without carcinoma in situ (CIS) can be reassured that this option is safe in terms of progression [3], although there is a slightly higher risk of recurrence. Patients with CIS could be offered a reduced dose of BCG for years 2 and 3.

Second, if possible, patients should be offered a one-third dose of BCG for induction and maintenance courses up to 1 yr. This approach is based on a randomised trial by the European Organisation for Research and Treatment of Cancer that showed no difference in progression rates between full-dose and one-third-dose BCG [3]. Recurrence rates, however, will be higher. It is recognised that this approach will present logistical problems. It will not be possible to use the *closed* system to administer one-third-dose BCG, and three patients will need to be treated at the same time using one vial of BCG. However, these problems are not insurmountable: One-third-dose BCG has been adopted successfully throughout Canada in response to the BCG shortage there, with the divided doses being drawn up under sterile conditions in pharmacy [4].

Third, if administering one-third-dose BCG is not possible, urologists should consider either an induction course of mitomycin C (MMC) that should be followed by maintenance [5] or full-dose BCG as a 6-wk induction course with further BCG reserved for only the one-third of patients who recur [6]. The latter is associated with an increased risk of long-term recurrence compared with the SWOG maintenance BCG regimen [7]. Progression rates are difficult to compare between these two studies because different end points were used, but BCG induction without maintenance was associated with an 11% progression rate at 5 yr [6]. The optimal MMC maintenance regimen is unknown, but following confirmation of response at cystoscopy, monthly instillation from months 3–12 would be a pragmatic option.

Fourth, patients should not be offered only a single BCG instillation instead of three instillations for each BCG maintenance cycle because this has been shown to be less effective [8].

Fifth, in circumstances in which BCG supplies have run out or are insufficient to allow reduced doses, then intravesical chemotherapy should be considered. Patients with lowest risk high-risk NMIBC (G3 Ta) can be offered an induction course of MMC followed by maintenance, as described above. High-risk NMIBC patients with T1 or CIS should be offered intravesical chemotherapy using DAT with thermotherapy [9]. If this option is not available locally, the patient should be referred to the nearest centre that has it available. Moreover, if treatment with MMC-DAT is impractical or the patient has previously had MMC and

failed or is allergic to it, then an induction course of gemcitabine 2000 mg in 50 ml once a week for 6 wk may be given [10]. In case of local toxicity, this can be reduced to 1000 mg in 50 ml.

Sixth, high-risk patients who are already on BCG therapy and who relapse with further high-risk NMIBC should be offered RC if they are fit and DAT if they are unsuitable or unwilling to undergo RC.

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