It is 35 yr since Morales described the use of intravesical bacillus Calmette-Guérin (BCG) for non–muscle invasive bladder cancer (BC). In the intervening years we have learned much about this treatment. Although BCG is one of the most studied medicines in urology, many questions regarding its use remain [1]. In this month’s European Urology, Herr et al report their use of induction BCG for high-risk BC [2]. The authors demonstrate excellent outcomes in BCG complete responders and suggest the need for a new trial to reevaluate induction and maintenance BCG. Their findings and suggestion highlight the gaps in our knowledge and point to issues that need resolving with BCG in this context.

The current dilemmas with BCG are well illustrated using a historical perspective. In 1991, Lamm et al reported that BCG was more effective than intravesical doxorubicin at reducing BC recurrence [3]. When compared, 20% more patients were disease free, and the time to recurrence was around 1 yr longer for BCG-treated patients. In 2000, the Southwest Oncology Group (SWOG) reported a comparison of induction and maintenance BCG [4]. In 348 randomised patients, maintenance BCG reduced the 5-yr recurrence, worsening disease (including cystectomy), and death rates by a further 19%, 6%, and 5%, respectively, when compared with induction BCG. These data were the largest trial included in key meta-analyses (eg, Sylvester et al [5]), whose findings are central to our current use of BCG and require exploration. First, maintenance BCG reduced progression and death by 4% and 2.1%, respectively, when compared with induction BCG and other treatments. Second, the natural history of high- and intermediate-risk non–muscle-invasive BC appeared relatively indolent. By 2.5 yr (median follow-up), progression to invasive disease had occurred in only 9.8–13.8% and death from BC in only 5.6–7.7% of patients. Thus maintenance BCG appeared an effective treatment for a relatively safe disease. These findings defined a role for maintenance BCG in the first-line management of high- and intermediate-risk BC [6].

However, there were weaknesses in the data reported by these meta-analyses. First, patient follow-up was short (median: 2.5 yr). Natural history reports clearly show that progression and BC death rates are directly proportional to the length of follow-up (reviewed in Kulkarni et al [7]). The median time to BC mortality from these cancers is 3–5 yr and was therefore not reached by tumours in the meta-analyses. Second, few tumours were high risk (8% were grade 3). As progression rates rise from 10–15% for grade 2 to 25–75% for grade 3 tumours [8], the meta-analyses potentially underestimated the risk of muscle invasion in poorly differentiated tumours. Third, the benefit of maintenance BCG, over induction, probably relied on the power generated by a single trial (the SWOG trial). Other randomised controlled trials (RCTs) have failed to show a benefit for maintenance BCG over induction treatment alone (reviewed in Gontero et al [1]). To address aspects of these concerns, a newer meta-analysis with longer follow up (median: 4.4 yr) and a higher proportion of grade 3 tumours (16%) was reported in 2009 [9]. This analysis used individual patient data, which is the most rigorous method of comparison, but which is not included in key meta-analyses (eg, Sylvester et al [5]), whose findings are central to our current use of BCG and require exploration. First, maintenance BCG reduced progression and death by 4% and 2.1%, respectively, when compared with induction BCG and other treatments. Second, the natural history of high- and intermediate-risk non–muscle-invasive BC appeared relatively indolent. By 2.5 yr (median follow-up), progression to invasive disease had occurred in only 9.8–13.8% and death from BC in only 5.6–7.7% of patients. Thus maintenance BCG appeared an effective treatment for a relatively safe disease. These findings defined a role for maintenance BCG in the first-line management of high- and intermediate-risk BC [6].
and BC-specific survival with maintenance BCG, and they suggest that perhaps the low sample size precluded statistical significance. However, if significance is not reached with 800 cases, then one wonders if the difference is of clinical benefit.

The perceived downsides of maintenance BCG are toxicity and compliance. Around half of treated patients complain of side effects, which are judged to be serious in up to 5% [1]. Toxicity has an impact on compliance such that, even in the most enthusiastic hands, only a third of patients complete the 3-yr regimen [4]. Few studies have prospectively evaluated quality of life on maintenance BCG. The poor compliance, frequent side effects, and anxiety regarding tumour status suggest life quality is compromised and support the need for alternative treatments/schedules. With this in mind, Herr et al report the long-term outcomes of complete responders to induction BCG [2]. Induction BCG should avoid some of the toxicity and compliance issues affecting a maintenance regimen. Complete responders were defined as those free of tumour at 6 mo, following resection and 6 wk of induction BCG, and they represented 7% of the initial patient cohort. As detailed within the report, most of these tumours were high grade, half were invading the lamina propria, and pTis was present in the majority (62%). With a minimum 5-yr follow-up, the authors observed recurrence of any tumour in half of these patients (50% of which occurred within 2 yr) and progression to muscle invasion in 11%. Radical cystectomy was performed in 8% of cases, and BC-specific death occurred in 4%. These data compare favourably with those from maintenance BCG reports, as detailed within the report’s discussion. For example, the most recent meta-analysis reported progression to invasion and BC-related death in 12% [8].

Where does this report now leave us? First, these data reopen the debate regarding maintenance and induction BCG. Herr et al have shown good outcomes with induction BCG, and so we must recognise this is a viable treatment. Second, we should wonder why this group has produced outcomes not reliably replicated in multicentred studies. Although authors and statisticians focus on BCG, this is only part of the treatment for BC. Of equal or more importance is the transurethral resection (TUR). It is likely that high-quality TUR and careful patient selection contributed significantly to these reported outcomes. TUR should clear all possible tumour, adequately stage the disease (including detrusor muscle from the correct region), and assess the urothelium (including from the prostatic fossa). The differences reported in residual tumour and upstaging rates demonstrate the wide variation in TUR quality [10]. A poor quality TUR may not only leave residual tumour but also fail to obtain sufficient information to assess the bladder adequately. We should imagine the difference in outcomes from an RCT comparing high- and low-quality TUR. This current report suggests we should also focus our attention on TUR quality. Finally, Herr et al support the first-line use of BCG for high-risk disease. But what was the outcome of all patients treated by BCG? Specifically, did patients within the 21% of nonresponders lose out by their 3-mo trial of BCG and check cystoscopy? We know in muscle-invasive disease that a delay of 3 mo can adversely affect outcome. So, despite numerous RCTs on these cancers, we still do not know what the maximum possible survival is for newly diagnosed high-risk disease. Without this context it is hard to place BCG treatment data. Retrospective series suggest immediate radical cystectomy provides a survival benefit over delayed surgery in BCG failures (reviewed in Kulkarni et al [7]). However, the benefit is not uniform and so is likely to include selection bias.

In summary, these data suggest that complete responders to induction BCG have a good prognosis, if managed carefully. Rather than the need for a new trial, I suggest we accept these findings and include induction BCG as an option when counselling patients. Further RCTs are needed, but these should be aimed at placing BCG in context and evaluating newer therapies/delivery strategies to reduce progression and cancer-specific death.

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References