



Letter to the Editor

Reply to Donald Lamm, Andreas Böhle, Joan Palou, et al.'s Letter to the Editor re: Per-Uno Malmström, Richard J. Sylvester, David E. Crawford, et al. An Individual Patient Data Meta-Analysis of the Long-Term Outcome of Randomised Studies Comparing Intravesical Mitomycin C versus Bacillus Calmette-Guérin for Non-Muscle-Invasive Bladder Cancer. Eur Urol 2009;56:247–56

We appreciate the comments of Lamm and colleagues regarding our meta-analysis [1]. They bring up three main issues concerning the choice of therapy: (1) Is mitomycin C (MMC) better than other chemotherapies? (2) What is the carcinogenic risk associated with long-term use of MMC? (3) Does bacillus Calmette-Guérin (BCG) decrease the risk of progression?

The question of whether MMC (an alkylating agent), and especially an optimized MMC, is more effective than other chemotherapies such as epirubicin (an anthracycline) has never been properly studied. MMC has a lower molecular weight than epirubicin, and hence, at least theoretically, MMC may be more readily absorbed into the layers of the bladder wall.

No randomized trials have directly compared MMC to epirubicin in patients with non-muscle-invasive bladder cancer. Two small European Organization for Research and Treatment of Cancer phase 2 chemoresection studies showed similar response rates for epirubicin and MMC [2]. Similarly, in the meta-analysis of a single, immediate, postoperative instillation, there was no suggestion that epirubicin might be less effective than MMC [3]. However, a meta-analysis of randomized studies of the treatment of patients with carcinoma in situ suggested that MMC might be more effective than either adriamycin or epirubicin [4]. Thus, some very limited evidence suggests that MMC might be more effective than epirubicin, but proper randomized studies have not been carried out.

All chemotherapies have DNA-damaging capacities because that is their main functional activity. Unfortunately, benign tissue may also be affected, and it is well known that prior chemotherapy increases the risk of later malignancy. The authors refer to data in animal models about this risk after MMC instillations, but it is not always the case that effects seen in animal models can be directly translated to humans. An interesting example is the studies

in laboratory rats during the early 1970s that linked saccharin, an artificial sweetener, to the development of bladder cancer. Based on those studies, the US government warned about the use of saccharin. Further studies showed that the results applied only to rats, and no association with the incidence human bladder cancer was found. Subsequently, the US government's warning about saccharine was removed. For MMC, we think that even the theoretical risk should be considered. Thus, treatment should not be given without a proper indication and for no longer than is necessary. The same applies even more to BCG therapy, which has a real risk of life-threatening toxicity.

The question of whether BCG reduces the risk of progression compared to an optimized MMC cannot be answered due to a lack of data. Previous meta-analyses comparing BCG and MMC were not based on individual patient data [5,6]. The largest meta-analysis comparing BCG to all other treatments showed a significant reduction in the risk of progression with BCG, but a subgroup comparison in studies randomizing between BCG and MMC was inconclusive [5]. Another meta-analysis that claimed to show an advantage for BCG compared to MMC in reducing the risk of progression included several nonrandomized studies [6]. Although BCG reduces the risk of progression, data are lacking about whether or not maintenance BCG reduces the risk of progression compared to an optimized MMC, especially in current practice, where patients may receive an immediate instillation and have a second-look transurethral resection. Unfortunately, it is unlikely that such a study will ever be done.

Conflicts of interest: The author has nothing to disclose.

References

- [1] Malmström P-U, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. *Eur Urol* 2009;56:247–56.
- [2] Bono AV, Hall RR, Denis L, Lovisolo JA, Sylvester R. Chemoresection in Ta-T1 bladder cancer. *Eur Urol* 1996;29:385–90.
- [3] Sylvester RJ, Oosterlinck W, van der Meijden APM. A single immediate postoperative instillation of chemotherapy decreases the

- risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol* 2004;171:2186–90.
- [4] Sylvester RJ, van der Meijden APM, Witjes JA, Kurth KH. Bacillus Calmette-Guérin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2005;174:86–92.
- [5] Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized trials. *J Urol* 2002;168:1964–70.
- [6] Bohle A, Bock PR. Intravesical bacilli Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology* 2004;63:682–6.

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