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Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non–Muscle-invasive Bladder Cancer

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Abstract

Background: Despite adjuvant intravesical therapy, recurrences in non–muscle-invasive bladder cancer (NMIBC) are still high; therefore, new treatment options are needed. The use of chemohyperthermia (CHT) as an alternative treatment is expanding in Europe. To date, however, there has been a lack of prospective randomised data.
Objective: To compare CHT using mitomycin C (MMC) with bacillus Calmette-Guérin (BCG) as adjuvant treatment for intermediate- and high-risk NMIBC.
Design, setting, and participants: Between 2002 and 2012, 190 NMIBC patients were randomised in this controlled, open-label, multicentre trial for 1-yr CHT (six weekly treatments and six maintenance treatments) and 1-yr BCG immunotherapy (six weekly treatments and three weekly maintenance treatments at months 3, 6, and 12). Patients and physicians giving the interventions were aware of assignment. This study is registered with ClinicalTrials.gov (NCT00384891).
Outcome measurements and statistical analysis: The primary end point was 24-mo recurrence-free survival (RFS) in the intention-to-treat (ITT) and per-protocol (PP) analyses in all papillary NMIBC patients ($n = 147$). Analyses were done with the log-rank test and Fisher exact test. All tests were two-sided.
Results and limitations: The 24-mo ITT RFS was 78.1% in the CHT group compared with 64.8% in the BCG group ($p = 0.08$). The 24-mo RFS in the PP analysis was 81.8% in the CHT group compared with 64.8% in the BCG group ($p = 0.02$). Progression rates were $<2\%$ in both groups. Regarding the side-effects, no new safety concerns were identified. A concern is that this study closed prematurely and thus is underpowered. Furthermore, blinding of treatment for patients and physicians was impossible; this may have resulted in unavoidable bias.
Conclusions: CHT is a safe and effective treatment option in patients with intermediate- and high-risk papillary NMIBC. A significantly higher 24-mo RFS in the CHT group was seen in the PP analysis. Based on the results above, CHT is an option for BCG therapy as adjuvant treatment for intermediate- and high-risk papillary NMIBC.
Patient summary: Recurrences in non–muscle-invasive bladder cancer are common, despite adjuvant therapies. We compared 24-mo recurrence-free survival (RFS) with chemohyperthermia (CHT) versus bacillus Calmette-Guérin (BCG) therapy. According to these data, CHT therapy appears to be safe and has higher 24-mo RFS than BCG therapy.

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1. Introduction

Treatment strategies for intravesical therapy of non–muscle-invasive bladder cancer (NMIBC) have not changed significantly over the past three decades. Intravesical irrigation is usually done with mitomycin C (MMC), epirubicin, and valrubicin. An upcoming agent is gemcitabine, but this is not yet considered standard. Besides chemotherapeutics, there is immunotherapy with bacillus Calmette-Guérin (BCG), with better efficacy than intravesical chemotherapy [1] but with more frequent and severe side-effects. Despite extensive research, no major changes have been realised in adjuvant treatment regimens; however, new drugs and strategies are currently studied. The combination of intravesical chemotherapy and hyperthermia by radiofrequency has been used in clinical practice for >15 yr, but experience remains limited, as are reported data. The first randomised controlled trial was published in 2003 [2], showing a clear advantage of chemohyperthermia (CHT) over treatment with MMC alone. This trial was updated in 2010, resulting in similar conclusions [3]. A recent review evaluated the results of CHT with regard to recurrence and progression, including toxicity [4]. Because CHT is used in combination with MMC, this review focussed on the comparison of CHT with MMC alone. A reduction in recurrence rates of 59% for CHT was found. Nevertheless, data were insufficient to make statements on progression. Furthermore, CHT had more local toxicity and complications compared with MMC alone, but differences were not significant. Lammers et al concluded that although this review showed a reduced recurrence rate for CHT, more conclusions could not be drawn due to limited data from randomised trials and different design of studies [4].

In this study, we reported the results of intermediate- and high-risk NMIBC patients who were randomised between intravesical CHT with MMC and BCG.

2. Methods

In this international, multicentre, prospective, randomised phase 3 trial, 11 institutions participated from six different countries: Israel ($n = 3$), Italy ($n = 3$), the Netherlands ($n = 1$), Austria ($n = 1$), France ($n = 2$), and Belgium ($n = 1$). Ethics committee approval was obtained at all participating hospitals. The study was conducted in accordance with good clinical practices, with the Declaration of Helsinki (version 1996), and with local laws and regulations [5,6]. This study is registered with ClinicalTrials.gov (NCT00384891).

2.1. Patient selection

Patients with intermediate- and high-risk NMIBC according to the 2001 European Association of Urology risk category definitions were eligible [7]. Inclusion criteria were patients with any pT1 or grade 3 urothelial carcinoma (UC) and/or carcinoma in situ (CIS) or multifocal (six or more) pTa lesions and/or multiple (three or more) recurrences of pTa lesions in the last 24 mo. All patients required a presumed transurethral resection of the bladder tumour (TURBT), confirmed by negative cytology and video cystoscopy with negative biopsies from suspected areas before intravesical therapy started. In high-risk NMIBC patients, re-resection of the tumour bed and random biopsies were mandatory. In CIS patients, positive cytology and/or CIS-positive biopsies were allowed. Further criteria were World Health Organisation performance status ≤2, life expectancy >24 mo, and patient willingness to sign informed consent statements according to International Conference on Harmonisation/European Union guidelines on Good Clinical Practice and national and local regulations.

Exclusion criteria were histology other than UC, another primary malignancy (basal cell carcinoma excluded), UC involving the urethra or upper urinary tract, previous history of UC stage T2 or higher, intravesical MMC treatments during the previous 12 mo, any previous BCG therapy <48 mo, previous pelvic radiotherapy or systemic chemotherapy, partial cystectomy, bladder diverticulum >1 cm, residual urine >100 ml, bladder volume <150 ml, urinary incontinence, urethral stricture impeding 20F catheterisation, persistent haematuria, active intractable or uncontrollable urinary tract infection (UTI), active tuberculosis or BCG infection, patients with previous BCG life-threatening sepsis, known MMC or BCG allergy, known impaired immune response, positive HIV serology, receipt of systemic steroids or immunosuppressives, haematological disorders, leukocytes <3500, platelets <100 000, kidney or liver function disorders (>1.5 times upper normal limit), and pregnant/lactating women. All patients gave written informed consent.

2.2. Treatment schedules

The hyperthermia device (Synergo system; Medical Enterprises Europe B.V., Amstelveen. The Netherlands) has been described in detail previously [2]. In summary, it is a computer-embedded intravesical irrigation system combined with an energy-delivering unit. The irrigation system has a disposable catheter system that delivers radiofrequency energy through an antenna. This system uses hyperthermia of the bladder wall induced by emission of radiofrequency energy, monitored by deployable thermocouples, combined with intravesical chemotherapy. The drug is cooled by a heat exchanger in a continuously circulated closed circuit.

After randomisation, patients in group 1 were treated with intravesical CHT with MMC weekly for 6 wk, followed by six maintenance sessions at 6-wk intervals during the rest of year 1. Sessions consisted of two 30-min treatments with 20 mg MMC (Kyowa Hakko Kogyo Co, Ltd, Tokyo, Japan) dissolved in 50 ml distilled water, combined with local hyperthermia at 42 ± 2 °C. In group 2, BCG (OncoTICE, full dose; Merck, Kenilworth, NJ, USA) was given as a 1-yr schedule: six weekly induction sessions and three weekly repeated maintenance sessions at months 3, 6, and 12. Patients retained BCG in the bladder for 120 min. Intravesical therapy started between 38 wk after initial TURBT or 3–6 wk after the second TURBT in cases of high-risk tumours.

2.3. Follow-up and evaluation of therapy

Patient follow-up was at least 24 mo after randomisation at 3-mo intervals, including blood analysis, urinalysis, cytology, cystoscopy, and biopsies of suspicious areas.

Study termination was defined as adverse events (AEs) causing treatment delay for ≥2 wk or withdrawal of informed consent. Patients with a tumour recurrence during the 12 mo of treatment underwent presumed radical TURBT and continued treatment as planned, unless this recurrence was T1G3 or muscle invasive. Patients with a second recurrence went off study but were followed for at least 24 mo.

2.4. Side-effects

AEs (using Common Toxicity Criteria of Adverse Events 2.0) were recorded at every treatment or follow-up visit. In case of side-effects, no dosage modifications were allowed, only treatment delay. For CHT, in case of severe pain due to the heating, increased pump flow and/or reduction of radiofrequency power was applied. For other side-effects, treatment recommendations were protocol given.

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