
Safety and Tolerability Analysis of Hyperthermic Intravesical Mitomycin to Mitomycin Alone in HIVEC I and HIVEC II: An Interim Analysis of 307 Patients

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Introduction: There is increasing evidence that hyperthermic MMC (HM) is an effective treatment for non-muscle invasive bladder cancer (NMIBC). The COMBAT BRS system is a novel hyperthermia delivering device which allows temperature controlled delivery and recirculation of HM via a urethral catheter using an external heat source. HIVEC I and II are two randomised control trials to determine if HM is superior to MMC alone in intermediate risk NMIBC. We report safety and tolerability outcomes comparing the two treatment arms.

Methods: HIVEC I and II are multicentre, open-labelled phase II randomised controlled trials recruiting patients from 25 Spanish and UK centres. The HIVEC I randomises patients to either MMC, HM for 30 mins and HM for 60 mins (HM 60). Patients receive 4 once weekly treatments followed by 3 one monthly treatments. HIVEC II randomises patients to MMC or HM 60 where both treatment arms receive 6 weekly treatments. Both trials use 40 mg MMC in all arms diluted in either 50 ml (HIVEC I) or 40 ml (HIVEC II) of sterile water. We compared all HIVEC I and II patients who were randomised to MMC (n=154) or HM 60 (n=153). Main inclusion criteria included complete resection of visible tumour prior to enrolment into the trial. Patients with urothelial cell carcinoma of the prostatic urethra or upper urinary tracts were excluded. HM was delivered by heating MMC to 43°C and delivered using a 16 Fr catheter. Adverse events (AE) were reviewed by the independent data monitoring committee. HIVEC I was registered with the EudraCT (2013-002628-18) while HIVEC II was registered with ISRCTN (23639415).

Results: 307 patients were included for analysis. 88.9% and 94.8% of HM and MMC patients completed adjuvant inductive therapy respectively. Reasons for stopping therapy in 17 HM patients include: MMC allergy (n= 11), urinary symptoms (n=2), pain (n=1), haematuria (n=1), pneumonia (n=1) and in 8 MMC patients include: MMC allergy (n=7) and angina (n=1). AE which led to early termination of treatment were Grade II. 218 and 137 related AE were reported in HM and MMC arms respectively. There was no significant difference in AE between HM (n=78, 51%) and MMC (n=66, 42.9%) (p=0.154). There were 118 unrelated AE in the HM arm and 140 unrelated AE in the MMC arm. Most AE were Grade ≤II (HM: 97.7%, MMC: 98.5%). Grade III AE included: pain (N=1) and MMC allergy (n=2) in the HM arm and pyrexia (n=1) and MMC allergy (n=1) in the MMC arm. There was no Grade >III related AE. There was no difference in pain (HM: 13.1% vs MMC: 8.4, p=0.190), dysuria (HM: 5.2% vs MMC: 6.5%, p=0.617), urgency (HM: 11.8% vs MMC: 3.9%, p=0.067), incontinence (HM: 3.3% vs MMC: 0.6%, p=0.097), nocturia (HM: 3.9% vs MMC: 3.9%, p=0.991), urinary tract infection (HM: 3.3% vs MMC: 2.6%, p=0.728) and rash/ allergic reaction (HM: 7.8% vs MMC: 5.2%, p=0.327). HM treated patients were significantly more likely to develop urinary frequency (HM: 15.0% vs MMC: 5.8%, p=0.008), haematuria (HM: 11.8% vs MMC: 3.9%, p=0.010) and bladder spasm (HM: 6.5% vs MMC: 0.6%, p=0.006). No urethral strictures were reported in either treatment arm.

Conclusions: HM delivered using the COMBAT BRS system is safe and well tolerated. The majority of AE observed in the HM arm were low grade with urinary frequency and haematuria more common in HM in comparison to MMC treated patients. HM represents a safe and well tolerated intravesical treatment for NMIBC.