CHEMO-RESECTION WITH HYPERTHERMIC INTRAVESICAL INSTILLATION (HIVEC-R) VS STANDARD TREATMENT IN PATIENTS WITH INTERMEDIATE-HIGH RISK NMIBC: COMPARATIVE, PROSPECTIVE, RANDOMIZED, CONTROLLED STUDY OF EFFICACY AND TOLERABILITY

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Introduction:
The rationale about neoadjuvant chemo-hyperthermia (NCHT) in NMIBC is based on the concept of “immunogenic cell death (ICD)”. Some kinds of antineoplastic treatments, including CHT, may destroy tumoral cells by ICD. We hypothesized that NCHT may stimulate patient’s immune response acting as a vaccine against cancer.

Material and Methods:
A Phase III comparative, prospective, randomized, controlled clinical trial with Mitomicyn C (MMC) was designed to compare the efficacy and tolerability of NCHT with 8 neoadjuvant weekly doses of 80 mg MMC recirculating at 43 ºC with the BRS system, Combat Medical (Hertfordshire. UK) vs 15 passive, normothermic, standard, adjuvant doses (4 weekly + 11 monthly) of 40 mg MMC after TURBT.

The primary endpoint of the study was 24-months recurrence free survival (RFS) of NCHT compared with standard treatment. Secondary endpoints were efficacy of NCHT in terms of complete and partial response (CR, PR) after 4 and 8 doses. Tolerability, Quality of life and cost-effectiveness of NCHT compared with standard instillation.

Inclusion criteria: Histological confirmed previous urothelial cell carcinoma (UCC), NMIBC following recurrence of G1-3 pTa or G1-2 pT1, ≤6 number of tumours, Aged ≥18 years.

Exclusion criteria: Patients with solid tumour, muscle infiltrating aspect or CIS suspicious, positive citology and recurrence of previous T1G3 or CIS tumours in the last 12 months.

Calculating a 45% recurrence risk (average of intermediate-high NMIBC), a 5% α-error, a 80% statistical power and an estimated rate of follow up loss of 5%; the population needed for each arm was 34 patients. Between march 2015 and June 2019, 68 patients were treated at ISUH (13 pts) and CHM (55 pts). Mean follow up was 38 months (4-54 months).

Results:
Initial pathological response (NCHT arm): 21 patients showed CR (pT0) 61.8%, 10 patients showed PR 29.4%, 3 patients showed NR 8.8%. After 38 months, in the NCHT arm 7/34 (20.5%) patients showed recurrences and 1/34 (2.9%) progression to T1G3/Cis. In the standard MMC arm, 13/34 (38.2%) patients showed recurrences, 3/34 (8.8%) local progression and 1/34 (2.9%) muscular invasion (T2G3). Differences were statistically significative for recurrence (p<0.02), superficial (p<0.05) and muscular progression (p<0.01).

Tolerance and adverse effects were similar in both groups (p<0.3) . In the NCHT arm, 18/34 pts (52.9%) showed grade 1-2 AE (irritative symptoms, bladder spasms, pain, hematuria,
urinary infection and MMC allergy) and 3/34 (8.8%) grade 3 (bladder retraction, bladder calcification and urethral stenosis). Among the St MMC arm 15/34 pts (44.1%) showed grade 1-2 AE (irritative symptoms, bladder spasms, pain, hematuria, urinary infection and MMC allergy) and 2/34 (5.8%) grade 3 (bladder retraction and urethral stenosis).

Conclusions:
A 60% of patients showed complete response after NCHT and the recurrence and progression rates after a mean follow up of 3 years were significantly better in the NCHT arm. Further studies are needed to confirm a protector effect of NCHT against tumoral recurrence and progression.