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Zazzara M, Nazaraj A, Scarcia M, Cardo G, Carando R, Ludovico GM. Electromotive Drug Administration mitomycin C versus intravesical immunotherapy with Bacillus Calmette-Guérin in intermediate and high-risk non muscle invasive bladder cancer.
Uro Int. Dec 2021:1-8. doi: 10.1159/000520630.

Background

Although TURB of tumor (TURBT) by itself can eradicate a non-muscle-invasive bladder cancer (NMIBC) completely, these tumors commonly recur and can progress to MIBC. It is, therefore, necessary to consider adjuvant therapy in most patients. The primary objective of the present study was to report our experience with EMDA/MMC and BCG, considering efficacy, progression, and recurrence, as adjuvant therapy in NMIBC patients; the secondary objective was to assess the efficacy of EMDA/MMC versus BCG as a comparative treatment.

Methods

Between April 2016 and February 2020, a series of 216 patients, with a diagnosis of intermediate- and high-risk NMIBC after TURBT, underwent adjuvant intravesical therapy. In 26 cases with a failure of the treatment, in patients unfit and unwilling for radical cystectomy, a repeated intravesical therapy was performed (2 had a twice repetition). Out of 244 adjuvant therapies, 140 EMDA/MMC and 104 BCG treatments were done. The following data were collected for each patient: baseline demographics and clinical data and perioperative and postoperative data. Overall patients' adjuvant intravesical therapies were included in a prospectively maintained institutional database, and a retrospective chart review was performed. We collected data on 2 main outcomes, recurrence-free survival (defined as a negative cystoscopy, cytology, and/or histology at the evaluation time point) and progression-free survival (defined as a negative cystoscopy or a nonprogressive tumor recurrence).

Results

The NMIBC progression rate was higher in BCG than EMDA/MMC but not statistically significant (respectively, 4.2% vs. 2.5%; $p = 0.703$). In the overall population, the risk of NMIBC recurrence was higher after BCG than EMDA/MMC ($p = 0.025$). In the subgroups of 59 paired patients with similar characteristics, no difference was observed between groups in NMIBC progression and recurrence.

Conclusions

Our findings suggest that EMDA/MMC and BCG are safe and reproducible approaches as adjuvant treatment in NMIBC EMDA/MMC permits to achieve a fine oncological management as adjuvant treatment in NMIBC, which is not less than that obtained with BCG.

Carando R, Soldini E, Cotrufo S, Zazzara M, Ludovico GM. " Electro-mediated drug administration of mitomycin C in preventing non-muscle-invasive bladder cancer recurrence and progression after transurethral resection of the bladder tumour in intermediate- and high-risk patients" Arab J Urol. 2020 Aug;19(1):71–77. doi: 10.1080/2090598X.2020.1816150.

Objective

To evaluate the effectiveness of electro-mediated drug administration of mitomycin C (EMDA/MMC) after transurethral resection of the bladder tumour (TURBT) in preventing non-muscle-invasive bladder cancer (NMIBC) recurrence and progression and to explore clinical and demographic factors associated with treatment response.

Patients and methods

Between April 2016 and August 2019, 112 patients diagnosed with intermediate- or high-risk NMIBC underwent a TURBT followed by an EMDA/MMC treatment. The percentage of treatment responders and progression-free survivors at 3 and 6 months were evaluated.

Results

Follow-up data were available for 101 patients (90%) at 3 months and 92 (82%) at 6 months. Response rates to EMDA/MMC treatment were 85% at 3 months and 75% at 6 months, and progression-free rates were 94% and 90%, respectively. No statistically significant differences were seen between intermediate- and high-risk patients. A higher risk of tumour recurrence and progression was associated with previous Bacillus Calmette-Guérin (BCG) failure. According to the Clavien-Dindo classification, only low-grade complications were observed.

Conclusions

EMDA/MMC after TURBT was associated with high response and progression-free rates at 3 and 6 months, with only low-grade adverse events. These results confirm the efficacy and safety of EMDA/MMC as a therapeutic option for both intermediate- and high-risk patients. However, patients with BCG failure responded poorly to EMDA/MMC.

Carando R, Zazzara M, Cotrufo S, Ludovico GM. " Intravesical Treatment with Electro-Mediated Administration of Mytomicin C as Prophylaxis for Intermediate and High-Risk Non-muscle Invasive Bladder Cancer: A Retrospective Multicenter Study" Urol Int. 2019;103(3):285–290. doi: 10.1159/000502663.

Background

Topical therapy of non-muscle invasive bladder cancer (NMIBC) is based on immunotherapy with Bacillus Calmette-Guerin and chemotherapy administered by passive instillation, but an active drug administration achieves a better concentration of the drugs in the bladder.

Aim

This study aimed to investigate the effectiveness of electromotive drug administration (EMDA) of mitomycin C (EMDA/MMC) in intermediate- and high-risk NMIBC patients 6 months after the end of induction treatment.

Materials and methods

Sixty-five patients diagnosed with histologically confirmed NMIBC, with a complete transurethral resection of all visible tumors underwent EMDA/MMC. Primary endpoint was the proportion of responders at 3 or 6 months.

Results

Data on follow-up were available for 62 subjects at 3 months and 45 at 6 months. EMDA was effective in intermediate- and high-risk patients: because of the small number of cases no conclusions can be drawn on the efficacy in the low-risk group. No difference in the response to treatment between intermediate- (83.3%) and high-risk (84%) patients could be seen.

Conclusions

EMDA/MMC is a useful technique for an effective and safe treatment of primary and recurrent NMIBC, and a valuable therapeutic option in intermediate - and high-risk NMIBC patients.

Lane J, Abdille Z, Gan C, Chatterton K, Amery S, Thurairaja R, Khan S, Malde S, O'Brien T et al. "Will long-term disease specific outcomes of bladder conservation with sequential Bacillus Calmette-Guérin (BCG) and electromotive drug administration Mitomycin-C (EMDA-MMC) for high-risk non -muscle invasive bladder cancer (HR-NMIBC) influence adoption?"- Guy's and St. Thomas' NHS Foundation Trust, London Bladder Cancer Translational Research Meeting, King's College London, UK, March 29, 2019.

Background

Superior short-term outcomes of sequential BCG with EMDA-MMC when treating HR-NMIBC have been reported. Despite this, the regimen has not been widely adopted for bladder conservation and the optimal regimen is yet to be determined. An understanding of long-term oncological outcomes would be important in understanding its true role and may encourage wider adoption.

Methods

This is a prospective single-centre study of 464 patients, presenting with new HR-NMIBC between June 2009 and July 2017. The bladder conservation schedule followed TURBT with adjuvant 9-week induction consisting of 3 consecutive and identical cycles of; BCG in weeks 1 and 2, followed by EMDA-MMC in week 3. Maintenance was 3-weekly BCG. Cystoscopy was used to assess response at 8 weeks post induction. Primary outcome measures evaluated were recurrence free survival, progression rates and outcomes following salvage treatment.

Results

249 patients received sequential BCG/EMDA-MMC with a median follow-up of 54 months (4-108). 206/249 (83%) received treatment for high-grade (Ta/T1) disease, and 13/249 (5%) for primary carcinoma in situ. A further 30/249 (12%) received treatment for recurrent or large volume low-grade disease. Of the 196/249 (79%) patients who completed the induction course of treatment 123/196 (63%) have remained disease-free during follow-up. 53/196 (27%) patients developed bladder recurrence, of which 22/53 (42%) demonstrated stage migration (≥T2 disease). Of note, 28/53 (53%) developed recurrence within the first three years of treatment. Of the 15/53 (28%) who subsequently underwent radical cystectomy, upstaging on final histopathology was demonstrated in 8/15 (53%) patients, 1/15 (6%) died of metastatic bladder cancer.

Conclusion

If induction BCG/EMDA-MMC treatment is completed, over two-thirds of patients remain disease-free during long term follow-up. This is twice the efficacy quoted for intravesical BCG alone and adds further weight to the adoption of this sequential regimen in bladder preservation for HR-NMIBC.

Di Stasi SM, Ambrosi Grappelli V, Pagliarulo V, Fede Spicchiale C, Giannantoni S. “Intravesical adjuvant electromotive mitomycin-C in patients with primary intermediate-risk urothelial non-muscle invasive bladder cancer: a randomized controlled trial” Eur Urol. 2019;18(9): e3248. https://doi.org/10.1016/S1569-9056(19)33633-4.

Aim of the study

In laboratory and clinical studies, intravesical electromotive drug administration (EMDA) increased mitomycin-C (MMC) bladder uptake, improving clinical efficacy in high-risk non-muscle invasive bladder cancer (NMIBC). Our aim was to compare transurethral resection of bladder tumor (TURBT) and adjuvant intravesical electromotive EMDA/MMC with TURBT and adjuvant intravesical passive diffusion (PD) MMC and TURBT alone in patients in patients with primary intermediate-risk urothelial NMIBC.

Materials and methods

225 patients were randomly assigned to: TURBT alone (n = 75), TURBT and adjuvant intravesical 40 mg PD/MMC dissolved in 50 ml sterile water infused over 60 minutes once a week for 6 weeks (n = 77), or TURBT and adjuvant intravesical 40 mg EMDA/ MMC dissolved in 100 ml sterile water with 23 mA pulsed electric current for 30 minutes once a week for 6 weeks (n = 73). Patients in the intravesical adjuvant EMDA/MMC and PD/MMC groups who were disease-free 3 months after induction treatment, were scheduled to receive monthly intravesical instillation for 10 months, with the same dose and methods of infusion as initial assigned treatment. All patients were assessed for safety. Our primary endpoints were recurrence rate and disease-free interval. Analyses were done by intention to treat.

Results

Median follow-up was 86 months (IQR 53–123). Patients assigned to receive TURBT and adjuvant intravesical EMDA/MMC had a lower rate of recurrence (26/73 [36%]) than those assigned to receive TURBT and adjuvant intravesical PD/MMC (46/77 [60%]) and TURBT alone (47/75 [63%]; log-rank $p < 0.0004$). Patients assigned to receive TURBT and adjuvant intravesical EMDA/MMC also had a higher median disease-free interval (19 months, 95%CI 11–27) than those assigned to receive TURBT and adjuvant intravesical PD/MMC (10.5 months, 10–16) and TURBT alone (10 months, 7–13; log-rank $p < 0.0001$). In patients who underwent adjuvant intravesical MMC local side-effects and symptoms were recorded in 19/77 (25%) in the PD/MMC group, and in 19/73 (26%) in the EMDA/MMC group. Treatment was stopped because of chemical cystitis side-effects in 3/ 77 (4%), and 1/73 (1%) patients of these groups, respectively.

Discussion

Adjuvant Intravesical EMDA/MMC is feasible and safe; moreover, it reduces recurrence rates and enhances the disease-free interval in patients with in patients with primary intermediate-risk urothelial NMIBC compared with TURBT and adjuvant intravesical PD/ MMC and TURBT alone.

Di Modugno F, Pagliarulo V, Ditonno P et al. “Intravesical sequential BCG/electromotive drug administration Mitomycin C (EMDA-MMC) in high risk non muscle invasive bladder cancer – results from a retrospective analysis” Eur Urol. Supplements September 2018;17(8): 357-357 https://doi.org/10.1016/S1569-9056(18)33383-9.

Purpose

Intravesical sequential BCG/Electromotive drug administration Mitomycin C (EMDA-MMC) is reported to be superior to BCG alone, but is not widely adopted.
The goals of the present study were to establish our experience with sequential administration of intravesical BCG and EMDA-MMC in terms of patient’s compliance, clinical response and complications rate.

Materials and methods

From January 2011 to December 2017 all patients with high risk non muscle invasive bladder cancer undergoing sequential administration of intravesical BCG and EMDA-MMC at our department of Urology and represented the cohort of interest for the present retrospective study. The patient were followed for 43 months.
In all cases, administration of EMDA was delivered at a dose of 40 mg, for 20 minutes at a current of 25 mA.
The protocol for treatment induction was: BCG in weeks one and two, EMDA-MMC in week three, repeated thrice for nine weeks in total. Maintenance: EMDA-MMC in months three and four, BCG in month five, repeated thrice for nine months in total.
Correlations were established using the statistical methodology: to compare continuous variables has been used Student’s Test for independent samples. To evaluate association between analysis parameters has been used simple linear regression.
In addition we have been calculated odds ratio and has been used test z score. For every test has been considered significant a p-value<0,05.

Results

In the selected period of time we found 87 patients that were adherent to our inclusion criteria and that underwent sequential administration of intravesical BCG and EMDA-MMC. The characteristics of our cohort are described in table 1.
Among the entire cohort, the treatment was interrupted before completion in 8/87 (9,2%) for the following reasons: 1/8 (12,5%) voluntarily, 1/8 (12,5%) for urethrorrhage, 1/8 (12,5%) for lower urinary tract symptoms and 5/8 (62,5%) for unknown reasons. Disease recurrence was found in 17/87 (19,5%) patients (CI 95% = 11,8% - 29,4%) and, on average, disease recurrence appeared 16,4±11,3 (range = 2,0-36,0) months after the induction of the therapy. Only 2/87 (2,3%) patients had a disease progression (CI 95% = 0,3% - 8,1%; n = 2/87) and, on average, disease progression appeared 5,0 ± 2,8 (range = 3,0 - 7,0) months after the induction of the therapy.
Finally, 9/87 (10,3%) patients showed the following side effects: 4/9 (44,4%) recurrent urinary tract infections, 2/9 (22,3%) severe lower urinary tract symptoms, 1/9 (11,1%) urethrorrhage and 1/9 (11,1%) haematuria.

Conclusion

Intravesical sequential BCG/Electromotive drug administration Mitomycin C (EMDA-MMC) is well-tolerated. Drop out is low and, in particular, clinical response is excellent in terms of recurrence and progression during the period of study.

Racioppi M, Di Gianrancesco L, Ragonese M., Palermo G, Sacco E, Bassi PF." Electromotive drug administration (EMDA) of Mitomycin C as First-line salvage therapy in high risk "BCG Failure non muscle bladder cancer: 3 years follow-up outcomes" BMC Cancer. 2018 Dec 6; 18(1):1224. doi: 10.1186/s12885-018-5134-7.

Background

In case of high grade non-muscle invasive bladder cancer (HG-NMIBC), intravesical BCG represents the first-line treatment; despite the "gold" standard therapy, up to 50% of patients relapse, needing radical cystectomy. Hence, alternative therapeutic strategies have been developed. The aim of the study was to evaluate a first-line salvage treatment with EMDA®-MMC in patients with HGNMIBC unresponsive to BCG.

Methods

We carried out a prospective, single-center, single-arm Phase II study in order to evaluate the efficacy (in terms of recurrence and progression) and the safety of the EMDA®-MMC treatment in 26 (21 male, 5 female) consecutive patients with "BCG refractory" HGNMIBC on a 3 years follow-up. EMDA®-MMC treatment consisted of 40 mg of MMC diluted in 100 ml of sterile water retained in the bladder for 30 min with 20 mA pulsed electric current. EMDA®-MMC regimen consisted of an induction course of 6 weekly instillations followed by a maintenance course of 6 monthly instillations. Follow-up was performed with systematic mapping biopsies of the bladder (with sampling in the prostatic urethra for men), voiding and washing urinary cytology, radiological study of the upper urinary tract.
We performed Survival Kaplan-Meier curves and Log-rank test in order to analyze high grade disease-free survival.

Results

At the end of follow-up, 16 patients (61.5%) preserved their native bladder; 10 patients (38.4%) underwent radical cystectomy, in 6 patients (23.1%) for recurrent HGNMIBC and in 4 patients (15.4%) for progression to muscle-invasive disease. At the end of follow-up, stratifying patients based on TNM classification (TaG3, T1G3, Cis, TaT1G3 + Cis), disease-free rates were 75, 71.4, 50 and 25%, respectively; survival curves showed statistically significant differences (p value < 0.05). Regarding toxicity, we reported severe adverse systemic event of hypersensitivity to the MMC in 3 patients (11.5%), and local side effects in 6 patients (26.1%).

Conclusions

In the field of alternative strategies to radical cystectomy, the EMDA®-MMC could be considered safe and effective in high-risk NMIBC unresponsive to BCG, as a "bladder sparing" therapy in selected patients. Multicenter studies with a larger number of patients and a longer follow-up might confirm our preliminary results.

Gan C, Amery S, Chatterton K, Khan MS, Thomas K, O'Brien T. "Sequential bacillus Calmette-Guérin/Electromotive Drug Administration of Mitomycin C as the Standard Intravesical Regimen in High Risk Non muscle Invasive Bladder Cancer: 2-Year Outcomes" J Urol. 2016 Jun;195(6):1697-1703. doi: 10.1016/j.juro.2016.01.103.

Purpose

Sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C is reported to be superior to bacillus Calmette-Guérin alone but it has not been widely adopted.

We aimed to determine the efficacy and tolerability of sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C in high risk, non-muscle invasive bladder cancer.

Materials and methods

Starting in 2009 bacillus Calmette-Guérin/electromotive drug administration of mitomycin C was introduced as the standard induction regime in patients with high risk, non-muscle invasive bladder cancer undergoing bladder conservation.

As induction bacillus Calmette-Guérin was administered in weeks 1 and 2. Mitomycin C was administered in electromotive fashion (40 mg and 20 mA current for 30 minutes) in week 3 and repeated thrice for a total of 9 weeks.

As maintenance 3 doses of bacillus Calmette-Guérin were given 3 months after induction and then every 6 months for 3 years.

Outcome measures were disease recurrence at first check, 1 and 2-year cystoscopy, and treatment tolerability.

Results

Of the 151 patients with high risk, non-muscle invasive bladder cancer treated between June 2009 and 2013, 44 underwent primary cystectomy and 107 received sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C. Disease was high grade Ta/T1 in 86 patients (80%), of whom 34 (32%) also had carcinoma in situ. A total of 19 patients (18%) had primary carcinoma in situ and 2 had recurrent large volume, low grade disease. Of 107 patients 104 underwent first check cystoscopy, including 90 (87%) who were clear. Of the 90 complete responders 86 underwent 1-year cystoscopy, including 74 (86%) who were recurrence-free. Of the 74 patients 71 underwent 2-year cystoscopy, of whom 66 (93%) remained recurrence-free. The full induction schedule was not completed in 30 patients (28%), including 16 and 14 with minor and major schedule alterations, respectively. There was no difference in recurrence between patients who received a full vs a reduced induction schedule.

Conclusions

This study confirms the excellent oncologic efficacy of sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C in cases of high risk, non-muscle invasive bladder cancer. Tolerability is a challenge but alterations to the 9-week schedule appeared to have a negligible impact on outcomes.

Rehme C, Niedworok C, Rübben H et al. “Non muscle Invasive bladder cancer: safety of postoperative EMDA-assisted instillation of mitomycin” Urologe A. 2015, Feb; 54(2): 234-238. doi: 10.1007/s00120-014-3649-3.

Background

The immediate instillation of mitomycin after transurethral resection of bladder tumor (TURBT) is widely used and recommended in the guidelines. Recently it was shown that pre-TURBT intravesical electromotive drug administration (EMDA) of mitomycin reduces the recurrence rate of non-muscle invasive bladder cancer. Our aim was to describe the pharmacokinetics and patient safety after post-TURBT EMDA.

Methods

We performed a single centre study with 25 patients diagnosed with non-muscle invasive bladder cancer. All patients underwent complete resection of all visible tumors and post-TURBT intravesical electromotive drug administration (EMDA) of mitomycin (40 mg) for 30 min. Blood samples were taken before starting the electrical current and 15, 30, 60, and 120 min after starting the procedure for quantification of mitomycin serum levels.

Results

In 24 patients, the measured serum level of mitomycin was below the detection threshold of 50 ng/ml. In one patient serum level was elevated 15 min (155 ng/ml) and 30 min (65 ng/ml) after intravesical instillation. Nine patients reported a slight tingling sensation in the bladder during mitomycin administration. Discreet pressure in the suprapubic area was reported by one patient. One patient had a first degree skin burn at the site of one skin electrode.

Conclusion

Postoperative EMDA with mitomycin is a safe procedure. The measured mitomycin serum levels were below toxic concentrations. These findings encourage the initiation of large randomized controlled trials with postoperative EMDA-assisted instillation of mitomycin to test its influence on the recurrence rate of non-muscle invasive bladder cancer.

Bassel G, Bachir MD, Alice Dragomir PhD, Armen G, Aprikian MD et al. “Contemporary cost-effectiveness analysis comparing sequential bacillus Calmette-Guerin and electromotive mitomycin versus bacillus Calmette-Guerin alone for patients with high-risk non–muscle-invasive bladder cancer” Cancer. 2014;120(16):2424-2431. DOI: 10.1002/cncr.28731.

Background
Sequential bacillus Calmette-Guerin (BCG) and electromotive mitomycin (sequential therapy) have been shown in a randomized prospective trial to be superior to therapy with BCG alone in patients with high-risk non–muscle-invasive bladder cancer. The objective of the current study was to compare the costs and benefits of these 2 treatment strategies by performing a 5-year and 10-year cost-effectiveness study.

Methods
A Markov model was developed to estimate the incremental cost-effectiveness ratio over a 5-year and 10-year period. Estimates of disease progression, death, and treatment efficacy were obtained from what to the authors’ knowledge is the only randomized trial comparing the 2 therapies. Costs included: 1) medical costs (physician fees); 2) drug costs (preparation and instillation); and 3) hospital costs (procedure fees, admission fees, and tests and procedures done during surveillance). Patients were allowed a second course of induction therapy.

Results
Sequential therapy was found to be associated with a higher initial material cost for induction and maintenance. The average effectiveness for the patients treated with therapy with BCG alone was 4.39 years with a mean cost of $9236 (95% confidence interval, $9118-$9345) per patient. The sequential group resulted in an average effectiveness of 4.65 years, with a mean cost of $16,468 (95% confidence interval, $16,371-$16,527). The 5-year incremental cost-effectiveness ratio of sequential versus BCG-alone therapy was $27,815 per life-year gained. The corresponding figure over a 10-year period was $8618 per life-year gained.

Conclusions
The results of the current study suggest that sequential therapy is a cost-effective treatment for patients with high-risk non–muscle-invasive bladder cancer.

Savino SM, Verri C et al. “Electromotive mitomycin versus bacillus calmette-guérin alone for stage pt1 urothelial bladder cancer” J Urol. April 2012;187 (4S): e674 abstr 1670 https://doi.org/10.1016/j.juro.2012.02.1528.

Introduction and objectives

In 2006, we reported that intravesical sequential bacillus Calmette-Guérin (BCG) and electromotive mitomycin, in patients with stage pT1 urothelial bladder cancer, leads to higher disease-free interval, lower recurrence and progression, and to improved overall survival and disease-specific survival compared with BCG alone. After an additional 6 years of follow-up, we now report estimated 16-year results.

Methods

From January 1994 through June 2002, we randomly assigned 212 patients with stage pT1 urothelial bladder cancer to 81 mg BCG infused over 120 min once a week for 6 weeks (n=105) or to 81 mg BCG infused over 120 min once a week for 2 weeks, followed by 40 mg electromotive mitomycin (intravesical electric current 20 mA for 30 min) once a week as one cycle for three cycles (n=107). Complete responders underwent maintenance treatment: those assigned BCG alone had one infusion of 81 mg BCG once a month for 10 months, and those assigned BCG and mitomycin had 40 mg electromotive mitomycin once a month for 2 months, followed by 81 mg BCG once a month as one cycle for three cycles. The primary endpoint was disease-free interval; secondary endpoints were time to progression; overall survival; and disease-specific survival. Analyses were done by intention to treat.

Results

Median follow-up was 121 months (IQR 70.5–163.5). Patients assigned sequential BCG and electromotive mitomycin had higher disease-free interval than did those assigned BCG alone (79 months [95% CI 27–139] vs 26 months [11–113]; difference between groups 53 months [39–67], log-rank p=0.0002). Patients assigned sequential BCG and electromotive mitomycin also had lower recurrence (45% [35–55] vs 62% [50–72], difference between groups 17% [6–28], log-rank p=0.0002); progression (12% [3–21] vs 28% [17.5–38.5], difference between groups 16% [5–27], log-rank p=0.003); overall mortality (44% [33–55] vs 59% [43–75], difference between groups 15% [2–28], log-rank p=0.01); and disease-specific mortality (9% [2.5– 15.5] vs 23% [11–34], difference between groups 14% [4–24], log-rank p=0.0055). Side-effects were mainly localised to the lower urinary tract. Mitomycin pharmacokinetics showed that plasma levels remained well below toxic concentrations.

Conclusions

In patients with stage pT1 urothelial bladder cancer intravesical BCG combined with electromotive mitomycin provided better results than BCG alone in terms of higher response rates and longer remission times.

Di Stasi SM, Valenti M, Verri C et al. “Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial” Lancet Oncol. 2011 September;12(9) :871-879. doi: 10.1016/S1470-2045(11)70190-5.

Background

The clinical effect of intravesical instillation of chemotherapy immediately after transurethral resection of bladder tumours (TURBhas recently been questioned, despite its recommendation in guidelines. Our aim was to compare TURBT alone with immediate post-TURBT intravesical passive diffusion (PD) of mitomycin and immediate pre-TURBT intravesical electromotive drug administration (EMDA) of mitomycin in non-muscle invasive bladder cancer.

Methods

We did a multicentre, randomised, parallel-group study in patients with primary non-muscle invasive bladder cancer in three centres in Italy between Jan 1, 1994, and Dec 31, 2003. Patients were randomly assigned to receive treatment by means of stratified blocked randomisation across six strata. Patients and physicians giving the interventions were aware of assignment, but it was masked from outcome assessors and data analysts. Patients were randomly assigned to receive TURBT alone, immediate post-TURBT instillation of 40 mg PD mitomycin dissolved in 50 mL sterile water infused over 60 min, or immediate pre-TURBT instillation of 40 mg EMDA mitomycin dissolved in 100 mL sterile water with intravesical 20 mA pulsed electric current for 30 min. Our primary endpoints were recurrence rate and disease-free interval. Analyses were done by intention to treat. Follow-up for our trial is complete. This study is registered with ClinicalTrials.gov, number NCT01149174.

Findings

124 patients were randomly assigned to receive TURBT alone, 126 to receive immediate post-TURBT PD mitomycin, and 124 to receive immediate pre-TURBT EMDA mitomycin. 22 patients were excluded from our analyses because they did meet our eligibility criteria after TURBT: 11 had stage pT2 disease and 11 had carcinoma in situ. Median follow-up was 86 months (IQR 57-125). Patients assigned to receive EMDA mitomycin before TURBT had a lower rate of recurrence (44 [38%] of 117) than those assigned to receive PD mitomycin after TURBT (70 [59%] of 119) and TURBT alone (74 [64%] of 116; log-rank p<0·0001). Patients assigned to receive EMDA mitomycin before TURBT also had a higher disease-free interval (52 months, IQR 32-184) than those assigned to receive PD mitomycin after TURBT (16 months, 12-168) and TURBT alone (12 months, 12-37; log-rank p<0·0001). We recorded persistent bladder symptoms after TURBT in 18 (16%) of 116 patients in the TURBT-alone group (duration 3-7 days), 37 (31%) of 119 in the PD mitomycin post-TURBT group (duration 20-30 days), and 24 (21%) of 117 in the EMDA mitomycin pre-TURBT group (duration 7-12 days); haematuria after TURBT in eight (7%) of 116 patients in the TURBT-alone group, 16 (13%) of 119 in the PD mitomycin post-TURBT group, and 11 (9%) of 117 in the EMDA mitomycin pre-TURBT group; and bladder perforation after TURBT in five (4%) of 116 patients in the TURBT-alone group, nine (8%) of 119 in the PD mitomycin post-TURBT group, and seven (6%) of 117 in the EMDA mitomycin pre-TURBT group.

Interpretation

Intravesical EMDA mitomycin before TURBT is feasible and safe; moreover, it reduces recurrence rates and enhances the disease-free interval compared with intravesical PD mitomycin after TURBT and TURBT alone.

G. Leprini , R. Massoud , S. Dolci et al. “Concentration-depth profiles of mitomycin-C in the human bladder wall after passive diffusion, thermochemotherapy, and electromotive drug administration” Journal of Clinical Oncology 2010 28(15); abstr 4568.

Background

Device-assisted intravesical mitomycin-C (MMC), including electromotive administration (EMDA) and thermochemotherapy (TC), shows promise and offers the prospect of greater efficacy than passive diffusion (PD). Integration of drug delivery with tissue pharmacodynamic data provides a means to rational design of intravesical treatments. We compared concentration-depth profiles of MMC in the bladder wall after PD, TC and EMDA.

Methods

During each experiment, 3 full thickness sections of viable human bladder wall were placed between the two chambers of individual diffusion cells, with urothelium exposed to donor compartments containing 40 mg of MMC in 100 ml water and with serosa-facing receptor compartments containing 100 ml of 0.9% NaCl solutions. Fifteen paired experiments were conducted over a 30-min period. In TC experiments, the two chamber cells were placed in a 37°C incubator with the donor compartments filled with heated MMC solutions at 44°C. In EMDA experiments an anode was placed in the donor compartment and a cathode in the receptor compartment. The electrodes were connected to the current generator and experiments were performed with pulsed direct current of 23 mA. No electric current or TC were applied in PD control experiments.

Bladder wall sections were cut serially into 40-mm slices parallel to the urothelium, the tissues were homogenized and analyzed by high-performance liquid chromatography for MMC concentration.

Results

Concentration-depth profiles of MMC in bladder wall tissues following PD, TC or EMDA are reported below (Table). Data are expressed as µg of MMC/mg of wet tissue, the means ± standard error of the mean (SEM) of 15 replicates per experimental group.

Conclusions

EMDA significantly enhances MMC transport into all of the layers of the bladder wall, compared to both PD and TC. The latter had no effect whatsoever on MMC transport into bladder wall tissues compared to PD.

	PD	TC	EMDA	p value
Urothelium (80-200 µm)	53.057 ± 8.240	58.270 ± 8.820	207.991 ± 23.440	<0.001
Lamina propria (200-1200 µm)	18.095 ± 2.139	20.935 ± 3.205	85.339 ± 5.882	<0.001
Muscle layer (1200-4000 µm)	2.120 ± 0.326	2.424 ± 0.297	24.888 ± 3.645	<0.001

Sockett LJ, Borwell J, Symes A, Parker T, Montgomery BSI, Barber NJ. "Electromotive drug administration (EMDA) of intravesical mitomycin-C in patients with high-risk non-invasive bladder cancer and failure of BCG immunotherapy" BJU Int. 2008;101(5):50 abstract #U17.

Objectives

Patients with high risk superficial TCC who fail to respond to intravesical BCG, and who are not suitable for radical cystectomy, have limited management options.
We have assessed the use of electromotive drug administration of intravesical mitomycin-C (EMDA-MMC) in this group.

Patients and methods

Over a 15 month period, 13 patients with recurrent CIS or T1G3 TCC following at least one induction course of BCG and were unsuitable for cystectomy, received a 6 week course of weekly EMDA-MMC. Following treatment, patients were re-assessed with cystoscopy, biopsy and urine cytology.

Results

At 3 months, 9/13 patients (69%) were disease-free and 6/9 (67%) remained so at 6 months. Four patients remain free of recurrence. Those with recurrent disease at 3 months (4/13) had no evidence of disease progression. The 3 patients who recurred at 6 months had lower grade tumours.

Conclusions

This small, short term study suggests that EMDA-MMC is a promising therapy in patients with high risk, non- invasive transitional cell carcinoma who fail to respond to intravesical BCG and who are unfit for radical cystectomy. It would, therefore, seem to represent a useful option in the otherwise limited list of treatments available for this difficult group of patients.

Di Stasi SM, Giannantoni A, Capelli G, Giurioli A, Valenti M, Zampa G, Storti L, Attisani F, De Carolis A, Capelli G, Vespasiani G, Stephen RL. "Sequential BCG and electromotive mitomycin C versus BCG alone for high risk superficial bladder cancer: a randomised controlled trial" Lancet Oncol. 2006 Jan, 7(1): 43-51. doi: 10.1016/S1470-2045(05)70472-1.

Background

The rationale for combining anticancer drugs has not been applied consistently to use of intravesical agents for treatment of superficial bladder cancer, for which immunotherapeutic BCG and chemotherapeutic mitomycin seem to be a potentially effective combination. We aimed to do a prospective, randomised comparison of BCG alone with that of sequential BCG and electromotive mitomycin in patients with stage pT1 bladder cancer.

Methods

After transurethral resection and multiple biopsies, 212 patients with stage pT1 bladder cancer were randomly assigned to: 81 mg BCG infused over 120 min once a week for 6 weeks (n=105); or to 81 mg BCG infused over 120 min once a week for 2 weeks, followed by 40 mg electromotive mitomycin (intravesical electric current 20 mA for 30 min) once a week as one cycle for three cycles (n=107). Complete responders underwent maintenance treatment: those assigned BCG alone had one infusion of 81 mg BCG once a month for 10 months, and those assigned BCG and mitomycin had 40 mg electromotive mitomycin once a month for 2 months, followed by 81 mg BCG once a month as one cycle for three cycles. The primary endpoint was disease-free interval; secondary endpoints were time to progression; overall survival; and disease-specific survival. Analyses were done by intention to treat. This trial has been submitted for registration at the US National Cancer Institute website.

Findings

Median follow-up was 88 months (IQR 63-110). Patients assigned sequential BCG and electromotive mitomycin had higher disease-free interval than did those assigned BCG alone (69 months [95% CI 55-86] vs 21 months [15-54]; difference between groups 48 months [42-54], log-rank p=0.0012). Patients assigned sequential BCG and electromotive mitomycin also had lower recurrence (41.9% [32.7-51.5] vs 57.9% [48.7-67.5]; difference between groups 16.0% [2.7-29.3], log-rank p=0.0012); progression (9.3% [3.8-14.8] vs 21.9% [17.9-25.9]; difference between groups 12.6% [3.0-22.2], log-rank p=0.004); overall mortality (21.5% [13.5-29.5] vs 32.4% [23.4-41.4], difference between groups 10.9% [0.6-21.2], log-rank p=0.045); and disease-specific mortality (5.6% [1.2-10.0] vs 16.2% [6.1-23.3], difference between groups 10.6% [2.5-18.7], log-rank p=0.01). Side-effects were mainly localised to the bladder.

Interpretation: BCG-induced inflammation might increase the permeability of the bladder mucosa such that mitomycin can reach the target tissue more easily and exert its anticancer effect.

Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Navarra P, Massoud R, Vespasiani G. "Intravesical electromotive mitomycin C vs passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study vs BCG" J Urol. 2003 Sep,170(3): 777-782. doi: 10.1097/01.ju.0000080568.91703.18.

Purpose

In laboratory studies electromotive mitomycin C (MMC) demonstrated markedly increased transport rates compared with passive transport. We performed a prospective study in patients with high risk superficial bladder cancer to assess the efficacy of intravesical electromotive vs passive MMC using bacillus Calmette-Guerin (BCG) as a comparative treatment.

Materials and methods

Following transurethral resection and multiple biopsies 108 patients with multifocal Tis, including 98 with T1 tumors, were randomized into 3 equal groups of 36 each who underwent 40 mg electromotive MMC instillation with 20 mA electric current for 30 minutes, 40 mg passive MMC with a dwell time of 60 minutes or 81 mg BCG with a dwell time of 120 minutes. Patients were scheduled for an initial 6 weekly treatments, a further 6 weekly treatments for nonresponders and a follow-up 10 monthly treatments for responders. Primary end points were the complete response rate at 3 and 6 months. MMC pharmacokinetics were assessed.

Results

The complete response for electromotive vs passive MMC at 3 and 6 months was 53% versus 28% ($p = 0.036$) and 58% versus 31% ($p = 0.012$). For BCG the responses were 56% and 64%. Median time to recurrence was 35 vs 19.5 months ($p = 0.013$) and for BCG it was 26 months. Peak plasma MMC was significantly higher following electromotive MMC than after MMC (43 vs 8 ng/ml), consistent with bladder content absorption.

Conclusions

Intravesical electromotive administration increases bladder uptake of MMC, resulting in an improved response rate in cases of high risk superficial bladder cancer.

Di Stasi SM, Giannantoni A, Massoud R, Dolci S, Navarra P, Vespasiani G and Stephen RL. "Electromotive versus passive diffusion of mitomycin C into human bladder wall: concentration-depth profiles studies" Cancer Res. 1999, Oct 1 59(19):4912-4918.

The objectives of these investigations were: (a) to make a preliminary study to assess concentration-depth profiles of mitomycin C (MMC) in the bladder wall at specified time intervals after passive diffusion (PD); and (b) to conduct a major study to compare concentration-depth profiles after PD and electromotive drug administration (EMDA) of MMC. Full thickness sections of viable human bladder wall were placed in two-chamber cells with urothelium exposed to donor compartments containing 40 mg of MMC in 100 ml of 0.96% NaCl solutions and with serosa-facing receptor compartments containing 0.9% NaCl solutions.

In the preliminary study during each of nine experimental sessions, five sections of bladder wall were individually exposed to MMC for either 5, 15, 30, 45, or 60 min. In the major study, an anode and a cathode were sited in the donor and receptor compartments, and 14 paired experiments—current (20 mA)/no current—were conducted over a 30-min period. Bladder wall sections were cut serially into 40-μm slices parallel to the urothelium and analyzed by high-performance liquid chromatography for MMC concentration (μg/g wet tissue weight).

Tissue viability and morphology and MMC stability were assessed by trypan-blue exclusion test, histological examination, and mass spectrometry analysis. In the preliminary study (PD only), mean MMC concentrations (μg) at 5, 15, 30, 45, and 60 min were: (a) for urothelium, 15.3, 60.0, 58.2, 60.1, and 57.8, respectively; (b) for lamina propria, 2.2, 18.9, 19.3, 16.1, and 17.3, respectively; and (c) for muscularis, 0.4, 2.0, 1.8, 1.3, and 2.4, respectively.
In the comparative study, MMC concentrations and coefficients of variation (CV) were as follows: (a) for urothelium after PD, 46.6 with CV = 69%, and after EMDA, 170.0 with CV = 43% ($P < 0.0001$); (b) for lamina propria after PD, 16.1, with CV = 60%, and after EMDA, 65.6 with CV = 29% ($P< 0.0001$); and (c) for muscularis after PD, 1.9 with CV = 82%, and after EMDA, 15.9 with CV = 82% ($P < 0.0005$). All of the bladder sections remained viable, and the chemical structure of MMC was unchanged.

It was concluded that EMDA significantly enhances MMC transport into all of the layers of the bladder wall, and sections of viable human bladder are a reliable tool for assessing different modes of drug delivery.

Riedl CR, Knoll M, Plas E, Pflüger H. “Intravesical electromotive drug administration technique: Preliminary results and side effects” J. Urol. 1998 Jun;159(6):1851–1856. doi: 10.1016/S0022-5347(01)63174-4.

Purpose
We performed intravesical electromotive drug administration (EMDA) for various bladder disorders during a 3-year period and assessed the technique, possible applications, complications and outcomes of this procedure.

Materials and methods
Intravesical EMDA was performed with local anesthetics for transurethral surgery and in combination with dexamethasone for the treatment of non-infectious chronic cystitis (interstitial/radiation cystitis), with mitomycin C for recurrence prophylaxis of high risk superficial bladder cancer and with oxybutynin/bethanechol for the hyperreflexive/acontractile detrusor. A standardized power source and electrode catheter were used for 215 treatments in 84 patients.

Results
Transurethral bladder tumor resections were pain-free in 10 of 12 patients. Of the 25 patients with chronic non-infectious cystitis 15 were free of symptoms for a mean of 6.6 months, and there was a 73% increase in mean bladder capacity from 244 before to 421 cc after EMDA. Of the 16 patients with superficial bladder cancer 9 were free of recurrence for a mean of 14.1 months. In 10 of 14 patients with acontractile detrusors urodynamic examination showed detrusor contraction during EMDA of bethanechol. There were no contractions without electric current. EMDA of oxybutynin reduced detrusor hyperreflexia. A bladder ulcer was the single severe local complication and 4.6% of patients, mainly those with chronic cystitis, reported significant post-EMDA bladder/urethral pain. Minor side effects accounted for 23% of all treatments. No systemic side effects occurred.

Conclusions
Intravesical EMDA is effective and innocuous. The therapeutic concept combines the advantages of increased drug administration without systemic side effects.

Brausi M, Campo B, Pizzocaro G et al. “Intravesical electromotive administration of drugs for treatment of superficial bladder cancer: a comparative phase II study” Urol.ogy 1998 Mar; 51(3):506-509. doi: 10.1016/S0090-4295(97)00625-0.

Objectives

To evaluate the efficacy of electromotive administration (EMDA) of intravesical mitomycin-C (MMC) in patients with superficial bladder tumors and to evaluate the toxicity of the treatment.

Methods

Thirteen patients with multifocal Stages Ta-T1 and G1-G2 transitional cell carcinoma (TCC) of the bladder, primary or recurrent (group A), received MMC 40 mg (retained in the bladder for 2 hours) once a week for 8 weeks.
Fifteen patients with the same characteristics (group B) were treated with EMDA/MMC at a current of 15 mA for 20 minutes once a week for 8 weeks.
All lesions in the bladder except one (marker) were resected in each patient.

Results

In group A, 5 of 12 patients (41.6%) demonstrated complete macroscopic and histologic disappearance of the marker lesion (complete response [CR]). In group B, 6 of 15 patients (40%) had a similar CR. Recurrence rate in responders was 60% in group A versus 33% in group B after 7.6 and 6 months, respectively. Disease-free interval was 14.5 months in the EMDA/MMC group compared to 10.5 months in the MMC group. Side effects were few.

Conclusions

In intermediate risk patients with TCC of the bladder, EMDA/MMC was not superior to MMC alone with a CR rate of 41% versus 41.6%. In responders, a lower recurrence rate and a longer disease-free interval were observed in the EMDA/MMC group.

Di Stasi SM, Vespasiani G, Giannantoni A, Massoud R, Dolci S and Micali F. “Electromotive delivery of mitomycin C into human bladder wall” Cancer Res. 1997, 57: 875-880.

The aim of this investigation was to establish an appropriate tissue pharmacokinetic model to compare concentrations of mitomycin C (MMC) in the human bladder wall after either passive delivery or electromotive administration (EMDA) and to evaluate the effects of EMDA on tissue morphology and MMC structure.

Tissue sections of human bladder were inserted into two chamber cells with urothelium exposed to donor compartments containing MMC (10 mg in 100 ml of 0.24% NaCl solution) and an anode and with serosa exposed to receptor compartments containing 100 ml of 0.9% NaCl solution and a cathode. Fourteen paired experiments (“current 5 mA/ no current”) were conducted over 15 min; MMC tissue content was assessed by high-pressure liquid chromatography.

Tissue viability and morphology and MMC stability were assessed by trypan blue exclusion test, tissue pH, histological analysis, and mass spectrometry analysis.

MMC concentrations were increased, and variability in drug delivery rate was reduced in all tissue in samples exposed to electric current. Tissues were viable and undamaged histologically, and no MMC structural modification was observed.

In conclusion, EMDA enhances administration of MMC into viable bladder wall tissue and reduces the variability in drug delivery rates.

Gürpinar T, Truong LD, Wong HY, Griffith DP." Electromotive drug administration to the urinary bladder: An animal model and preliminary results" J.Urol. 1996 Oct;156(4):1496–1501. doi: 10.1016/S0022-5347(01)65638-6.

Purpose

Electromotive drug delivery (EMDA) is the use of an electrical field to enhance penetration of ionized drugs into local tissues. Intraurinary EMDA may be of value in the treatment of various pathological conditions involving the urinary bladder, prostate gland and urethra. We have developed an animal model to study this hypothesis.

Materials and methods

Anesthetized adult mongrel dogs were studied. An intravesical anode was inserted through a Foley catheter into the urinary bladder. Two patch electrodes were positioned on the animals' abdominal skin. Both skin and intravesical electrodes were attached to a direct current generator. The bladder was then distended with an anionic blue dye (methylene blue). Fifteen milliamperes (15 mA) pulsed direct current was applied for 40 minutes. After EMDA, the bladder was surgically removed and representative sections of full thickness bladder wall were immediately frozen in liquid nitrogen. Methylene blue was used to visually demonstrate EMDA-enhanced anion penetration into bladder submucosa and muscularis.

Result

This experimental model demonstrates significant submucosal and muscularis methylene blue penetration in the presence of the electric field.

Conclusion

Electromotive drug delivery technology may have applications for treating bladder pathology.

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