Innovations in bladder cancer p.4

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Congress Organizer/Chairman: Prof. PF Bassi, Chairman Department of Urology, Catholic University Medical School, University Hospital "A. Gemelli"

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Local hyperthermia and intravesical chemotherapy for superficial TCC of the bladder Clinical studies: An overview; R. Colombo U.O. di Urologia Istituto Scientifico Universitario “Vita e Salute” San Raffaele, Milano

The rationale: endovesical cytostatic agents plus microwave-induced local hyperthermia have a synergistic antitumor effect on many solid tumors, including transitional cell carcinomas

Ablative treatment: 1994-2002: n. of Pts: 81

Cumulative multicentric neo-adjuvant study for debulking and bladder sparing patients1994 – 1998, 81 recurrent patients; 42 patients had Ta tumors, 39 had T1. Grade I tumors-11, grade 2-52, grade III- 18. Patients had an average of 4.8 recurrences. Duration of treatment: 8 weekly + 4 monthly sessions; Duration of single session: 40-60 min.

Drug: MMC: 40 mg/50 ml replaced after 30 min in 76 Pts

EPI: 50 mg/50 ml replaced after 30 min in 5 Pts

Average Temperature: 43°C

--Outpatient basis

--Only urethral anaesthetic gel

Complete Tumor Eradication: 71/81 Pts 88%.

Complete eradication by Thermo-chemotherapy only: 58/81 Pts 72%

Complete eradication by T-C + TUR: 13/81 16%

Non Responder: 10/81 12%

Mean time for Complete Tumor Eradication: 61 days

Major Complications: 3 cases of reduced bladder capacity

Cystectomy: 13 Pts

10 NR; 1 stage progression; 2 reduced bladder capacity

Disease-Free Patients: 47/71 Pts 66%, Average Follow-Up: 24 months

Local microwave hyperthermia and intravesical chemotherapy as bladder sparing treatment for select multifocal and unresectable superficial bladder tumors. Colombo R, Da Pozzo LF, Lev A, Salonia A, Rigatti P, Leib Z, Servadio C, Caldarera E, Pavone-Macaluso M.Department of Urology, Scientific Institute H. San Raffaele, Milan, Italy.J Urol. 1998 Mar;159(3):783-7 PubMed

Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma.Colombo R, Da Pozzo LF, Salonia A, Rigatti P, Leib Z, Baniel J, Caldarera E, Pavone-Macaluso M.Department of Urology, University Vita-Salute, San Raffaele Hospital, Via Olgettina 60, 20132 Milan, Italy. J Clin Oncol. 2003 Dec 1;21(23):4270-6.* J Clin Oncol. 2003 Dec 1;21(23):4259-60. PubMed

PURPOSE: To compare the efficacy and local toxicity of the intravesical instillation of a cytostatic, chemotherapeutic drug (CT) versus the same agent in combination with local hyperthermia(LH) as an adjuvant treatment, after complete transurethral resection (TURB) of superficial transitional cell carcinoma (TCC) of the bladder.

PATIENTS AND METHODS: The study was designed as a prospective, multicentric, randomized trial. Eighty-three patients suffering from primary or recurrent superficial (Ta-T1) TCC of the bladder, after a complete TURB, were randomly assigned to receive intravesical instillations of mitomycin C (MMC) alone, for 41 patients, and MMC in combination with local microwave-induced hyperthermia, for 42 patients. For the combined approach, a new system, Synergo101-1 (Medical Enterprises, Amsterdam, the Netherlands) was used. The effectiveness evaluation end points of the study were evaluation of recurrence-free survival and the estimated probability of recurrence. The safety evaluation end points included subjective and objective side effects and clinical complications. For the efficacy end point, Kaplan-Meier analysis was employed, with the log-rank test for significance. Minimum follow-up time was 24 months.

RESULTS: Of the 83 randomly assigned patients, 75 completed the study according to the protocol and had valid cystoscopy results. Survival analysis of the 75 assessable patients demonstrated a highly significant difference in the survival curves in favor of thermochemotherapy. Subjective intolerance and clinical complications were significantly higher but transient and moderate in the combined treatment group.

Rrecurrent free survival - 57.5% of the combination group (Hyperthermia+chemotherapy) had no recurrences by the 24 month mark as opposed to 17.1% in the group that received chemotherapy alone. Age and sex had no significant (p>0.05) effect on recurrence in either treatment group; previous local CT did not significantly (p>0.05) influence the

results; the total number of treatment sessions had a significant (p<0.0001) association with the recurrence rates of the treatment groups pts who received 8+4 treatment sessions had a lower recurrence.

Safety Analysis: thermal reaction of the posterior bladder wall (“posterior-wall medallion”) appeared as a painless, superficial, black discoloration patch surrounded by hyperemia confined (=3cm) and self-healing from a few days to several weeks. “Posterior-wall medallion” corresponds to the location of the radio-frequency antenna inside the bladder during the operative procedure. Overall, local side effects (namely, cystitis symptoms, suprapubic pain and thermal reaction of the posterior bladder wall) were more frequent and more severe in Group 1, however, local side effects did not influence the completion of the treatment and were transitory and self-recovering shortly after the end of treatment. There was no significant difference in side effects and clinical complications observed in the 3 participating centers nor between groups.

Study Limitations: these results were preliminary and needed to be confirmed by large prospective, multicentric studies. LHT+CT was more expensive and cumbersome than routine instillation a larger catheter had to be used and it insertion may become more invasive

CONCLUSION: In our series, endovesical thermochemotherapy appears to be more effective than standard endovesical chemotherapy as an adjuvant treatment for superficial bladder tumors at 24-month follow-up, despite an increased but acceptable local toxicity.

Pharmacokinetics - HPLC study:

Effect of local hyperthermia of the bladder on mitomycin C pharmacokinetics during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma Paroni R, Salonia A, Lev A, Da Pozzo LF, Cighetti G, Montorsi F, Rigatti P, Colombo R.Department of Laboratory Medicine, IRCCS H San Raffaele, via Olgettina 60,20132 Milan, Italy, Br J Clin Pharmacol, 52:273-278, 2001PubMed

Aims: To assess the effect of local hyperthermia on the systemic absorption of mitomycin C (MMC) during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma of the bladder, and to establish the likely safety of this procedure.

Methods: Group 1 (n = 12) received 20 mg intravesical MMC plus local hyperthermia, group 2 (n = 13) 20 mg MMC alone, group 3 (n = 16) 40 mg MMC plus local hyperthermia and group 4 (n = 10) 40 mg MMC alone. Patients in groups 1, 2, and 4 underwent post-tumour resection adjuvant treatment, whereas those in group 3 still had tumour present and were treated to eradicate it. Intravesical instillation lasted 60 min, with the solution (50 ml) being replaced after the first 30 min. Blood samples were taken before, and every 15 min during instillation. MMC concentrations in plasma and in urine were determined by h.p.l.c:High Performance Liquid Chromatography (HPLC)

detection limit of plasmatic MMC of 0.5 ng/ml; HPLC is one of the most suitable technique for rthe study of drug pharmacokinetics

Results: The highest MMC plasma concentration (67.9 ng ml(-1)) occurred in a patient in group 3. This value was well below the threshold concentration (400 ng ml-1) for myelosuppression. Local hyperthermia associated with the intravesical chemotherapy enhanced plasma MMC concentrations at 30, 45 and 60 min compared with chemotherapy alone (Group 1 vs 2, P < or = 0.008). Systemic exposure to MMC was not significantly increased by doubling the intravesical dose when intravesical chemotherapy alone was administered. Patients in group 3 displayed the highest degree of MMC absorption and the greatest variability in pharmacokinetics between patients.

Safety Analysis - Local hyperthermia microwave-induced, performed by Synergo® System, appared to be safe on HPLC investigation with regard to systemic side effects (MMC plasma concentration has been always below the myelotoxicity cut-off of 400 ng/ml), thus, no evidence of myelosuppression was detected in any patients.

Conclusions: Local hyperthermia enhances the systemic absorption of MMC during intravesical chemotherapy for bladder cancer. In the doses used, plasma MMC concentrations were always more than six times lower than those shown to cause toxicity.

Long Term Follow up - median 8 years AUA 2006, submitted

36 pts at hSR

with primary or recurrent stage Ta and T1, grade G1 and G3 TCC of the bladder

treated by a complete TURB

randomly assigned to either to receive:

Group 1: local termochemotherapy (20 + 20 mg MMC)

Group 2: local MMC alone

Complete data collection: 31/36 (86.1%) pts

Group 1: 16 pts

Group 2: 15 pts

mean age at the date of FU:

Group 1: 64.2±11.8 years

Group 2: 69.1±11.6 years

Overall number of disease progression:

Group 1 = 3 - Group 2 = 1

Radical cystectomy:

Group 1 = 1 - Group 2 = 1

Overall number of deaths for any cause:

Group 1 = 2 - Group 2 = 4

2 pts from Group1 and 4 pts from Group 2 died from other causes

N. of pts negative for recurrences: 37.5% for Group 1 and 20% for Group 2.

Recent and ongoing trials for local hyperthermia and endovsesical chemotherapy

Preliminary European Results of Local Hyperthermia and Chemotherapy Treatment Intermediate or High Risk Superficial Bladder Cancer

van der Heijden AG, Kiemeney LA, Gofrit ON, Nativ O, Sidi A, Leib Z, Colombo R, Naspro R, Pavone M, Baniel J, Hasner F, Witjes JA. Department of Urology, University Medical Centre Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Eur Urol. 2004 Jul;46(1):65-71; discussion 71-2. PubMEd

Patients and methods: Ninety eligible patients from nine European centers received adjuvant treatment with a combination of mitomycin-C (MMC) and local microwave hyperthermia. All patients had multiple or recurrent Ta or T1 TCC of the bladder and were classified as intermediate or high risk (IR, HR) according to EAU criteria. In total, 41 patients were BCG failures. The treatment regimen included 6 to 8 weekly sessions followed by 4 to 6 monthly sessions. Follow-up consisted of video-cystoscopy and urine cytology every 3 months. All patients were observed for 2 years.

Results: Kaplan-Meier analyses of the total group (N = 90) indicated that 1 year after treatment only 14.3% (SE 4.5%) of all patients experienced a recurrence. After 2 years of follow-up the risk of recurrence was 24.6% (SE 5.9%). No progression in stage and grade was observed.

Time to first recurrence.

% Pts recurrence-free at 1 y: 85.7

% Pts recurrence-free at 2 y: 75.4

Time to first recurrence for HR and IR

% HR-Pts at 2 y: 64

% IR-Pts at 2 y: 92

Time to first recurrent for Pts with prior BCG

% Pts recurrence-free at 1 y: 76.9

% Pts recurrence-free at 2 y: 58.8

Conclusion: Microwave induced hyperthermia combined with MMC has promising value in intermediate or high risk superficial bladder cancer patients compared to literature data of BCG and/or intravesical chemotherapy, particularly where other treatments, i.e. BCG, have failed.

SYNERGO for BCG FAILURES 1996 – Ongoing

Overall Pts : 110 eligible for efficacy : 76

Mean follow up (Clean patients): 16.5 months

Total recurrences: 21 (28%)

M edian time to recurrence: 15 months

83% disease free at 1y, 62% at 2 y

Combined local bladder hyperthermia and intravesical chemotherapy for the treatment of high-grade superficial bladder cancer. Gofrit ON, Shapiro A, Pode D, Sidi A, Nativ O, Leib Z, Witjes JA, van der Heijden AG, Naspro R, Colombo R. Department of Urology, Hadassah University Hospital, Jerusalem, Israel. Urology. 2004 Mar;63(3):466-71. PubMed

Objectives: To evaluate the effectiveness of combined local bladder hyperthermia and intravesical chemotherapy for the treatment of patients with high-grade (G3) superficial bladder cancer.

Methods: Patients with G3 bladder tumors (Stage Ta or T1) were treated with combined intravesical chemotherapy with mitomycin-C and local radiofrequency hyperthermia of the bladder wall. The patients were treated with either a prophylactic protocol (40 mg mitomycin-C) after complete transurethral resection of all tumors or with an ablative protocol (80 mg mitomycin-C) when visible tumor was seen on video-cystoscopy or bladder biopsies were positive for carcinoma in situ.

Results: Combined chemo-thermotherapy was administered to 52 patients with high-grade superficial bladder cancer (40 patients with Stage T1 tumor, 11 with Ta, and 3 with concomitant or isolated carcinoma in situ). At a median follow-up of 15.2 months (mean 23, range 6 to 90), no stage progression to T2 or disease-related mortality had occurred. The bladder preservation rate was 86.5%. The prophylactic protocol was administered to 24 patients. After a mean follow-up of 35.3 months, 15 patients (62.5%) were recurrence free. The bladder preservation rate was 95.8%. The ablative protocol was administered to 28 patients. Complete ablation of the tumor was accomplished in 21 patients (75%). After a mean follow-up of 20 months, 80.9% of these patients were recurrence free. The bladder preservation rate for the ablative group was 78.6%.

Conclusions: Combined local bladder hyperthermia and intravesical chemotherapy has a beneficial prophylactic effect in patients with G3 superficial bladder cancer. Ablation of high-grade bladder tumors is feasible, achieving a complete response in about three quarters of the patients.

Thermochemotherapy for Intermediate or High Risk Recurrent Superficial Bladder Cancer Patients Moskovitz B, Meyer G, Kravtzov A, Gross M, Kastin A, Biton K, Nativ O. Department of Urology Bnai Zion Medical Center, Technion, Institute of Technology, Haifa, Israel.Ann Oncol. 2005 Apr;16(4):585-9. Epub 2005 Feb 25. PubMed

Background: The purpose of this study was to evaluate the efficacy of combined local hyperthermia and intravesical

mitomycin-C (MMC) in a selected group of patients with intermediate or high-risk recurrent transitional cell carcinoma (TCC) of bladder.

Patients and methods: Forty-seven patients with multiple or recurrent Ta or T1 TCC of the bladder were treated with intravesical MMC and local hyperthermia of the bladder wall. Patients were treated with either a prophylactic protocol (40 mg MMC) after complete transurethral resection of all tumours or with an ablative protocol (80 mg MMC) in patients with viable tumours.

Results: Thirty-two patients were eligible for analysis. The prophylactic protocol was administered to 22 patients. After a mean follow-up of 289 days, 20 patients (91%) were recurrence free. Two patients (9%) had tumour recurrence after a mean period of 431 days. The ablative protocol was administered to 10 patients. Complete tumour ablation was achieved in eight patients (80%) after a mean follow up of 104.5 days.

Prophylaxis Protocol, after follow up of 289 days, 20/21 (91%) recurrence-free

Ablative Protocol, complete response was seen in 8/10 (80%); Time to CR: 104.5 days

Conclusions: Our efficacy and safety results confirm those reported in previously published studies, suggesting the promising value of this combined treatment modality for both prophylactic and ablative patients. The ablative protocol offers an alternative therapy for a selected patient population for whom no other treatment option exists.

Thermo-chemotherapy: Preliminary results of current international studies Prof. Fred Witjes Radboud UMC Nijmegen, the Netherlands Innovations in Urology: Bladder cancer Rome, December 2, 2005

Health economics of bladder cancer [Botteman et al., Pharmacoeconomics 2003]: Because of long- term survival and the need for lifelong routine monitoring and treatment, the cost per patient of bladder cancer from diagnosis to death is the highest of all cancers, ranging from 96000-187000 US dollars (2001 values) in the US. Overall, bladder cancer is the fifth most expensive cancer in terms of total medical care expenditures, accounting for almost 3.7 billion US dollars (2001 values) in direct costs in the US.

Some possible reasons:

Current diagnostics not cost effective

Current therapies not cost effective

Current frequent follow up not cost effective

No new developments

This is studied “marginally”

No awareness

New and effective treatments are urgently needed. Thermo-chemotherapy has been shown to be an effective approach.

Advantages with the Synergo technique:

Homogenous heating whole mucosa

Transurethral cooling to prevent overheating

Fast change temperature possible

In vitro research

2005: Effect of Hyperthermia on the cytotoxicity of 4 chemotherapeutic agents currently used for the treatment of transitional cell carcinoma of the bladder: An in vitro study van der Heijden AG, Verhaegh G, Jansen CFJ, Schalken JA, Witjes JA The Journal of Urology - April 2005 (Vol. 173, Issue 4, Pages 1375-1380:

Purpose: Hyperthermia combined with chemotherapy is not a novel cancer treatment. However, the working mechanism of this combination therapy is not fully understood. In the current in vitro study we investigated the differences in cytotoxicity of 4 chemotherapeutic agents at 37C or 43C.

Materials and Methods:

The human transitional cell carcinoma cell lines used were RT4, RT112, 253J and T24. Cells were seeded in 96-well microtiter plates. After 24 hours cells were treated for 60 minutes with increasing concentrations of mitomycin C, epirubicin, gemcitabine and EO9 at a temperature of 37C or 43C. After treatment cells were rinsed 3 times and left for 24 hours in the incubator at 37C. The influence of chemotherapy and temperature on cell survival was determined by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) assay.

Results: Decreased cell proliferation with increasing concentrations of chemotherapeutic agents was demonstrated. EO9 proved to be the most potent agent at each temperature. Hyperthermia alone did not demonstrate decreased cell proliferation. However, a synergistic effect on decreased cell proliferation was demonstrated in all cell lines and chemotherapeutic agents used, although each had a maximum at a different chemotherapy concentration and to a different extent. Synergism was most obvious in cell lines treated with low dose epirubicin.

Conclusions: Synergism with hyperthermia and chemotherapy was clearly demonstrated for epirubicin, EO9, mitomycin C and to a lesser extent gemcitabine. Hyperthermia alone did not cause decreased cell proliferation. Synergism was most prominent with low drug doses and the most potent drug used in this in vitro study was EO9.

In vivo research (van der Heijden, submitted)

Bladder biopsies after MMC and/or heat

Histology, Ki67, p53 IH were investigated

Hyperthermia decreases proliferation activity and p53 IH

No induction of inflammation

Conclusions: This is an effective and safe treatment

Neoadjuvant Combined Microwave Induced Local Hyperthermia and Topical Chemotherapy Versus Chemotherapy Alone for Superficial Bladder Cancer Renzo Colombo, Luigi F. Da Pozzo, Avigdor Lev, Massimo Freschi, Giuseppe Gallus, Patrizio Rigatti Volume 155, Issue 4, Pages 1227-1232 (April 1996)

Purpose: We evaluated the effectiveness of local bladder hyperthermia and intravesical chemotherapy compared to intravesical chemotherapy alone in the treatment of superficial transitional cell carcinoma.

Materials and Methods: A new system designed to deliver simultaneously local bladder hyperthermia and intravesical chemotherapy has been developed at our institute. The system consists of a computerized 915 MHz. microwave source that directly heats the bladder walls (within a temperature range of 42.5 to 45.5C) using a transurethral catheter. From February 1989 to December 1993, 52 patients 44 to 81 years old (mean age 64.3) with superficial stages Ta to T1, grades 1 to 3 transitional cell carcinoma of the bladder were selected for neoadjuvant intracavitary treatment. Tumors were left intact as marker lesions. Of the patients 29 were randomly assigned to receive combined neoadjuvant intravesical chemotherapy and local hyperthermia (group 1), while 23 received intravesical chemotherapy alone (group 2). The treatment protocol included multiple sessions performed on an outpatient basis. Mitomycin C (40 mg. in 50 cc distilled water) was used for intravesical chemotherapy in both groups. All patients underwent transurethral resection of residual tumors and of all suspicious areas 7 to 10 days after completion of treatment. Only a complete response was considered for statistical analysis.

Results:A pathological complete response was documented in 19 cases (66 percent) in group 1 and 5 (22 percent) in group 2 (chi-square p less than 0.01).

Conclusions; According to these preliminary data, microwave induced hyperthermia combined with local intravesical chemotherapy seems to be a feasible, safe and promising approach for neoadjuvant and minimally invasive treatment of superficial bladder cancer.

Tumor Response rate

	MMC+HT	MMC
CR	19 (66%)	5 (22%)
PR	10 (34%)	6 (26%)
NR	-	12 (52%)

2005 update: European ablative pts (MMC40/40):

All patients: n=156

CIS subgroup (19/19): 100% response

CR: 78% (122/156)

PR: 13% (21/156)

NR: 8% 13/156

Some recent prophylactic results (Colombo, JCO, dec 2003)

Multicentric Study Comparing Intravesical Chemotherapy Alone and With Local Microwave Hyperthermia for Prophylaxis of Recurrence of Superficial Transitional Cell Carcinoma Renzo Colombo, Luigi Filippo Da Pozzo, Andrea Salonia, Patrizio Rigatti, Zvi Leib, Jack Baniel, Emanuele Caldarera, and Michele Pavone-Macaluso; From the Department of Urology, University Vita-Salute San Raffaele, Milan, Italy; the Department of Urology, Beilinson Hospital, Tel Aviv, Israel; and the University of Palermo, Palermo, Italy. JCO Dec 1 2003: 4270–4276 pubMed (see above)

Results: Of the 83 randomly assigned patients, 75 completed the study according to the protocol and had valid cystoscopy results. Survival analysis of the 75 assessable patients demonstrated a highly significant difference in the survival curves in favor of thermochemotherapy. Subjective intolerance and clinical complications were significantly higher but transient and moderate in the combined treatment group.

Conclusion: In our series, endovesical thermochemotherapy appears to be more effective than standard endovesical chemotherapy as an adjuvant treatment for superficial bladder tumors at 24-month follow-up, despite an increased but acceptable local toxicity.

Synergo in intermediate and high risk patients:

-90 EAU intermediate or high risk patients (41 BCG failures)

-Recurrence risk at 1 and 2 year: 14.3% and 24.6%

-No progression

Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder.van der Heijden AG, Kiemeney LA, Gofrit ON, Nativ O, Sidi A, Leib Z, Colombo R, Naspro R, Pavone M, Baniel J, Hasner F, Witjes JA. Department of Urology, University Medical Centre Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Eur Urol. 2004 Jul;46(1):65-71; discussion 71-2. PubMed

Introduction: Superficial bladder cancer can be treated by transurethral resection (TUR) and adjuvant intravesical therapy. Intravesical bacillus Calmette-Guerin (BCG) has been proven to be more efficacious with respect to recurrence prevention than intravesical chemotherapy, although at the cost of more severe side effects. There is a need for a new treatment modality with higher efficacy and less toxicity. The subject of this study is the efficacy of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma (TCC) of the bladder.

Patients and methods: Ninety eligible patients received adjuvant treatment with a combination of mitomycin-C (MMC) and local microwave hyperthermia. All patients had multiple or recurrent Ta or T1 TCC of the bladder and were classified as intermediate or high risk according to EAU criteria. In total, 41 patients were BCG failures. The treatment regimen included 6 to 8 weekly sessions followed by 4 to 6 monthly sessions. Follow-up consisted of video-cystoscopy and urine cytology every 3 months. All patients were observed for 2 years.

Results: Kaplan-Meier analyses of the total group (N = 90) indicated that 1 year after treatment only 14.3% (SE 4.5%) of all patients experienced a recurrence. After 2 years of follow-up the risk of recurrence was 24.6% (SE 5.9%). No progression in stage and grade was observed. CONCLUSION: Microwave induced hyperthermia combined with MMC has promising value in intermediate or high risk superficial bladder cancer patients compared to literature data of BCG and/or intravesical chemotherapy, particularly where other treatments, i.e. BCG, have failed.

Comparisons: Literature in intermediate and high risk patients (vd Heijden et al, Eur Uro '04l]

O'Donnell
Current

Eur. Update

Risk profiles
BCG failures
I/H
BCG Failures
Highly Recurrent
BCG failures "only"

therapy
BCG+IFN
Synergo (n=90)
Synergo (n=90)

Synergo (n=28)
Synergo (n=28)

1 year% recrurrence
44%
14%
23%
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--

2 year % recurrence
52%
25%
41%
44%
21%

Clinical trial: 102.1 Synergo® protocol

- Randomized BCG versus Synergo

-10 international centres

-in I/H risk patients, including CIS

-One year treatment: 15x BCG; 12x Synergo

-Induction course = minimal for evaluation

Interim Analysis:

BCG
Synergo

#pts
44
32

Time to recurrence (in days)
157
249

recurrences
12
5 (all Ta)

Side effects:

Before
During
After

Daytime Freq.
2.6+0.8
3.5+0.6
2.8+0.6

Nocturia
2.8+1.0
3.7+0.8
3.3+0.4

Dysuria
1.9+1.2
2.3+1.1
2.1+0.8

Urethral burning
2.2+0.8
2.9+0.8
2.2+0.4

Hematuria
0.9+0.6
1.4+0.4
0.8+0.6

Some posterior wall necrosis is seen after treatment.

Summary Synergo® Thermo-chemotherapy causes more side effects than Mitomycin C alone. Nevertheless, all are transient and acceptable. After 24 months of follow up, thermo-chemotherapy is very effective, even in I/H risk patients and BCG failures and as ablative therapy

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Thermochemotherapy - Current Italian Studies Rodolfo Hurle U.O. Urologia Humanitas Gavazzeni Bergamo

As reviewed by Prof. Witjes in his presentation (above), the costs of treating recurrent bladder tumors is astronomically high. The equipment and costs associated with a new technology like Synergo® can be justified if it defers one

cystoscopy and one instillation per year, per patient. That alone would represent a huge savings.

Current Italian Studies Lombardia Synergo Project 2005-2008

N patients - 240; Time span for ° the project, 3 years

Inclusion criteria: superficial bladder cancer, Ta, T1; G1-2-3

Exclusion criteria

CIS and any bladder tumour different to TCC

Coexistence of another primary malignant tumor other than TCC

BCC (Carcinoma Basocellulare).

TCC of the bladder involving the urethra or upper urinary tract

Previous history of TCC stage T2 or higher.

Previous pelvic radiotherapy or systemic chemotherapy

Partial cystectomy

Diverticle of bladder larger than 1cm in diameter.

Bladder volume < 150cc measured by ultrasound.

Urethral stricture impeding size 20F catheterization

Active intractable or uncontrollable UTI

Known allergy to MMC

Pregnant or lactating women

Patients who cannot be followed up properly or are unable to collaborate

Prophylactic treatment regimen:

6 weekly sessions MMC 20+20 mg

Cystoscopy

6 monthly sessions MMC 20+20 mg

Cystoscopy every 3 months

Follow up 2 years

Participting Centers:

S. Raffaele Milano

S. Anna Como

IEO Milano

Ospedale Treviglio-Caravaggio

Ospedale G. Fornaroli Magenta

Istituto Humanitas Gavazzeni

Bladder Salvage - Women's protocol

A highly selective homogenous subset of female patients affected by SBC "high bladder carcinogenity" do not respond to repeated TUR and instillations.

Qualification criteria for the BSWP:

Superficial TCC (Ta, T1, G1, G2)

female patients

at least 3 TCC episodes in the past 12 months

all conventional intravesical instillations failed (BCG included)

more than 3 lesions

Extremely high-risk patients:

Any patients with TCC of 2 or more years duration that had 4 or more occurrences in the last 2 years despite multiple resections and failed at least 2 trials of a conventional intravesical insillations

Objective: The primary objective is to obtain at least 50% of the patient NED at 12 months

Patients are followed for 24 months with compulsory biopsies at 3 and 12 months and at each neoplastic or cytological doubt

Only histologically proven positivity will determine recurrences

Exclusion criteria

CIS, G3 and any bladder tumour

different to TCC

Coexistence of another primary malignant tumor other than BBC

BCC (Carcinoma Basocellulare).

TCC of the bladder involving the urethra or upper urinary tract

Previous history of TCC stage T2 or higher.

Previous pelvic radiotherapy or systemic chemotherapy

Partial cystectomy

Diverticle of bladder larger than 1cm in diameter.

Bladder volume < 150cc measured by ultrasound.

Urethral stricture impeding catheterization with 20Fr catheter

Active intractable or uncontrollable UTI

Known allergy to MMC

Pregnant or lactating women

Patients who cannot be followed up properly or are unable to collaborate

Participating centers

BERGAMO: Istituto Clinico Humanitas Gavazzeni

GENOVA: Ospedale Galliera

ROMA: Ospedale Sant’Andrea

PATIENTS RECRUITING

SINCE JANUARY 2005

RECRUITED PATIENTS

NO. 8

ASSESSABLE PATIENTS AT TIME “0”

NO. 6