

Intravesical chemotherapy

Last Updated Tuesday, 21 April 2009

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New treatments: Electromotive (EMDA) intravesical Mitomycin C followed by BCG [click here](#)

EOquin

New Technology Improves Mitomycin's Effect- "Synergo®"

Hyperthermia has been under investigation for use in advanced bladder cancer as well as other cancers, with some degree of success. New evidence shows improvements using Synergo® treatments for Mitomycin C intravesical chemo instillations. [click here](#)

Dr. Au's Mitomycin protocol:

For new data about method's to improve the effectiveness of Mitomycin C by manipulating the body's pH balance, [click here](#).

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This information is an extension of the page [Non-muscle-invasive Bladder Cancer](#)

Drugs used are reviewed below.

Potential drawbacks and risks are reviewed below.

Systemic chemotherapy is considered less effective than the intravesical (instilled in the bladder) agents in treating locally confined, non-muscle-invasive bladder tumors, therefore systemic therapy is reserved for muscle invasive, later stage cancers to fight systemic dissemination of blood-borne microscopic metastases.

Intravesically implanted chemo agents are much easier to tolerate than systemic chemo, as the unique environment of the bladder contains the drug while protecting the body from systemic poisoning. There are some side effects experienced after the instillation, i.e; irritation, burning, pain, cramps, diarrhea, bladder inflammation. As in all cancer treatments, these unpleasant side effects vary widely with the individual.

All intravesical chemo drugs studied have been shown to reduce recurrence rates though none has yet been proven to stand out significantly above the other. At this time no proof exists showing that intravesical chemotherapy prevents muscle invasive disease or metastases. However, TUR alone results in a higher recurrence rate than TUR followed by instillation therapy, whatever drug used. 1

The mechanism of action for prophylactic [used to prevent recurrence] intravesical chemotherapy remains unclear. Though proven useful in delaying recurrence cellular abnormalities remain basically unstable. Because most intravesical chemotherapy drugs are cell cycle specific, repeated instillations seem to be more effective than a single one. 2

Decades of ongoing research has supported the concept that recurrences may arise from tumor cell implantation at the time of transurethral management of bladder tumors ("re-seeding") and may be reduced effectively by concomitant intravesical chemotherapy. Immediate instillation of chemotherapy after TUR is considered safe as long as there is no injury (cuts, perforations or tears) to the bladder. The case of injury would present the risk of absorption into the bloodstream followed by immunosuppression and the systemic toxicity usually associated with chemotherapy.3

One instillation [currently most often epirubicin or Mitomycin C] at the time of TUR (transurethral resection, the minimally invasive surgery performed to remove bladder tumors) is now being recommended to delay recurrence of superficial, non-invasive bladder tumors:

New Standard: As of 2003, a single instillation after TUR has become the treatment of choice in patients with a single, low risk papillary tumor and is often recommended as the initial treatment after TUR in patients with higher risk tumors. For more info, See WebCafe's review, Research: Perspectives in Bladder Cancer, 2003, " meta-analysis of randomized trials investigating transurethral resection plus one immediate instillation of chemotherapy R.J. Sylvester, ScD, European Organization for Research and Treatment of Cancer, Brussels, Belgium

Update 2006

After 177 instillations of MMC immediately following TUR, only 2 minor complications were noted by UK researchers. They concluded that an immediate administration of mitomycin C in theatre after TURBT is feasible and safe for patients and staff. It provides the earliest and surest prophylaxis against tumour cell re-implantation at TURBT.25

Until these agents prove to decrease recurrence rates and delay progression of high-risk non-muscle-invasive bladder cancer, cystectomy remains the standard of care for the patient who is a good surgical candidate and willing to undergo such major surgery. 4

Intravesical chemotherapy reduces short-term (2 year) tumor recurrence by 20% or less when compared to surgery alone. Long-term (5-8 year) recurrence is reduced by 7%. The use of intravesical chemotherapy has a significant effect on the duration of disease free intervals, though no clear advantage has been proven with respect to progression to invasive disease or distant metastasis, or duration of survival and progression-free survival. Although approximately 40% to 50% of people initially respond to intravesical treatments, the maximum benefit of these agents in preventing recurrence during long-term follow-up is less than 10% compared with those who receive no other treatment after TUR. 5

After 20 years of experience with treatment approaches to Ta-T1 bladder tumors, the conclusions drawn at a recent European Congress were;

Primary, solitary, low stage, low grade tumors should not be treated by adjuvant intravesical therapy, but a single instillation of a chemotherapeutic agent soon after TUR favorably influences the recurrence rate.

A related study from Dr. Kurth states:

- Patients with < 1 recurrence/year or with a primary solitary bladder tumor category Ta G2-3 or T1 G1-3 may benefit from a single, early instillation of a cytotoxic agent
- Solitary Ta G1 lesions may be treated with TUR alone
- Adjuvant therapy with cytotoxic agents should be instituted as soon as possible after TUR (this is not feasible with immunotherapy)
- For patients treated within 6 hours after or on the day of TUR, a 6-month course of therapy is sufficient, whereas a 12-month course provides better results for patients in whom such early intravesical instillation is not feasible.⁶

Drugs Used

It is plausible that one single instillation, if performed immediately after transurethral resection, may destroy viable floating tumour cells which otherwise may lead to implantation. In most cases intravesical chemo is well tolerated.

Thiotepa

Thiotepa was first used for non-muscle-invasive bladder cancer in 1961. Immunosuppression has been reported with the use of thiotepa. "Recent tumor resection, extensive tumor, or concurrent cystitis can markedly increase absorption. WBC count and platelet count should be checked prior to each treatment. When intravesical thiotepa is administered with these precautions, it is safe and effective." ⁷

Experts in the Netherlands concluded in 2003 that ThioTEPA is better than no additional therapy, but is no longer frequently used due to its higher risk of systemic toxicity and limited efficacy. ²

Ethoglucid (Epodyl)

In a randomized controlled EORTC trial, Kurth and associates reported that ethoglucid was more effective than intravesical doxorubicin or TUR alone. Ethoglucid decreased the recurrence by 31%, while doxorubicin decreased recurrence by 13% compared with controls. ⁸

Epodyl is poorly absorbed and not frequently used anymore.²

Adriamycin (Doxorubicin, ADM)

Expert Lamm reviewed 4 large controlled studies where ADM was used as prophylactic, the percentage of patients with a recurrence in the ADM groups was 38% versus 56% in the control groups, indicating an advantage for ADM of 18%.⁹ Nevertheless, the three largest series showed no significant advantage for ADM. Though proven safe with almost no systemic side effects, as well as more effective than no adjuvant treatment, these figures often are not significant. ADM is more effective when combined with verapamil [a blood pressure .]. Maintenance has been shown to be of no additional value.²

Epirubicin (EPI)

Epirubicin is in the same family as ADM/doxorubicin, and its anti-tumor effect is similar to ADM.¹⁰ In the EORTC study (30863) which used a single 80 mg EPI instillation, the frequency of drug induced cystitis was also only 6.8%. The most effective dose is still controversial. A randomized UK study with 122 patients showed that a double dose was not superior in efficacy regarding tumor response, time to first recurrence or recurrence rate. The number of instillations remains controversial.²

Epirubicin instillation after TUR reduces recurrence

After TUR for non-muscle-invasive bladder cancer, intravesical epirubicin prophylaxis decreases recurrence rates compared with placebo or TUR alone, says an article which sites many studies to back this claim; Go to Medscape.com, registering is free; article found at <http://www.medscape.com/adis/DTP/2000/v15.n09/dtp1509.01/dtp1509.01-01.html>].

In a study done on 253 patients, epirubicin compared better to doxorubicin, with both a lower toxicity and higher response rate.¹¹

With regard to maintenance therapy many studies have been performed with conflicting results. In conclusion, the efficacy of EPI seems similar to other chemotherapeutic drugs but with less drug induced cystitis. The additional advantage of EPI maintenance therapy is controversial.²

Mitomycin C (MMC)

Mitomycin C has long been in use; one study with 125 participants reported response rates of 36% at the 36 month follow up; the response rate was identical for both papillary and in situ tumors.¹² Maintenance therapy may be advised, though other studies have suggested that this may be of limited value in the presence of large tumors or CIS.¹³

MMC is an alkylating agent that has rarely been shown to cause myelosuppression. The dose varies between 20 and 80 mg per instillation. In a meta-analysis of 181 articles published from 1966 to 1998, an average of 20% of patients experienced bacterial cystitis. Allergic reactions, mainly skin symptoms, ranged between 8 and 19% with a mean of 13%.¹⁴

When applied as a single immediate, post TUR instillation in patients with low risk non-muscle-invasive bladder cancer, recurrences developed during the first 12 months in 59% of the control group but only 22.2% of the MMC group ($p = 0.005$). However, at long-term follow-up these differences were not statistically significant.¹⁵

For prophylactic use, after complete TUR, data from 23 clinical trials were analyzed and confirmed although the short term recurrence rate decreased, disease progression was not influenced by MMC. Studies directly comparing BCG and MMC give conflicting results. Two possible causes might be patient selection and the use of different MMC and especially BCG schedules.²

MMC Maintenance

The advantage of MMC maintenance therapy is controversial. In one group of complete responders no beneficial effect of maintenance therapy was seen in patients with papillary tumors. For CIS patients the 2-year recurrence rate after maintenance therapy was significantly better ($p < 0.05$), but the curves suggest that with a longer follow-up this difference will disappear. Nevertheless, some studies showed an advantage of maintenance therapy.

A possible explanation for this controversy in advantage of maintenance therapy is that the effect of the short-term intensive MMC therapy may be of more importance than the long-term maintenance therapy.

BCG was superior in preventing recurrence compared to maintenance MMC, but no difference was found for progression and survival. The response rates of MMC seem higher than other chemotherapeutic drugs, though not all studies show a significant advantage of MMC over no additional treatment. The advantage of MMC maintenance therapy remains controversial.²

Update 2006: AUA presentation- Maintenance MMC:

Maintenance MMC is superior to induction BCG alone, or induction MMC alone. Side effects were not significantly increased, further supporting a maintenance strategy for MMC. An increased therapeutic benefit was observed in patients with moderate- to high-grade Ta disease as well as those with T1 tumors. In a randomized, multicenter, phase 4 study design, there was demonstrated a 3-year recurrence-free survival of 66% in 163 patients treated with a 6-week induction course of BCG; 69% in 176 patients treated with a 6-week induction course of MMC (20 mg); and 86% in 153 patients treated with a 6-week induction course of MMC followed by monthly instillations for 3 years ($P = .001$).²⁶

Three improvements in the use of Mitomycin:

Dr. Au's protocol small changes produce benefit

Synergo® Hyperthermia plus Mitomycin

EMDA - electromotive drug administration of Mitomycin C (+BCG)

Valrubicin (AD32)

Valrubicin, trade name Valstar, approved in 1998 in the US as intravesical chemotherapeutic agent for refractory

CIS [carinoma in situ which has not responded to BCG or other intravesical therapies], for those who refuse cystectomy. Valstar is in Phase 3 clinical trials for non-muscle-invasive TCC. In the clinical trials conducted prior to its FDA approval for CIS patients, Valstar showed response rates of 18%. The drug is instilled immediately following TUR. During the clinical trials, only 3 of 90 patients experienced drug-related adverse effects.¹⁶ See also survivor stories on WebCafé: Paul Carr

Valrubicin (AD32) is a derivative of the anthracycline ADM/doxorubicin [see above]. Additional follow-up and more studies are needed to define the role of valrubicin in the treatment of non-muscle-invasive bladder cancer.

Pirarubicin (THP)

Another anthracycline under investigation is pirarubicin. In a randomized study of single early THP instillation for a single non-muscle-invasive bladder carcinoma 84 patients were treated with either THP within 6 hours after TUR versus the controls who underwent TUR alone. The recurrence free rate at 1 year was 92% versus 67%, and 79% versus 53% after 3 years. This indicates that a single THP instillation immediately after TUR reduces the recurrence of TCC.²

Gemcitabine Gemzar

Gemcitabine is a relatively new chemo drug being used both intravesically for non-muscle-invasive bladder cancer as second or third line treatment for BCG or chemotherapy drug failures, and systemically for invasive/advanced bladder cancer (GC=Gemzar/Cisplatin, the new 'gold standard' replacing the more toxic combination of MVAC-see invasive bladder cancer-chemos used).

Single intravesical instillation of gemcitabine immediately after TUR and multiple random biopsies for non-muscle-invasive bladder cancer have been shown to be safe and well tolerated with low toxicity and side effects. Future phase II studies with this agent are underway world-wide.¹⁷

This link will take you to a pre-searched page of medical abstracts about Gemcitabine for non-muscle-invasive bladder cancer published in the Library of Medicine: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pubmed>

Sequential chemo/immunotherapy

The theory behind this approach is that the combination of different working mechanisms would possibly increase the anti-tumor effect. A second advantage might derive from drug-induced cystitis or bladder inflammation which can help BCG particles to better adhere to the bladder wall. A disadvantage of combining immunotherapy and chemotherapy drugs could be increased toxicity.

European studies seem to conflict, although data points to a higher response with sequential chemo/immunotherapy for those with CIS, while the results of the combination of BCG + MMC vs. MMC alone seem to be similar for papillary tumors. Side effects were found to be similar in groups using MMC alone or MMC with BCG.²

In the pipeline:

BCG followed by Electromotive (EMDA) intravesical Mitomycin C

Experts in Italy have been working with Physion, the company that designed the electromotive delivery system. BCG combined/ followed by electromotively delivered Mitomycin C preceded by BCG are showing some of the best response rates ever seen in non-muscle-invasive bladder cancer treatments. sequential BCG and electromotive mitomycin (EMDA) versus BCG alone:

disease-free interval 69 months vs. 21 months

recurrence rates: 41.9% vs 57.9

progression 9.3% vs 21.9%

overall mortality 21.5% vs 32.4%

disease-specific mortality 5.6% vs 16.2%

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 (EUA, 2006) ."27

More on WebCafe, EMDA

EOquin® - (Apaziquone)

An investigational new drug from Spectrum pharmaceuticals is showing promise as an intravesical treatment for non-muscle invasive bladder cancer. EOquin® (Apaziquone) is the first new drug to be used for bladder cancer in more than 20 years and is a derivative of the commonly used Mitomycin C (MMC).

Phase 2 trials in Europe delivered favorable results and further studies concur that early recurrences after treatment with apaziquone are significantly lowered. The interval between tumor recurrences were also extended for the patients studied.

A single immediate post-TUR instillation of apaziquone has been shown to be well tolerated with an expected good safety profile leading to further study of apaziquone in this setting.

The treatment is intended for those with stage Ta-T1 recurrent papillary, non-muscle invasive bladder cancer (NMIBC) grades 1-2 (low to intermediate grade).

FDA approval is pending the results of Phase III clinical trials.

For more information and complete eligibility requirements see:

Phase 3 Trial of Single-Dose Intravesical EOquin® as a Surgical Adjuvant for Noninvasive Bladder Cancer; NCT00598806

Trial of Single-Dose Intravesical EOquin® as a Surgical Adjuvant Instilled in the Early Postoperative Period in Patients Undergoing TUR-BT; NCT00461591

Two-year follow-up of the phase II marker lesion study of intravesical apaziquone for patients with non-muscle invasive bladder cancer.

Hendricksen K, van der Heijden AG, Cornel EB, Vergunst H, de Reijke TM, van Boven E, Smits GA, Puri R, Gruijs S, Witjes JA. Nijmegen, The Netherlands, 2009 Feb 13 World J Urol DOI 10.1007/s00345-009-0382-4

PMID: 19214526

Safety and Side Effects of Immediate Instillation of Apaziquone Following Transurethral Resection in Patients With Nonmuscle Invasive Bladder Cancer

K. Hendricksen, D. Gleason J. M. Young, & dagger; D. Saltzstein, A. Gershman, S. Lerner and J. A. Witjes Journal of Urology, 2008 Jul;180(1):116-20. PMID: 18485407

Response of Multiple Recurrent TaT1 Bladder Cancer to Intravesical Apaziquone (EO9): Comparative Analysis of Tumor Recurrence Rates

Arun Jain, Roger M. Phillips, Andrew J. Scally, Gino Lenaz, Mario Beer, and Rajiv Puri Urology 2008; doi:10.1016/j.urology.2007.12.062

PMID: 19232688

Phase II Marker Lesion Study With Intravesical Instillation of Apaziquone for Superficial Bladder Cancer: Toxicity and Marker Response

Antoine G. van der Heijden, Paula M. J. Moonen, Erik B. Cornel, Henk Vergunst, Theo M. de Reijke, Erika van Boven, Evert J. Barten, Rajiv Puri, Coenraad K. van Kalken and J. Alfred Witjes* Journal of Urology, 2006 Oct;176(4 Pt 1):1349-53; discussion 1353 PMID: 16952629

Phase I/II Pilot Study of Intravesical Apaziquone (EO9) for Superficial Bladder Cancer

Rajiv Puri, Victor Palit, Paul M. Loadman, Michael Flannigan, Tariq Shah, Guzanfar A. Choudry, Saurajyoti Basu, John A. Double, Gino Lenaz, Shanta Chawla, Mario Beer, Coen Van Kalken, Richard de Boer, Jos H. Beijnen, Christopher J. Twelves and Roger M. Phillips THE JOURNAL OF UROLOGY® Copyright © 2006 by AMERICAN UROLOGICAL ASSOCIATION DOI:10.1016/j.juro.2006.06.047 5347/06/1764-1344/0

PMID: 16952628

Vicinium®; Beginning in 2007- small, phase II clinical study for the treatment of locally recurrent non-invasive bladder cancer; Dosed on a weekly basis for 6 weeks, Vicinium®; was very well tolerated at all dose levels, with significant anti-tumor responses were also observed in this study: 42% of patients demonstrated a complete response, 13% had a partial response, and 40% had stable disease, for an overall response rate of 95%.

Drawbacks and Risks?

After reviewing results of 4 decades of studies done on patients who received intravesical chemotherapy, Lamm and associates reported that among 2,011 randomized patients progression occurred in 7.5% of those receiving intravesical chemotherapy and 6.9% of those treated by surgery alone. Since intravesical chemotherapy has been demonstrated in animal models to be carcinogenic, these data raise the concern that intravesical chemotherapy might possibly be carcinogenic in humans. Furthermore, the team of experts questioned the advisability of routine prophylactic intravesical chemotherapy in the absence of demonstrated long-term benefit.¹⁸

Carcinogenic risk has been demonstrated in humans as well; two cases are reported of patients who developed a hematologic malignancy several years after intravesical chemotherapy of non-muscle-invasive bladder cancer with ethoglucid, doxorubicin, and mitomycin C. In this study [head of European Urology Association] Dr. Kurth concluded that "Intravesical chemotherapy may be associated with a risk of secondary malignancy." ¹⁹

A 1999 Japanese study determined by a log-rank test to be an unfavorable long term risk factor for progression to invasive disease "Four variables including presence of multiple tumors, involvement of the bladder neck, positive urine cytology, and intravesical chemotherapy were found by a univariate analysis to be significant risk factors for late progression." ²⁰

A retrospective study from 2000, done on 187 patients concluded that for those with low grade, stage Ta and T1 tumours TUR alone may be the best treatment modality. "Although intravesical chemotherapy is effective in decreasing short-term incidences of tumour recurrence, it has not decreased long-term incidences of tumour recurrence. The high cost and adverse side effects of intravesical chemotherapy should also be taken into consideration in non-muscle-invasive, single, low grade tumours of bladder." That article further states that regular follow-up urological assessments should be continued until at least 15 years of tumor-free existence, especially in patients treated by intravesical chemotherapy or those initially having multiple tumors.²¹

An immediate instillation of chemotherapy post-TUR is becoming a new standard in the treatment of low risk Ta, T1 bladder tumors. [see also: A meta-analysis of randomized trials investigating transurethral resection plus one immediate instillation of chemotherapy R.J. Sylvester, ScD, European Organization for Research and Treatment of Cancer, Brussels, Belgium,]

However, this approach carries the serious- though rare- risk of systemic toxicity that can even lead to death. In order to prevent such complications, this treatment should be avoided when there is overt or even suspicion of bladder wall perforation. Serious complications from bladder perforation have been reported with the use of epirubicin and Mitomycin C.²²

Antibiotics increase effectiveness of doxorubicin

Recent experiments combining the quinolone antibiotics Ciprofloxacin and ofloxacin with doxorubicin (adriamycin) in the

laboratory has shown that both drugs significantly enhance the cytotoxicity of adriamycin. The authors are suggesting that this data presents evidence to evaluate the use of quinolone antibiotics as an adjunct to intravesical chemotherapy. Quinolones might also prove beneficial in preventing seeding of cancer cells after transurethral resection of bladder tumors thereby decreasing tumor recurrence rates.²³ Read more about this here: [antibiotics for bladder cancer](#)

BCG is most often used in case of recurrence after intravesical chemo, high grade tumors or carcinoma in situ. If BCG has been used as first line of attack, the intravesical chemo can be tried in case of BCG failure.

Of the patients with high grade tumors and carcinoma in situ who fail a first course of BCG, 50% will respond to a second course of BCG. Patients who fail to respond to a second course of treatment should seriously consider cystectomy, as the likelihood of developing invasive or metastatic disease is 30%-60%.²⁴

Read also the article: Contemporary Management of Superficial Bladder Cancer Julio M. Pow-Sang, MD, and John D. Seigne, MB, BCh. Cancer Control, Journal of the Moffitt Cancer Center July/Aug 2000

[back to non-muscle-invasive bladder cancer](#)

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Additional Source;

<http://www.duj.com/Article/Schenkman.html> Superficial Bladder Cancer Therapy Emmanuel Schenkman, M.D. and Donald L. Lamm, M.D. Schenkman and Lamm's review of the latest statistics and treatments for management of superficial bladder cancer in the Digital Urology Journal