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Cooperative studies of chemoprophylaxis after transurethral resection of bladder tumors

Michele Pavone-Macaluso, Maria Tripi, and Giovan Battista Ingargiola

Institute of Urology, University of Palermo, Polyclinic Hospital, I-90127 Palermo, Italy

Summary. *Large cooperative trials are more likely than series studied by small groups to bring about significant progress in the field of intravesical adjuvant chemotherapy of superficial bladder tumor*

Multicenter randomized trials involving large numbers of patients have been conducted in Europe by the EORTC Urological Group. The Group's main objectives were to compare the efficacy of thio-TEPA, VM-26, epodyl, Adriamycin, and cisplatin, against no treatment, and to study the prophylactic effect of oral pyridoxine and evaluate the main prognostic factors. The results obtained so far are reported. Preliminary information is also given about the Blinst study, a multicenter open investigation of local chemotherapy with doxorubicin (Adriamycin), with special reference to evaluation of the importance of different modalities of treatment with a single drug.

Introduction

Many reports in recent years have dealt with intravesical chemotherapy as a prophylactic measure to prevent or to reduce recurrence of superficial papillary bladder tumors after transurethral resection (TUR) or other conservative procedures [1, 8, 10, 11, 14]. However, almost all such reports were based on the relatively limited experience of single centers or investigators and were lacking comparison with control groups. Their validity is therefore open to reasonable doubts; their results are often conflicting and no clear-cut conclusions can be reached at present, on the usefulness of topical chemoprophylaxis, the indications for it, or the best routes and schedules of administration. Very few studies have been based on the follow-up of large numbers of patients. One of these is the so-called Blinst study, and the EORTC Urological Group has conducted four randomized clinical studies of chemoprophylaxis after TUR, two of which have already been closed to entry.

We are very grateful to the active members, study coordinators and Data Center of the EORTC Urological Group, and also to the participants in Blinst study, who kindly gave us their permission to present an interim report illustrating some aspects and unpublished results of the on-going studies.

Reprint requests should be addressed to M. Pavone-Macaluso

1. Trials conducted by the EORTC Urological Group

EORTC stands for European Organization for Research on the Treatment of Cancer, and its Urological Group has been active for a few years in several aspects of urological oncology [4, 7].

The EORTC Urological Group has implemented four randomized trials to compare different drugs with each other and with lack of postoperative treatment. The design of the studies is indicated in Figs. 1–4, and the participants in the various trials are listed in Tables 1–4.

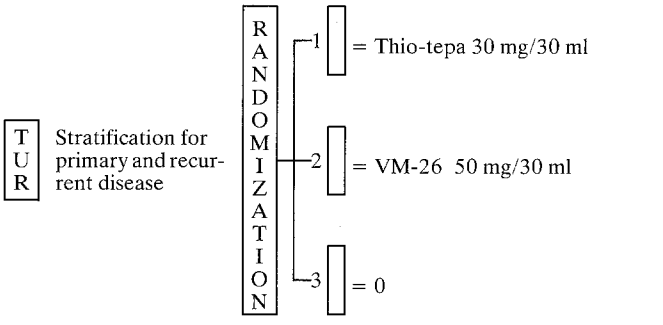

Fig. 1. EORTC trial 30751: Protocol study of T1 papillary carcinoma of the bladder

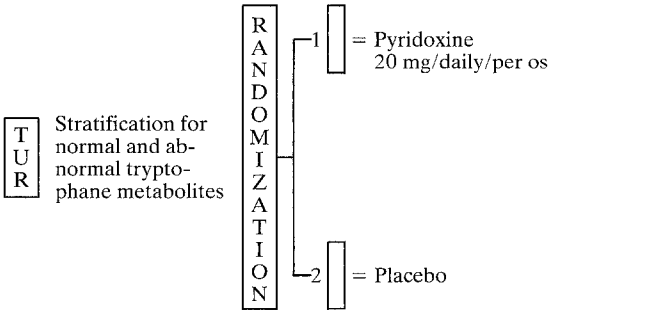

Fig. 2. EORTC trial 30781: Protocol study of T1 papillary carcinoma of the bladder

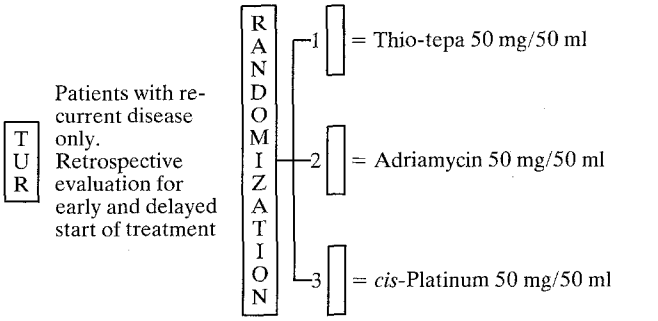

Fig. 3. EORTC trial 30782: Protocol study of T1 papillary carcinoma of the bladder

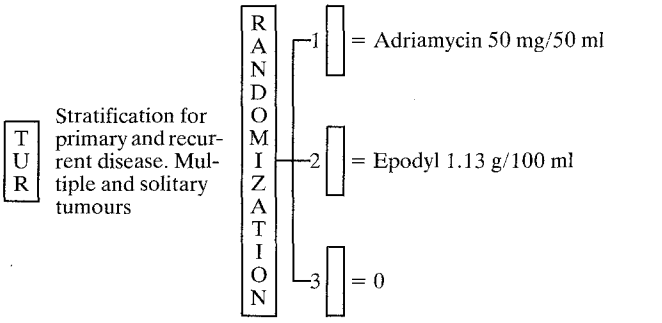

Fig. 4. EORTC trial 30790: Protocol study of T1 papillary carcinoma of the bladder

Table 1. Participants and patients entered in EORTC trial 30751 (thio-TEPA vs VM-26 vs no treatment)[a]

No.	Participants	City	Country	No. of patients
1	M. R. G. Robinson	Castleford	UK	53
2	L. Denis	Antwerp	Belgium	45
3	P. H. Smith	Leeds	UK	43
4	J. Auvert	Créteil	France	43
5	G. Viggiano	Mestre	Italy	32
6	M. Pavone	Palermo	Italy	29
7	C. Schulman	Bruxelles	Belgium	24
8	C. Bollack	Strasbourg	France	20
9	D. Newling	Hull	UK	17
10	C. Bouffioux	Liège	Belgium	13
11	B. Richards	York	UK	12
12	R. Glashan	Huddersfield	UK	10
13	S. Fantoni	Pavia	Italy	8
14	B. Lardennois	Reims	France	8

[a] Study coordinators: C. Schulman and M. Staquet. Other participants: F. Juraschek (Mulhouse, F); J. Vicente (Barcelona, Spain); C. Frey (Basel, CH); V. Nadalini (Genova, I); C. Bondavalli (Mantova, I); G. Shepheard (Oldham, UK)
Total number of patients entered 370

Table 2. Participants and patients entered in EORTC trial 30781 (pyridoxine vs placebo)[a]

No.	Participants	City	No. of patients
1	D. Newling	Hull	70
2	P. H. Smith	Leeds	54
3	M. R. G. Robinson	Pontefract	45
4	R. Glashan	Huddersfield	34
5	B. Richards	York	31
6	I. Appleyard	Airedale	27
7	G. Shepheard	Oldham	15
8	R. Adib	Pinderfields	12
9	J. R. Rhind	Hartlepool	3

[a] Study coordinator: M. Robinson, Castleford, UK. All participants from Yorkshire, England
Total number of patients entered 291

Table 3. Participants and patients entered in EORTC trial 30782 (thio-TEPA vs Adriamycin vs cisplatin 50 mg in 50 ml)[a]

No.	Participants	City	Country	No. of patients
1	L. Denis	Antwerp	Belgium	48
2	B. Vergison	Brugge	Belgium	35
3	W. Oosterlinck	Gent	Belgium	35
4	A. Barbui	Mestre	Italy	27
5	C. Bouffioux	Liège	Belgium	23
6	M. Pavone	Palermo	Italy	20
7	F. Debruyne	Nijmegen	NL	16
8	C. Bollack	Strasbourg	France	14
9	J. Casselman	Oostende	Belgium	11
10	C. Schulman	Brussels	Belgium	7
11	A. Thiry	Mons	Belgium	7
12	Dr Petit	Rouen	France	6
13	G. Viggiano	Gorizia	Italy	5
14	Dr Lesur	Lomme	France	3

[a] Study coordinators: C. Schulman and M. Pavone-Macaluso. Other participants: B. Lardennois (Reims, F); P. H. Smith (Leeds, UK); A. Akdas (Ankara, Turkey); Dr Consivine (Solihull, UK); J. Auvert (Creteil, F)
Total number of patients entered 265

Table 4. Participants and patients entered in EORTC trial 30790 (Adriamycin vs ethoglucide vs no treatment)[a]

No.	Participants	City	Country	No. of patients
1	K. H. Kurth	Rotterdam	NL	66
2	U. Tunn	Bochum	Germany	50
3	D. Newling	Hull	UK	28
4	H. Riedl	Weiden	Germany	27
5	F. Debruyne	Nijmegen	NL	25
6	M. Pavone	Palermo	Italy	20
7	G. Jackse	Innsbruck	Austria	15
8	H. De Voogt	Amsterdam	NL	11
9	Dr Carpentier	Rotterdam	NL	11
10	Dr Cauwbierg	Gouda	NL	9
11	H. Leisinger	Schaffhausen	CH	9
12	H. Mensink	Groningen	NL	6
13	B. Richards	York	UK	5
14	R. Janknegt	's Hertogenbosch	NL	4

[a] Study coordinator: K. H. Kurth, Rotterdam, The Netherlands. Other participants: R. Adib (Pinderfield, UK); Dr H. Oekstra (Den Bosch, NL); C. Bouffioux (Liège, B); C. Schulman (Brussels, B); Dr Van Es (Rotterdam, NL); K. Alkrock (Leer aus Grunland, Germany); P. H. Smith (Leeds, UK); M. Robinson (Castleford, UK)
Total number of patients entered 286

Trial 30751

A report of the first of such studies (EORTC protocol 30751) has been published by the Coordinators and other members of the EORTC Urological Group. The main points of interest, which have derived from a careful analysis of results, have been published in two different papers [3, 13], the first dealing chiefly with the results, the other with the value of the prognostic factors. The design of the study was as follows: there was a preliminary stratification into two groups: primary and recurrent tumors. After urethrocystoscopy and bimanual palpation under anesthesia the papillary tumors were resected by TUR. After histological confirmation of lack of muscular infiltration, but irrespective of the grade (therefore G1, G2, and G3 were all included), the patients were randomized into three groups: triethylene thiophosphoramide (thio-TEPA) 30 mg in 50 ml normal saline; teniposide (VM-26) 50 mg in 50 ml; and lack of treatment.

The drugs were retained in the bladder for 1 h. The first instillation was not given until 1 month after TUR. Subsequent instillations were then administered at weekly intervals for 1 month and then at monthly intervals for 1 year, up to a total number of 15 instillations. Blood counts were performed before each instillation. Cystoscopy was repeated every 3 months for the first year. If a recurrence was found, it was resected and considered a true recurrence only after histological confirmation. The drug was not changed, but a weekly regimen was again instituted for the next 4 weeks. After 370 patients had been admitted the trial was closed to entry, but the patients are still being followed up.

In our view, several interesting things have emerged from this study:

1) There is always *a risk* in *reporting preliminary results.* In fact, the first interim reports [12] appeared to show that VM-26 was not only useless, but could promote progression to a higher grade. A second analysis, based on a greater number of patients with a longer follow-up [13], failed to confirm progression, but showed that teniposide was marginally better than lack of treatment, though such a difference was not statistically significant (Table 5).

2) *Neither thio-TEPA nor teniposide reduced* the number of patients showing *recurrences* compared with patients receiving no treatment. However, the effects of the treatment can be shown by adopting a parameter which is defined as 'recurrence rate,' which takes into consideration the total number of recurrent tumors cumulatively discovered at all control cystoscopies per patient per month. To avoid the use of decimals this is multiplied by 100, so that our definition of recurrence rate in this and in the further studies is 'number of recurrent tumors per 100 patient-months.' Use of this formula showed that thio-TEPA was statistically better than no treatment.

3) *Neither a marked bone marrow depression nor a severe chemical cystitis* was produced by either thio-TEPA (30 mg) or teniposide instillations.

4) *Relevant prognostic factors were identified* (or confirmed). Recurrent versus primary, multiple versus single, large versus small, high-grade versus low-grade tumors showed a higher recurrence rate. However, the most important single prognostic factor leading to a high recurrence rate was the number of recurrent tumors at presentation, followed by the number discovered in the year preceding entry on the study. This high-risk group benefited the most from intravesical treatment, especially with thio-TEPA.

5) This study also showed that if frequent checks, with *biopsies of all suggestive lesions,* are performed the incidence of new-occurrences in untreated patients is even higher than anticipated, being almost 50% at the first follow-up check (which was performed a mean of 4 months after TUR), whereas increase in T and G categories was relatively low.

6) *Disease-free interval until first recurrence was not greatly modified by the treatment,* although a trend in favor of thio-TEPA can be suggested, especially in high-risk groups. Otherwise the results of instillation were more or less the same in both primary and recurrent urotheliomas.

In summary, these data showed that intravesical instillation of thio-TEPA or teniposide, using the modalities described in our protocol, had some merits, but the overall results were not very striking, and could not compare with the optimistic results suggested by previous uncontrolled trials.

Accordingly, our interpretation was that perhaps (1) the drugs themselves were not especially active, so that it was necessary to test new ones; (2) the fact of having run a controlled clinical trial instead of presenting a comparison with historical controls showed things in a more realistic light and might reopen a discussion of the whole idea of local postoperative chemotherapy, especially in primary cases; (3) the dose of thio-TEPA (30 mg) was probably too low (meanwhile an American study [6] has shown that 60 mg thio-TEPA may be more effective than 30 mg); (4) the interval between TUR and start of instillation may be too long, especially if the cell implantation theory is valid; (5) the

Table 5. Recurrence rate by treatment groups in EORTC trial 30751

	Thio-TEPA	VM-26	Control	Total
No. of patients randomized	122	124	124	370
No. of patients with follow-up	105	99	104	308
No. of patients with recurrences	62	68	72	202
Percent with recurrences	59	68.7	69.2	65.6
Total number of recurrences	105	111	142	358
Total months of follow-up	1,941	1,665	1,590	5,196
Recurrence rate/100 patient-months	5.41	6.67	8.93	6.89

Comparison	*P*
Thio-TEPA vs VM-26	0.26
Thio-TEPA vs control	0.008
VM-26 vs control	0.06

indications for intravesical chemotherapy should be re-evaluated and only patients belonging to high-risk groups should be subjected to the discomfort and inconvenience of repeated visits, blood tests, and catheterization, at least until an active oral non-toxic drug becomes available, rendering chemoprophylaxis simpler and more attractive. These points were taken in consideration in the design of the next studies of the EORTC Urological Group.

Trial 30781

Study 30781 was aimed at comparing oral pyridoxine with a placebo and at correlating recurrence rate with the changes in the urinary excretion of tryptophane metabolites, which are thought to be endogenous carcinogenic agents, and to be reduced by the oral administration of pyridoxine [2].

The need for a central laboratory performing the tryptophane metabolite determinations has restricted this study to investigators in Yorkshire. The study has been closed to entry, but according to our present policy no preliminary results have been given either for this or for the next study described.

Trial 30782

The design of study 30782 is similar to that of 30751. The main differences are as follows:
1) There is no control group.
2) Two new drugs have been tested, namely doxorubicin (Adriamycin) and cisplatin, while the dosage of thio-TEPA has been increased to 50 mg. All drugs are used at the dose of 50 mg in 50 ml.
3) Only patients with recurrent tumors are eligible.
4) The interval between TUR and first instillation has been shortened.

Two subgroups will be analyzed retrospectively, those starting treatment within 2–3 days from TUR and those approaching the maximum allowable interval of 2 weeks.

This study has recruited patients mainly from Belgium and Italy but, again, no interim results on efficacy have been reported. It was, however, considered appropriate to report some unpublished toxicity data that have emerged from this material.

The incidence of chemical cystitis appeared to be somewhat high in trial 30782, in which it was reported in 12% of patients given Adriamycin. Only in 3% was it severe enough to warrant discontinuation of the treatment. Chemical cystitis was also present in 14% of patients given cisplatin, but was never reported after thio-TEPA.

The systemic side-effects of local chemotherapy are even more interesting. Thio-TEPA 50 mg produced systemic side-effects in 10% of patients, in the form of leukopenia or, more often, of thrombocytopenia. The latter was quite severe in one patient (23,000 platelets/mm) requiring the treatment to be discontinued. This was not unexpected, although most toxicity data reported in the literature resulted from higher doses of thio-TEPA. Quite unexpected, in contrast, was the finding that cisplatin instillations were followed by rather severe systemic side-effects in 14% of the patients. The toxic effect took the form of anaphylactic shock, sometimes preceded by a rash, which required interruption of treatment in all patients and was considered life-threatening in some of them. It appeared as a late phenomenon, occurring in the last months of treatment, and was described independently by participants from different institutions.

This observation suggests that unless cisplatin is shown to be therapeutically more active than the other drugs, its use should not be encouraged as a topical agent for protracted use. The efficacy results of study 30782 are therefore awaited with the greatest interest.

Trial 30790

A third trial, still on-going, no. 30790, is running parallel to the previous one, and has the following features:
(1) a different geographical distribution (mainly from the Netherlands and Germany); (2) entry permitted not only to recurrent but also to primary disease patients; (3) randomization into three groups, one of which is a control group receiving no treatment while the two other receive instillations of either Adriamycin 50 mg, which represents an arm in common with the previous study, or ethoglucide (Epodyl), 1.3 g in 100 ml. The control group has recently been dropped, after the first analysis of the preliminary results. In study 30790 the only complaint was chemical cystitis, which occurred in 4% of patients in both treatment groups (Adriamycin and Epodyl).

Some preliminary results are available for study 30790, since an interim analysis showed that lack of treatment was significantly worse than treatment with either Adriamycin or Epodyl, with a P value less than 0.001 [5]. No significant difference between the two drugs was apparent, but the difference between recurrence rate in treated patients (2.91) and those not receiving treatment after TUR (9.17) was so great that the Study Coordinator, Dr Kurth, in agreement with the Data Center, decided to stop randomization of patients to the no-treatment arm.

2. The Blinst study

The Blinst study was designed to obtain efficacy and toxicity data on the intravesical use of doxorubicin (Adriamycin). This was an open study, which followed the general pattern of the EORTC trials, but each investigator was allowed to modify the protocol within certain limits, according to his preference or local requirements.

Briefly, the dose of doxorubicin ranged between 30 and 80 mg. The most widely used dose, 50 mg, was dissolved in 50 ml sterile water or saline, instilled into the bladder and retained for about 1 h. The instillations were started at varying intervals after TUR, from a few days to a month. They were performed weekly for 1 month, then monthly; control cystoscopies were performed every 3 months.

Table 6 sets out the number of patients treated with doxorubicin intravesically within the framework of the Blinst study. The large mass of data obtained from Italy and the other countries involved was analyzed for toxicity and activity. Analysis of the toxicity, in a total of 740 patients, showed that 143 (19.3%) patients experienced side-effects, 104 (14%) of whom were able to continue treatment, while 39 (5.3%) had to drop out (Table 7). A further breakdown showed that in 129 (17.4%) of the 143 patients the side-effects were of a local nature, mainly chemical cystitis; 10 experienced systemic effects and four cases both (Table 8). The type and total number of local side-effects are reported in Table 9.

Systemic side-effects are listed in Table 10; treatment was withdrawn in four cases. An analysis of all systemic side-effects mentioned in the patients' record forms, case by case, showed

Table 6. Intravesical chemoprophylaxis with doxorubicin: Distribution of patients evaluable for toxicity by country[a]

Country	No. of patients
Italy	524
Spain	71
Holland	35
Germany	28
Portugal	28
Belgium	27
Greece	13
Chile	10
United Kingdom	4
Total	740

[a] Acknowledgements are due to the various investigators in the different countries for their contribution to this multinational study

Table 7. Patients affected by side-effects in the Blinst study

Evaluable patients	740
Total patients with side-effects	143 (19.3%)
Patients with side-effects continuing treatment	104 (14.0%)
Patients discontinuing treatment because of side-effects	39[a] (5.3%)

[a] Local effects 35; systemic effects 3; both 1

Table 8. Overall toxicity recorded in the Blinst study of prophylactic treatment

Evaluable patients	740
Patients with local side-effects	129 (17.4%)
Patients with systemic side-effects	10 (1.3%)
Patients with local and systemic side-effects	4 (0.5%)

Table 9. Local side-effects recorded in the Blinst study of prophylactic treatment

Local side-effects	No. of patients
Scalding	44
Cystitis	42
Frequency	38
Hematuria	33
Dysuria	35
Strangury	24
Tenesmus	12
Spasm	7
Nocturia	4
Intravesical edema	2
Hemorrhagic cystitis	2
Urinary incontinence	2
Urgency	1
Urinary infection	22

Table 10. Systemic side-effects

	No. of patients
Decreased platelet count (never less than 100,000/mm^3	3
Renal insufficiency	2
Left facial paralysis	1
Sensation of abdominal discomfort[a]	1
Chills, headache	1
Dizziness, hot flushes	1
Weakness, nausea, sweating	1
Chronic arterial disease	1
Itching[a]	1
Shivering and paresthesia of the lower limbs	1
Epistaxis	1

[a] Probably drug-related. For other cases the drug-event relationship appeared very doubtful from the case-by-case analysis of the patient forms

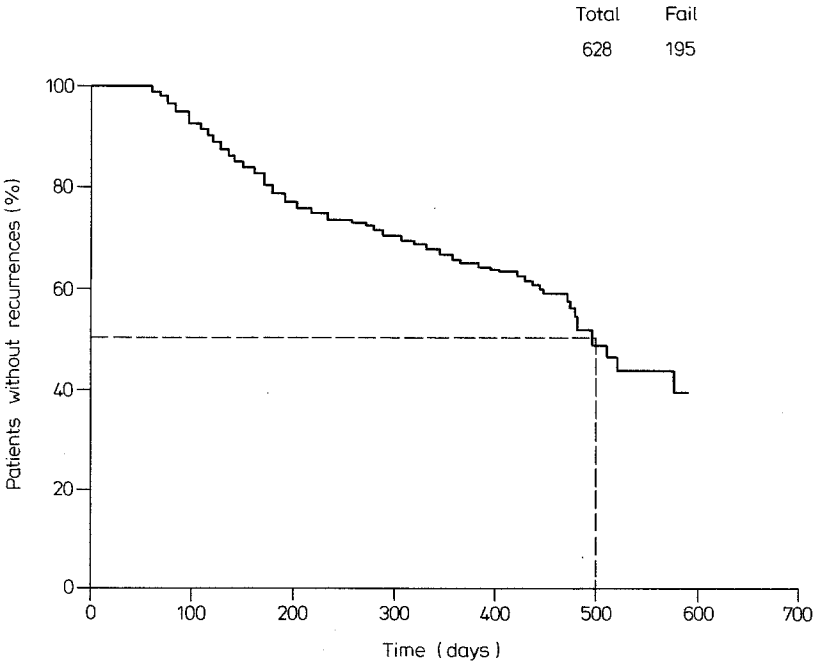

Fig. 5. Time to 50% incidence of recurrence calculated in the Blinst study in 628 patients treated with intravesical doxorubicin (Kaplan-Meier)

an extremely doubtful drug-event relationship in most cases. In fact only two events, i.e., itching and sensation of abdominal discomfort, can be considered drug-related.

As far as activity is concerned, the results relevant to 628 evaluable cases are represented in Fig. 1, plotted according to the Kaplan and Meier method, where the median time to recurrence is 500 days. Of 628 patients, 195 (31%) had recurrences within a median follow-up time of 8 months.

Discussion

Cooperative studies based on large numbers of patients have yielded important information on indications for and results of local chemotherapy of superficial bladder tumors. EORTC studies have shown that various drugs, such as thio-TEPA, Adriamycin and Epodyl, can effectively reduce recurrence rates.

Teniposide (VM-26) and cisplatin appear to be less active or more toxic.

Not all patients treated, respond to this form of treatment, however, and the local and systemic side-effects differ according to the drug employed. Local chemotherapy becomes necessary in conditions in which there is a high risk of multiple recurrence, and in this context multivariate statistical techniques showed that the number of tumors at presentation was the most important factor, followed, in descending order of importance, by the recurrence rate at entry and the size of the primary tumor.

The choice of the drug is important, but the local toxicity and therefore patient compliance may be markedly influenced by many factors, such as the modality of administration, including dose, concentration, early versus delayed start, and duration of treatment, as discussed in a previous paper [9]. The preliminary findings of the Blinst study illustrate the effectiveness of intravesical doxorubicin, although confirmation obviously calls for a longer follow-up.

It can be concluded, therefore, that any further trial designed to improve the safety and efficacy of intravesical chemotherapy should take into consideration a comparison not only of different drugs, but also of various modalities of treatment.

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