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Intravesical therapy with Adriamycin and 4-epirubicin for superficial bladder cancer: the experience of the EORTC GU Group*

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Summary. The anthracycline derivatives Adriamycin and 4-epirubicin are used to prevent recurrent tumors after transurethral resection of superficial bladder tumors. Both drugs are instilled intravesically. The present report describes the results of two multicenter, prospective, randomized phase III studies carried out by the EORTC GU Group. In protocol 30790, after a mean follow-up period of 26.6 months, the recurrence rate for 165 patients treated with Adriamycin was 0.29 and the tumor rate was 0.74. For 156 patients treated with Epodyl, the recurrence rate was 0.29 and the tumor rate was 0.57. This difference was not statistically significant. For 70 patients who received transurethral resection alone, the recurrence rate was 0.65 and the tumor rate, 2.04. In protocol 30863, patients with good prognostic factors were treated with one single instillation of 4-epirubicin versus sterile water. After a mean follow-up period of 16 months, in 190 patients treated with 4-epirubicin the recurrence rate was 0.20 and the tumor rate was 0.35; in 196 patients treated with sterile water, the recurrence rate was 0.37 and the tumor rate was 0.65 ($P = 0.0001$). Adriamycin and 4-epirubicin were efficacious, and severe side effects were not enountered. The superiority of Adriamycin over Epodyl could not be proven.

Introduction

Transurethral resection (TUR) of papillary superficial bladder cancer is accepted as being the first and most effective treatment for this disease. However, TUR alone is insufficient to treat a majority of these tumors definitively. In the absence of adjuvant therapy, most of the tumors recur (50%–70%) and about 15% of patients eventually suffer from muscle-invasive tumors. Intravesical administration of chemotherapeutic agents has been performed for 30 years to reduce the recurrence rate and, possibly, to prevent disease progression to muscle-invasive tumors, although the latter assumption has not yet been proven [4, 5, 9].

The primary goal in the treatment of cancer patients is to improve survival. Therefore, survival is the end point of interest in most clinical trials. However, superficial bladder cancer is usually a relatively benign disease and survival may easily exceed 5 or even 10 years. The achievement of statistically reliable conclusions based on this endpoint requires extremely large numbers of patients or a very long period of follow-up. Therefore, substitute endpoints have been introduced that may ultimately correlate with survival, including the recurrence rate and the invasion of muscle by tumors.

The EORTC GU Group has had experience with intravesical instillation therapy for 12 years. The conclusions drawn from the multicenter phase II and III studies [2] carried out thus are:

1. TUR alone results in a higher recurrence rate than does TUR plus instillation therapy.
2. Valid data indicating the superiority of a given drug do not exist.
3. Primary, solitary, low-stage, low-grade tumors probably do not need adjuvant intravesical instillation therapy.
4. Instillation therapy does prevent recurrence, but it remains uncertain whether it prevents disease progression to muscle-invasive tumors.

Most of the well-known intravesical agents have been investigated by the EORTC GU Group, including the anthracycline derivatives Adriamycin and 4-epirubicin [6, 10]. In EORTC protocol 30782, recurrent superficial papillary tumors were treated with intravesical thiotepa, Adriamycin, and cisplatin. Following this study, EORTC protocol 30790, coordinated by Kurth, was begun in an

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Table 1. Protocol 30790: recurrence and tumor rates/year

	Treatment		
	Adriamycin	Epodyl	TUR only
Patients (*n*)	165	156	70
Mean follow-up (months)	29.2	28.0	22.0
Recurrence rate/year	0.29	0.29	0.65
Tumor rate/year	0.74	0.57	2.04

Table 2. Protocol 30790: correlation of the observed recurrence rate with the rate recorded prior to study entry and the number of tumors at entry

Prior recurrence rate:	Observed recurrence rate:
Primary	0.27
Recurrence <1 year	0.38
Recurrence, >1 year	0.62
Number of tumors at entry:	
1	0.21
2 or 3	0.40
>3	0.55

attempt to investigate the efficacy of TUR alone versus Epodyl versus Adriamycin. In a third trial, the efficacy and toxicity of early versus delayed instillation of Adriamycin was studied, as was the difference between intermediate-term and long-term prophylaxis. The most recent study, protocol 30863, coordinated by Oosterlinck, has recently been completed. This was a randomized two-arm phase III trial. Patients with single primary or recurrent Ta–T1 tumors received one single instillation of 4-epirubicin versus sterile water (second arm) within 6 h after undergoing TUR.

The present article describes the results of an early study, EORTC protocol 30790, and those of the most recent trial, EORTC protocol 30863. Both trials were prophylactic studies, i.e., all patients initially underwent complete TUR of their tumors.

Patients and methods

From 1979 until 1983, protocol 30790 was carried out. It was designed for patients with primary or recurrent Ta or T1 tumors and compared the results obtained using intravesical administration of 50 mg Adriamycin in 50 ml saline weekly for 4 weeks and then monthly for 1 year with those obtained using intravesical administration of 1.13 mg Epodyl in 50 ml saline on the same instillation schedule. In the third arm, patients were treated by TUR alone. In contrast to previous studies, the end point of this trial was not the time to first recurrence but either the first recurrence after 1 year of treatment or disease progression. If a patient showed a recurrent tumor during the 1st year, a 4-week induction course of treatment was repeated after TUR, but the total duration of the treatment did not exceed 12 months. Control cystoscopy was performed every 3 months.

Protocol 30863 was launched in 1986 and was closed in 1990. Patients who were considered to be at low risk for recurrence or progression were selected for this study. Patients with single primary or recurrent papillary tumors of stage Ta or T1 were admitted to this two-arm trial. Within 6 h after undergoing TUR, patients were treated with one single instillation of 80 mg 4-epirubicin in 50 ml saline versus 50 ml sterile water (second arm). Control cystoscopy was performed after 1 month and then every 3 months for 2 years; the 1-month cystoscopic examination was carried out to ensure the adequacy of TUR. After recurrence, patients were treated with TUR followed by one single instillation of 4-epirubicin or sterile water. After the third recurrence, patients went off-study.

The purpose of both trials was to compare the recurrence rate, the tumor rate, the incidence of progression to invasive disease (T2 or higher), and the incidence and severity of side effects. The recurrence rate was defined as the number of cystoscopic examinations at which recurrence was detected, divided by the number of months of follow-up. The tumor rate was defined as the total number of recurrent tumors detected, divided by the number of months of follow-up.

Results

Protocol 30790

In protocol 30790, no difference was found between the three groups with regard to tumor stage, primary or recurrent disease, or G-grade. Recurrence and tumor rates per year are presented according to treatment group in Table 1. After a mean follow-up period of 26.4 months, the recurrence rate for 165 patients treated with Adriamycin was 0.29 and the tumor rate was 0.74. In 156 patients treated with Epodyl, the recurrence rate was 0.29 and the tumor rate was 0.57. In 70 patients who received TUR only, the recurrence rate was 0.65 and the tumor rate, 2.04. Interim analysis revealed a considerably higher rate of recurrence for patients treated with TUR alone, which led to the decision to close this arm before the entire study population had been recruited. No statistically significant difference was found between the Adriamycin and the Epodyl treatment arm. Patients recruited for this protocol were stratified with regard to both the recurrence rate calculated prior to their entry in the study and the number of tumors present in the bladder at entry.

Table 2 shows that the recurrence rate was 0.27 for primary tumors, 0.38 for patients experiencing less than one recurrence per year, and 0.62 for patients experiencing more than one recurrence per year. The recurrence rate was 0.21 for patients presenting with one tumor at study entry, 0.40 for those with two or three tumors, and 0.55 for those with four or more tumors.

It has been suggested that intravesical chemotherapy may lead to the formation of other cancers. Therefore, the development of second primary tumors was investigated. Of 68 patients treated with Adriamycin, 10 (15%) developed a second primary malignancy. In all, 7 of 59 (12%) patients in the Epodyl group and 4 of 34 (12%) subjects in the control group developed another cancer. These data show that there was no statistically significant difference between the three groups.

Protocol 30863

The results of protocol 30863 (epirubicin versus sterile water) were as follows. The two treatment arms were comparable in terms of tumor category, primary versus recurrent disease, or G-grade at entry. Cystoscopy performed after 1 month in 189 patients treated with epirubicin re-

Table 3. Protocol 30863: number of tumors present at cystoscopy carried out at 1 month after TUR

Treatment	Patients	Number of tumors		
		1	2	3
4-Epirubicin	189	4	0	0
Water	193	10	1	1
Totals	302	14	1	1

Table 4. Protocol 30863: recurrence and tumor rates/year

	Treatment	
	4-Epirubicin	Water
Patients (*n*)	190	196
Mean follow-up (months)	16.8	15.0
Recurrence rate/year	0.20	0.37
Tumor rate/year	0.35	0.65
	($P = 0.001$)	

Table 5. Protocol 30863: recurrence rate in patients with single primary Ta/T1 tumors

	Treatment	
	4-Epirubicin	Water
Patients (*n*)	149	148
Mean follow-up (months)	16.8	15.0
Patients with recurrence	28	49
Percentage of patients with recurrence	19%	33%
Recurrence rate/year	0.18	0.36
	($P = 0.005$)	

vealed 4 (2.1%) tumors. Two of these tumors were located at the site of previous resection and were considered to represent residual disease; the others were located outside the TUR area and were considered to represent existent tumors that had been missed during the TUR procedure.

Of 193 patients treated with sterile water, 10 (5.2%) showed residual tumors at the TUR location; moreover, 2 of these patients also had tumor outside the TUR area (Table 3). The recurrence and tumor rates per year of patients treated in protocol 30863 are depicted in Table 4. After a mean follow-up period of 16 months, the recurrence rate for 190 patients treated with one instillation of 4-epirubicin was 0.20 and the tumor rate was 0.35. For the 196 patients who were treated with sterile water, the recurrence rate was 0.37 and the tumor rate was 0.65. The difference between these two treatment arms was statistically significant ($P = 0.0001$).

A stratification between primary and recurrent single tumors was carried out. Even in patients with single primary Ta/T1 tumors, who are considered to be at low risk for recurrence, one single instillation of Adriamycin considerably reduced disease recurrence. In a group of 149 patients with single primary tumors who were treated with Adriamycin, the recurrence rate was 0.18, whereas it was 0.36 in 148 patients who were treated with sterile water ($P = 0.005$). These data are shown in Table 5.

Discussion

The conclusions to be drawn from the results of protocols 30790 and 30863 are:

1. Adjuvant intravesical therapy is superior to TUR only.
2. Adjuvant intravesical therapy prolongs the time to first recurrence.
3. There is no difference between the efficacy of Epodyl and that of Adriamycin.
4. Besides well-known factors such as the T-category and the G-grade, the number of tumors and the previous recurrence rate are of significant importance for the recurrence of superficial tumors.
5. A single early instillation of 4-epirubicin can significantly reduce the recurrence rate of tumors that are considered to be of low risk for recurrence (without any adjuvant treatment).

The last conclusion is of particular importance, as the first four are also known from other studies carried out in Japan, Europe, and the United States. The results of protocol 30863 may indicate that the implantation of tumor cells following endoscopic resection is prevented by early destruction of these tumor cells [11]. The urothelial surface is damaged by cutting and coagulation or by pressure applied by instruments during TUR. This may provide a fertile surface for the implantation of floating tumor cells. The present study also shows that TUR is not always complete but varies with the skill of the urologist and, probably, with the depth and spread of tumor growth subepithelially.

The efficacy of intravesical instillation of the anthracycline derivatives Adriamycin and 4-epirubicin has been demonstrated in several studies [1, 3, 12]. Following such treatment with 4-epirubicin in phase II studies, i.e., with tumor left in the bladder, a complete remission was achieved by 47% of patients [3]. Pharmacokinetic studies in 23 patients have demonstrated that serum drug levels resulting from the instillation of 50 mg 4-epirubicin in 50 ml saline into an empty bladder with a retention time of 1 h leads to detection limits of 0.3 ng/ml. This low level indicates that systemic reactions are not likely to occur [7], probably because of the high molecular weight of the drug. Local reactions classified as drug-induced cystitis were observed in protocols 30790 and 30863. Generally, local toxicity tends to be encountered more frequently in patients who receive their instillation immediately after undergoing TUR. In protocol 30863, drug-induced cystitis was observed in 6% of the patients.

In conclusion, it can be stated that Adriamycin and 4-epirubicin are efficacious in preventing tumor recurrence after TUR. Because of their lack of major side effects, they can be used safely. Prognostic factors may indicate which tumors should be treated with immediate short-term instillations and which should be treated on more intensive repeat-instillation schedules [8].

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