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CLINICAL TRIAL REPORT

Francesco Boccardo · Daniela Cannata
Michele Cussotto · Maurizio Schenone
Antonio Curotto

Intravesical idarubicin: a dose-finding study

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Abstract A total of 12 patients with completely resected, recurrent papillary tumors of the bladder were entered into a dose-finding study using intravesical idarubicin, a new anthracycline agent that has been shown in vitro to be more active than doxorubicin or daunorubicin, its parental compound. Patients were scheduled to receive eight weekly instillations with the following dose levels: 6.5, 12.5, and 20 mg, all of them diluted in 50 ml saline. Each dose level was initially studied in 3 patients. Dose escalation in the individual patients was not allowed so as to avoid undue toxicity and to evaluate the cumulative toxicity induced by each dose level. Overall, 4 patients were withdrawn due to severe local toxicity (chemocystitis) after a median of 2 instillations (range 1–3) and 3 more patients refused to continue treatment due to mild to moderate toxicity after a median of 4 instillations (range 2–4). Both the patients treated with 20 mg idarubicin and 2 of the 6 patients treated with 12.5 mg were withdrawn due to local toxicity. In contrast, no systemic toxicity was encountered at any dose level. We conclude that doses ranging from 6.5 to 12.5 mg and concentrations varying between 0.125 and 0.250 mg/ml are more appropriate for phase II studies, implying repeated instillations. At these doses and concentrations, however, it is unlikely that idarubicin might be more active than doxorubicin or epirubicin, whereas it might be more toxic.

F. Boccardo (✉) · D. Cannata[1]
Servizio di Oncologia Medica 2, Istituto Nazionale per la Ricerca sul Cancro, Largo Rosanna Benzi 10, I-16132 Genova, Italy

M. Cussotto · M. Schenone · A. Curotto
Istituto di Clinica Urologica "L. Giuliani", Università degli Studi, Largo Rosanna Benzi, 10, I-16132 Genova, Italy

Present address:
[1]Divisione di Medicina Generale, Ospedale Galliera, Via Mura delle Cappuccine, 14, I-16128 Genova, Italy

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Introduction

The major problem in the management of patients with superficial bladder cancer is the high incidence of recurrent disease after initial resection, which is primarily due to multifocal growth of the tumor [12]. Another contributing factor is thought to be implantation of tumor cells liberated during transurethral resection (TUR) [12]. Whatever the mechanism involved, it is estimated that 40–85% of patients suffer a recurrence after initial treatment, usually within the 1st year, the risk being a function of a number of variables that include the tumor size and grade, the depth of penetration, multifocality, and previous recurrent disease [4]. Because of this high risk of recurrence, prophylactic treatment with cytotoxic and immunomodulatory drugs has gained widespread use.

Mitomycin C and anthracyclines such as doxorubicin and epidoxorubicin have shown comparable effectiveness in reducing the risk of recurrence, but all these drugs produce sustained side effects [1, 2, 7]. Treatment with bacille Calmette-Guérin (BCG) has proved to be more effective than chemotherapy in reducing the risk of recurrence [7]. However, BCG treatment can produce relevant local and systemic toxicities [9]. Moreover, it is not clear whether intravesical treatment with either chemotherapy or immunomodulators can really alter the natural history of this disease by reducing the risk of developing infiltrating bladder cancer. Therefore, clinicians' attention remains focused on new drugs that might be more active than presently available cytotoxic agents and might be devoid of the systemic effects induced by BCG.

Idarubicin, a 4′-demethoxydaunorubicin, is a new anthracycline agent that has been shown in vitro to be significantly more active than daunorubicin or

doxorubicin [3]. The molecular properties of this drug render it very promising both in the treatment of patients with carcinoma in situ (CIS) or residual papillary disease after TUR and in the prophylaxis of superficial bladder cancer in patients whose disease has been completely resected. Indeed, the high molecular weight of idarubicin (533.97 Da) should prevent the possibility of a clinically relevant systemic uptake after intravesical instillation. On the other hand, its high degree of lipophilicity should imply rapid mucosal uptake and tumor penetration. Recently, the results of a phase I study using intravesical idarubicin have been reported, indicating that cytotoxic concentrations in the bladder mucosa can be reached at doses of over 15 mg and concentrations of over 0.5 mg/ml, with no systemic toxicity but with signs of local toxicity occurring in about 50% of the patients [10].

On the basis of these preliminary results, a total dose of 20 mg at a concentration of 1 mg/ml was selected by these investigators for a phase II study in patients with residual papillary disease or CIS [10]. Because this indication emerged from a study implying just a single drug administration before tumor resection and because limited data are presently available with respect to cumulative toxicity, a dose-finding study was planned to investigate both acute and cumulative toxicities occurring after repeated intravesical administration of idarubicin at different doses and concentrations.

Patients and methods

Patient selection

A total of 12 patients with completely resected, recurrent superficial bladder carcinomas were entered into the study, including 7 men and 5 women. The median age was 74 (range 67–77) years. The median recurrence-free interval since previous TUR was 9 (range 4–24) months. All 12 patients had previously been treated with intravesical mitomycin C (5 patients) or BCG (7 patients). All patients had: no prior history of infiltrating bladder cancer; a histologic diagnosis of superficial bladder cancer; and no concurrent condition that might alter their compliance with endovesical treatment, including chronic or untreated urinary infections. All of them also had an adequate bone marrow reserve (WBC $> 3,500$ /mm^3; platelet count $> 100,000$ /mm^3) and normal liver function (bilirubin < 1.5 mg%). All patients signed a written consent form after being informed about the investigational nature of the study, which had previously been approved by the Human Investigations Committee of the Tumor Institute in Genoa.

Drug dose and schedule

The drug was provided in ampoules containing 5 or 10 mg idarubicin hydrochloride plus 100 mg lactose. The dry powder was dissolved, diluted in 45 ml normal saline, and instilled through a urethral catheter after emptying of the bladder. Another 5 ml saline was then instilled to flush the catheter. After the instillation, patients were instructed to refrain from voiding for at least 1 h. Four dose levels were scheduled: 6.5, 12.5, 20, and 26.6 mg, corresponding to drug concentrations of 0.125, 0.250, 0.400, and 0.530 mg/ml, respectively. Treatment was started at least 2 weeks following TUR and was given on a weekly basis for 8 weeks. In case of moderate toxicity (see below), treatment was postponed for 1 week. If toxic effects lasted for 2 weeks or more, patients were withdrawn from the study.

Study end points and clinical assessment

Local and systemic toxicities were the main study end points. Local toxicity was scored according to the following criteria: grade 0, absence of any complaint; grade 1 (mild), complaints requiring no delay in treatment; grade 2 (moderate), complaints causing a delay in treatment; grade 3 (severe), complaints leading to treatment discontinuation.

Before each drug instillation a urine sample was taken for cytologic and chemical examination. Urine culture and cystoscopy were performed if indicated. Blood counts and chemistries were performed at the beginning of the study and every 4 weeks for 3 months. An electrocardiogram (ECG) was obtained at the beginning and the end of treatment. Although treatment effectiveness was not an end point of the present study, patients were followed until recurrence or progression with urinary cytologic examinations every 3 months. Cystoscopy was performed every 3 months during the 1st year and every 6 months thereafter.

Statistical considerations

Each dose level was initially studied in three patients. Dose escalation in individual patients was not allowed so as to avoid undue toxicity and to evaluate correctly the cumulative toxicity induced by each dose level. If even one patient in each series of three showed severe toxicity after any one of the eight scheduled instillations, three more patients without severe toxic effects were required to go on with dose escalation. If two patients showed grade 3 toxicity at a certain dose level, the previous dose level employed had to be considered the maximum tolerated dose, and three more patients would have to be treated at that dose without developing a major toxicity before it could be chosen for phase II studies.

Results

The results are summarized in Table 1. Four patients were entered in the first dose-level trial because the first patient refused treatment after the first four instillations due to mild toxicity, despite a complete recovery from side effects. Overall, 28 instillations were given, 25 of which produced no toxicity. Six patients were admitted to the second (12.5 mg) dose level. The last three patients were treated after treatment failure of the next programmed dose (20 mg). Overall, 27 instillations were completed (of the 42 that had been scheduled), 20 of which resulted in toxicity that ranged from mild to severe. Two patients were withdrawn after two and three instillations, respectively, due to severe toxicity; in both patients, cystoscopy revealed severe chemocystitis. Finally, two patients were treated with 20 mg idarubicin, and both were withdrawn after one and two instillations, respectively, due to hemorrhagic cystitis; again, cystoscopy revealed severe chemocystitis. In no patient experiencing local side effects was the urine culture positive. No systemic effect was recorded in any case. No patient was admitted to the fourth dose level.

Table 1 Results of intrvesical treatment with idarubicin

Dose level (concentration)	Number of patients	Number of patients with grade 3 toxicity[a]	Number of instillations	Number of instillations with toxicity
6.25 mg (0.125 mg/ml)	4[b]	None	28	3 (mild to moderate)
12.5 mg (0.25 mg/ml)	6[c]	2	27	20 (mild to severe)
20 mg (0.40 mg/ml)	2	2	3	3 (2 hemorrhagic) cystitis)
All levels, concentrations	12	4	58	26 (mild to severe)

[a] All patients with grade 3 toxicity were withdrawn
[b] One patient refused treatment after the first four instillations
[c] Two patients refused treatment after the first two and four instillations, respectively

Discussion

Both doxorubicin and epirubicin are commonly used as chemoprophylactic agents in superficial bladder cancer. These drugs have proved to be relatively well tolerated even after repeated instillations, inducing chemocystitis in 6.5% (doxorubicin) and 13.5% (epirubicin) of patients, although bladder irritation does occur in a substantially higher proportion of patients, particularly if treatment is initiated very early following TUR [5, 6]. The local toxicity of drugs instilled into the bladder mainly depends on their ability to penetrate the bladder mucosa. This, in turn, is a function of their lipophilicity, a property that plays a major role in their capability to penetrate tumor cells as well.

In a recent study by Schultze-Seemann et al. [10] a strong relationship was found between the total idarubicin dose or idarubicin concentration and the tissue concentrations of the drug in the tumor. It is noteworthy that relatively low doses (between 10 and 15 mg) or concentrations (0.5 mg/ml) of idarubicin were capable of producing a tissue concentration of the drug amounting to about 10 ng/mg, i.e., a tissue concentration equivalent to those showing satisfactory antiproliferative activity in vitro [10]. At those doses and concentrations the tissue levels in the bladder mucosa and in the muscle were very low. Nevertheless, hystological findings of chemocystitis were found in more than 50% of patients after just a single preoperative administration. Despite these findings, the German investigators selected a dose of 20 mg idarubicin/20 ml saline (an idarubicin concentration equal to 1 mg/ml) for a subsequent phase II study, the results of which are not yet available [10].

In our study, neither of the two patients treated with 20 mg idarubicin was capable of completing the planned course of instillation, although we used 50 ml saline to dilute the drug and therefore reached a concentration of 0.4 mg/ml. Indeed, both of these patients were withdrawn due to severe (grade 3) toxicity after the first and the second instillation, respectively. Moreover, a sustained local toxicity was observed even after lower doses and concentrations. Indeed, our results suggest that doses ranging between 6.25 and 12.5 mg or concentrations varying between 0.125 and 0.250 mg/ml might be more appropriate for phase II studies. However, according to Schultze-Seemann et al. [10], these dose levels and concentrations are not likely to achieve therapeutic tissue levels, although it cannot be ruled out that lower tissue levels might be required for idarubicin to exert its antiproliferative activity after repeated instillations.

It is noteworthy that no systemic effect was recorded in our patients, irrespective of the dose and concentration employed, as should be expected in view of the high molecular weight of idarubicin and of the low plasma levels of idarubicin and idarubicinol observed in Schultze-Seemann's study, even after administration of the highest doses and concentrations used [10].

Our findings are in keeping with the preliminary results of a phase I/II study on intravesical idarubicin that have recently been reported in abstract form [11]. In that study, 17 patients with residual ("marker") papillary disease after TUR were treated with repeated instillations of idarubicin at different doses and concentrations. Four patients received 15 mg diluted in 30 ml saline (an idarubicin concentration equal to 0.5 mg/ml), and all of them developed severe local toxicity. The remaining 13 patients were given 10 mg diluted in 40 ml saline (an idarubicin concentration equal to 0.250 mg/ml). Overall, 8 patients (47%) had to be withdrawn between the 1st and the 6th instillations due to chemical cystitis. Of the 9 patients who were capable of receiving the eight scheduled administrations, 5 showed mild to moderate toxicity. In all, 3 patients showed a complete disappearance of their marker lesion [11]. This is significantly lower than the 60–70% response rates obtained with the therapeutic instillation of epidoxorubicin for a residual marker lesion [8].

In conclusion, our findings and those reported in the literature show that, in contrast to previous suggestions, doses ranging between 6.25 and 12.5 mg (probably 10 mg or less) and concentrations varying between

0.125 and 0.250 mg/ml are appropriate for repeated idarubicin instillations. At these doses and concentrations, however, it appears that idarubicin might not be very effective and, specifically, that it might not be more effective than doxorubicin or epirubicin at the doses that are commonly employed, whereas it might be more toxic.

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