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Intravesical Gemcitabine: State of the Art

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Abstract

Intravesical gemcitabine has been tested in several phase 1 studies. The 2000-mg dose of gemcitabine in 50 or 100 ml normal saline when administered intravesically for up to 2 h once a week for 6 wk has unremarkable systemic and local side effects; therefore, this schedule should be considered the most convenient.

Phase 2 studies have assessed the activity of intravesical gemcitabine on a marker lesion in intermediate-risk superficial bladder cancers (SBCs), showing complete responses in up to 60% of cases. Few attempts have been made to test the activity of intravesical gemcitabine in high-risk SBC, achieving unexpected complete responses in carcinoma in situ refractory to Bacillus Calmette-Guérin. Initial trials have also documented ''clinically relevant'' responses in prophylaxis.

The current level of evidence indicates that gemcitabine possesses clinical activity, but further confirmation is awaited from additional exploratory phase 2 and, preferably, phase 3 trials.

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1. Introduction

According to the European Association of Urology guidelines [1], superficial bladder cancer (SBC) at ''intermediate risk'' should be preferably managed with prophylactic intravesical chemotherapy, leaving Bacillus Calmette-Guérin (BCG) immunotherapy as a second option in case of treatment failure. By contrast, BCG has become the standard treatment for ''high-risk'' SBC, with radical surgery remaining the sole valid alternative for any persistent or recurrent disease [2–9].

A potential limiting factor on the currently available intravesical agents concerns the side effect burden, particularly for BCG. In a recent review on the complications of intravesical therapies, BCG-induced, low urinary symptoms vary considerably between different series, from a minimum of 27% up to 90% of cases [10]. Similarly, systemic side effects of BCG like fever has been described in up to 17% of cases in one series [10], leading to stopping of the treatment in 10% of patients [11]. Chemotherapeutic agents, usually better tolerated than BCG, have provoked chemical cystitis in one of four patients in one series [10]. These limitations in tolerability for the most widely used intravesical agents across all risk categories of SBC have promoted the need for alternative therapies. A new treatment option should combine a good safety profile together with proven efficacy. These criteria are particularly true

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for intermediate-risk SBC in which the primary treatment end point resides in the prevention of recurrence for an otherwise good prognosis disease.

2. Rationale for intravesical administration

Gemcitabine (2′,2′-difluorodeoxycytidine [dFdC]) is a deoxycytidine analogue with a broad spectrum of antitumour activity. After being transported into the cell, it is phosphorylated and incorporated into the DNA and RNA, which cause inhibition of cell growth and trigger apoptosis [12]. Gemcitabine is then deactivated by deamination into 2′,2′-difluorodeoxyuridine (dFdU) and transported out of the cell.

When given systemically, gemcitabine has shown significant activity as a single agent against invasive bladder cancers, yielding response rates of 27–38% [13–14]. Gemcitabine has a molecular weight of 299 D, lower than that of commonly used intravesical chemotherapeutic agents such as mitomycin C (389 D) and doxorubicin (589 D). Its lower molecular weight may enable gemcitabine to penetrate the bladder mucosa with beneficial effects in the treatment of early invasive bladder cancers (T1 disease). At the same time the molecular weight is high enough to prevent significant systemic absorption in an intact bladder. Its pharmacokinetic properties also make gemcitabine an ideal candidate for regional therapy. When given intravenously, it is rapidly deaminated into the inactive metabolite, thus resulting in a high total body clearance. In an in vitro study, gemcitabine sensitivity was compared with adriamicin, epirubicin, and mitomycin C for relative potency on cell cultures of transitional cell carcinoma [15]. Gemcitabine at 10 mg/ml resulted in a more robust cytotoxic activity (90% lethality in all cell lines) than the other chemotherapeutic agents.

Preclinical animal studies have been performed with the specific aims of assessing organ-specific toxicity and identifying the possible systemic absorption of gemcitabine following intravesical administration. These studies, albeit limited by the use of an animal model, have proven the absence of bladder-specific toxicity as well as negligible systemic absorption even at high doses of 50 mg/kg (equivalent to around 3150 mg/m^2 in humans) in rabbits [16] and at 350 mg (equivalent to 1000 mg/m^2 in humans) in dogs [17].

3. Pharmacokinetics and tolerability

The pharmacokinetic and safety profile of gemcitabine has been assessed for three different treatment schedules (twice weekly for 6 wk, once weekly for 6 wk, and one single instillation immediately after transurethral resection [TUR], respectively) and for doses escalating from 500 to 2000 mg diluted in 50 or 100 ml of saline solution (maximum drug concentration of 40 mg/ml).

In the biweekly treatment scheme, gemcitabine was detectable in plasma at only the 2000 mg/100 ml concentration, with one of six patients developing grade 3 thrombocytopenia and neutropenia) [18]. When administered once a week for 6 wk, gemcitabine was detectable in plasma at low concentrations ($\leq$1 μmol/l) in only the four patients receiving 2000 mg [19] and occasionally (1 patient) at 1000 mg [20]. Otherwise plasma concentrations were always below the detection limit [21]. Finally, early postoperative instillation produced measurable plasma concentrations (4.5 and 6.1 μmol/l, respectively) in only the two patients with suspected bladder perforation [22]. Pharmacokinetic data have thus shown systemic absorption of intravesical gemcitabine at up to a 40 mg/ml concentration (2000 mg in 50 ml is minimal and transient across all three different schedules.

Table 1 lists systemic and local side effects recorded for different escalating doses in phase 1 studies. Local toxicity was generally described as minimal and rapidly self-resolving. With the possible exception of three cases of grade 3 urinary frequency (one in the study by Laufer [19] at 2000 mg and the other two reported by Dalbagni [18] following 1000 and 1500 mg administrations, respectively), genitourinary side effects were usually confined to the grade 1 toxicity level. Notably, this latter study was the only one to employ a buffered solution. Whether increase in the pH of the drug may result in fewer side effects without affecting its activity remains to be elucidated. A study is currently underway at our institution to assess possible changes in intratumoral concentration of gemcitabine and its metabolites according to different types of intravesical administration of the standard 2000 mg dose: 20 versus 40 mg/dl, 1-h versus 2-h intravesical exposure, and buffered versus unbuffered solution.

4. Activity on SBC marker lesions

Marker lesion studies have been specifically designed in SBC to test the ablative activity of a given drug on a single papillary marker lesion. At the same time, these phase 2 trials allow assessment of the incidence and severity of early side effects in relatively few patients [23,24]. Current intravesical