Actual experience and future development of gemcitabine in superficial bladder cancer

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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). This may enable gemcitabine to penetrate the bladder mucosa with beneficial effects in the treatment of early invasive bladder cancer (T1 disease). At the same time the molecular weight is high enough to prevent significant systemic absorption in an intact bladder. Based on the results of phase I studies, it appears that the 2000 mg dose of gemcitabine in 50/100 ml normal saline when administered intravesically for up to 2 h once a week for 6 weeks has unremarkable systemic and local side effects and therefore should be considered the most convenient schedule. The currently available phase II studies have assessed the activity of intravesical gemcitabine on a marker lesion in intermediate risk superficial bladder cancers (SBC), showing complete responses in up to 56% of cases. Few attempts have been made to test the activity of intravesical gemcitabine in high risk SBC achieving unexpected complete responses in BCG refractory CIS. Gemcitabine seems to have fulfilled the requirements to be a promising new candidate for standard intravesical therapy in SBC so far. Further phase II trials exploring the activity of gemcitabine on highly-recurrent intermediate risk or high risk SBC would provide additional information to foresee its efficacy in clinical practice and thus constitute the framework for large comparative phase III trials.

Key words: BCG refractory, gemcitabine, intravesical, superficial bladder cancer

introduction

The European Guidelines [1] distinguish three risk categories for SBC. Single Ta, G1 lesions < 3 cm in diameter are considered as low risk whereas high risk tumours are represented by T1, G3 or CIS. All other tumours Ta, T1, G1–G2, multifocal, recurrent, > 3 cm in diameter fall into the intermediate risk group. While observation following complete endoscopic eradication has been advocated for low risk SBC, several intravesical drugs have been proposed for intermediate and high risk diseases in an attempt to reduce or delay both recurrence and progression. Intermediate risk SBC is initially managed with prophylactic intravesical chemotherapy whereas Bacillus Calmette-Guerin (BCG) immunotherapy has become the standard treatment for high risk SBC including T1G3, CIS and some recurrent Ta diseases. Significant limitations in efficacy and tolerability for the most widely-used intravesical agents across all risk categories of SBC exist and hence the need for new treatment alternatives. Following conventional intravesical chemotherapy, the short-term recurrence rate of intermediate risk SBC cannot be reduced by more than 15–20% and the long-term risk of recurrence by 6% according to Lamm [2]. Recent meta-analyses have shown that BCG is superior to intravesical chemotherapeutic agents in reducing recurrences [3] although a 2-year recurrence rate of 40% has to be expected [4]. While the role of intravesical treatment for high-grade stage T1 SBC remains controversial, two recent meta-analyses have shown that BCG is able to reduce the risk of progression to muscle-invasive disease [5] provided maintenance treatment is employed [6]. However, it should be pointed out that the majority of the studies available in the literature included mixed series where only a minority of the recruited patients had high risk SBC. The real efficacy of BCG in pure T1G3 series has recently been questioned [7]. Until new agents can be shown to decrease recurrence rates and delay progression of high risk SBC, cystectomy remains the best option for such patients. The side effect burden may represent another limiting factor in the use of intravesical agents. Local side effects can be experienced by as many as 90% of patients undergoing BCG treatment. More seriously, BCG can cause severe systemic side effects like ‘BCG-osis’ and sepsis that have resulted in several deaths. Fever >39°C may occur in 14% to 30% of cases leading to stopping the treatment in 10% of patients [8]. Chemotherapeutic agents such as mitomycin C and doxorubicin, in spite of the low probability of systemic side effects, can give rise to severe forms of chemical cystitis [9]. A new treatment option for SBC would have a large population of treatable patients such as intermediate risk SBC patients recurring after conventional treatment, primary T1G3

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patients (where conventional treatment is still controversial) and BCG-refractory high risk SBC patients unfit for and/or refusing radical surgery.

feasibility of the intravesical administration of gemcitabine

Gemcitabine (2',2'-difluorodeoxycytidine, dFdC) is a novel deoxycytidine analogue with a broad spectrum of anti-tumour activity. After being transported into the cell it is phosphorylated and incorporated into the DNA and RNA. This causes the inhibition of cell growth and triggers apoptosis [10]. Gemcitabine is then deactivated by deamination into 2',2'-difluorodeoxyuridine (dFdU) and transported out of the cell.

When given systemically, a significant activity as a single agent against invasive bladder cancers has been shown, yielding response rates of 27–38%. 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). This 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 to adriamycin, epirubicin and mitomycin C for relative potency on TCC cell cultures [11]. Gemcitabine at 10 mg/ml resulted in a more robust cytotoxic activity (90% lethality in all cell lines) than the other chemotherapeutic agents.

Pre-clinical 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 proved 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/m² in humans) in rabbits [12] and at 350 mg (equivalent to the 1000 mg/m² in humans) in dogs [13].

pharmacokinetics and toxicity of intravesical gemcitabine (phase I studies)

In a dose escalation protocol 18 high risk BCG-refractory SBC patients received 500, 1000, 1500 and 2000 mg gemcitabine diluted in 100 ml for 1 h twice weekly for 3 weeks with each course separated by a week of rest. The levels of gemcitabine were undetectable up to 1500 mg, whereas at the 2000 mg dose 2 out of 6 patients had measurable plasma concentrations (including 1 patient with grade 3 thrombocytopenia and neutropenia) [14].

In a dose finding study reported by Laufer [15] 15 patients received 500, 1000, 1500 and 2000 mg in 100 ml (in 4 patients the 2000 mg dose was diluted in 50 ml) once a week for 6 weeks with an instillation time of 2 h. Very little gemcitabine was found in plasma; there were low plasma concentrations of gemcitabine (≤1 μM) in the 4 patients receiving 2000 mg in 50 ml. Most importantly, plasma concentrations of gemcitabine decreased during the time that gemcitabine was left in the bladder, indicating that it is the initial influx of gemcitabine into the bladder rather than the presence of the drug in the bladder which may be critical for systemic absorption.

In a similar study by De Berardinis et al. [16], gemcitabine resulted in plasma concentrations always below the detection limit when instilled in the bladder for 2 h at dosages up to 40 mg/ml (2000 mg/50 ml) and the concentrations of its inactive metabolite dFdU were also remarkably low. In the same study, the activity of the activating enzyme deoxycytidine kinase (dCK) and of the deactivating enzyme deoxycytidine deaminase (dCDA) were determined using post-treatment tumour samples collected during follow-up cystoscopy. dCK levels were lower than that in other sensitive tumours, in keeping with the possible low chemosensitivity of a recurrent tumour. Interestingly enough, dCK expression increased in one patient receiving various courses of gemcitabine, thus supporting a potential rationale for maintenance treatment cycles.

In the study by Witjes [17] six-weekly instillations with 1000, 1500 and 2000 mg for a duration of 1 h were performed in 3, 4 and 3 patients respectively. Blood samples were taken at 5, 30, 60 and 120 min after instillations 1, 3 and 6. The highest plasma level of gemcitabine (0.91 μM) was detected in the only patient (dose 1000 mg) who had a grade 1 myelosuppression at the first instillation. All other levels were immeasurable. The same patient was the only one to show measurable levels of the active metabolite dFdCTP. Plasma levels of dFdU were measurable in all patients with a peak of 4.19 μM in a patient treated with the 1500 dose.

Finally, Palou [18] assessed the pharmacokinetics and safety of an early single intravesical instillation of gemcitabine at dosages of 1500 and 2000 mg in 10 patients. Blood samples were taken at several time intervals starting 15 min from the onset of the instillation up to 3 h after urine voiding. Gemcitabine plasma concentrations were generally low but with a high inter-patient variability. Remarkably, the highest drug concentrations (4.5 and 6.1 mmol/L respectively) were found in the 2 patients in whom an unnoted bladder perforation was suspected because of the recovery of less than the instilled volume after bladder voiding. Similarly, overall maximum dFdU concentrations were also low, with a mean value of 7.8 μmol/L.

In conclusion, pharmacokinetic data from different phase I studies have clearly demonstrated that systemic absorption of intravesical gemcitabine at up to 40 mg/ml concentrations (2000 mg in 50 ml), when kept in the bladder for as long as 2 h, is minimal and transient, and thus unlikely to produce clinically significant adverse events. The presence of low levels of the inactive metabolite further reinforce the concept of the relative impermeability of bladder mucosa to the drug. Based on plasmatic drug concentrations, early intravesical instillation may be a feasible treatment option provided a significant bladder perforation has not occurred.

In agreement with the pharmacokinetic data, systemic toxicity was absent in the study of De Berardinis [16] and did
not go beyond grade 1 in the study by Witjes [17] and by Palou [18]. Overall, no systemic toxicity exceeding grade II was recorded in any of the five phase I studies, with the sole exception of a single case of grade 3 myelosuppression and thrombocytopenia reported by Dalbagni [14]. In that study two factors in the study design may have promoted an increased systemic absorption resulting in significant hematological toxicity: firstly, the drug was administered twice a week, a rather unusual schedule for an intravesical agent; secondly, the low pH gemcitabine solution was adjusted to levels of 5.5–7.0 in order to prevent bladder irritation [14]. The resulting increased nonionic form of the drug may have facilitated its diffusion through the bladder mucosa [19]. It is worth noting that intravesical instillation administered within a few hours after bladder resection proved to be well tolerated, even when bladder perforation has occurred [18].

Local toxicity was minimal and generally described as rapidly self-resolving. With the possible exception of 3 cases of grade 3 urinary frequency (1 in the study by Laufer [15] at 2000 mg and the other two reported by Dalbagni [14] following 1000 and 1500 mg administrations respectively), genitourinary side effects were usually confined to the grade 1 toxicity level.

Based on these results it appears that the 2000 mg dose of gemcitabine in 50 ml normal saline when administered intravesically for up to 2 h once a week for 6 weeks has unremarkable systemic and local side effects and therefore should be considered the most convenient schedule.

Higher drug concentrations produce clinically relevant side effects and do not allow optimal drug solubility whereas a higher volume may not be appropriate as it may exceed the maximum bladder capacity of a significant proportion of patients.

**phase II studies on intravesical gemcitabine**

**the marker lesion concept in intravesical therapy**

The ability of a new chemotherapeutic agent to prevent superficial TCC tumour formation relies on its cytotoxic efficacy on bladder cancer cells. To assess the activity of new agents in treating intermediate risk superficial bladder cancer, an ‘indicator lesion of some sort’ is necessary and this can be achieved by a marker tumour study [20, 21]. The EORTC GU Group and the MRC have conducted trials using marker tumours which provided evidence that this methodology is safe, logical and ethically acceptable [22, 23]. This type of study allows researchers to test the ablative activity of the investigational drug on a single papillary marker lesion and to assess the incidence and severity of early side effects in relatively few patients and in a relatively short period of treatment. Several marker lesion studies have evaluated the ablative activity of different drugs alone or in combination (mitomycin C, epirubicin, BCG) with a complete response of 50–60% (Table 1) [24–28]. These findings constitute the reference value of activity for any new intravesical agent.

**phase II studies on intermediate risk SBC**

The ablative efficacy of intravesical gemcitabine on a marker lesion tumour has been investigated by several authors (Table 2). The first published study [29] was designed as a two-stage phase II trial with the possibility of stopping the trial early if there was evidence that the drug had insufficient activity. Based on previous marker lesion series assessing other intravesical agents [24–28], it was determined that the treatment tested in this study would deserve further attention if it was able to produce responses in at least 21 out of 39 entered patients. Overall a complete response was achieved in 22 out of 39 cases (56%), meaning that intravesical gemcitabine possesses a cytoreductive activity in intermediate risk SBC. The authors underlined that almost 60% of cases were recurrences after previous BCG treatment.

Another similar studies have been recently published or reported in peer-reviewed abstracts. As shown in Table 2, complete responses ranged 44 to 66.6% [29–33] except in one study where the response rate was as low as 22% [34]. In the latter, a dose escalation regimen and the adoption of multiple marker lesions may partly explain the lower level of chemoresection achieved.

**phase II studies on high risk SBC**

Few attempts have been made to test the activity of intravesical gemcitabine in high risk SBC as shown in Table 3. Two considerations deserve attention in the studies reported by Dalbagni [14, 35]. The first is that complete responses were achieved in series that included also a significant proportion of BCG refractory CIS. The second is that gemcitabine was administered with a more extensive schedule (twice weekly for

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**Table 1.** Marker lesion studies on intravesical agents currently in use for SBC

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Schedule</th>
<th>Patients No</th>
<th>Tumours</th>
<th>CR* (N %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[24]</td>
<td>Epirubicin</td>
<td>weekly for 6 weeks</td>
<td>46</td>
<td>Ta-T1, G1-G2</td>
<td>(47)</td>
</tr>
<tr>
<td>[25]</td>
<td>Sequential MMC and BCG</td>
<td>4 weekly instillations of MMC followed by 6 weekly instillations of BCG</td>
<td>32</td>
<td>Multiple Ta-T1, G1-G2</td>
<td>16 (50)</td>
</tr>
<tr>
<td>[26]</td>
<td>Epirubicin</td>
<td>Single instillation of 50 mg or 100 mg</td>
<td>81</td>
<td>Ta-T1, G1-G2</td>
<td>(46)</td>
</tr>
<tr>
<td>[27]</td>
<td>Randomised BCG Evans 60 mg vs. BCG Pasteur 150 mg</td>
<td>Weekly for 6 weeks</td>
<td>51</td>
<td>Multiple recurrent Ta, T1</td>
<td>BCG Evans (22)</td>
</tr>
<tr>
<td>[28]</td>
<td>BCG Connaught 30 mg</td>
<td>Weekly for 6 weeks</td>
<td>44</td>
<td>Ta-T1, G1-G2</td>
<td>BCG Pasteur (42)</td>
</tr>
</tbody>
</table>

*CR, complete response (complete disappearance of the marker lesion with negative urine cytology and biopsy).
6 weeks) without significant side effects. In the study of Bartoletti [37], intravesical gemcitabine was administered as a prophylactic treatment in a mixed series of SBC that included also high risk tumours. Notably, the excellent results in terms of one-year recurrence-free survival were achieved employing a 3-year maintenance schedule identical to the one currently suggested for BCG.

**future development**

Intravesical gemcitabine has so far demonstrated an excellent safety profile and minimal toxicity at concentrations up to 40 mg/ml. Instillation time of 1 and 2 h have both been tested with excellent tolerability although a few patients may not be able to retain the drug in the bladder for more than 1 h particularly when the bladder compliance is reduced by a mild chemical cystitis.

The standard scheme of weekly instillations of gemcitabine for 6 weeks as an induction course has shown an excellent safety profile and should be adopted when designing a treatment protocol on intermediate risk SBC. Drug administration can be carried out as early as the third hour postoperatively with no remarkable toxicity provided no major bladder perforation has occurred. The question remains as to whether a more intense scheme (such as a 6 instillation course twice a week for 3 weeks or even a 12 instillations course biweekly for 6 weeks) may be more appropriate for high risk SBC.

Several phase II marker lesion studies have shown that the drug possesses an anti-tumour activity on a marker lesion that is comparable to similar studies conducted on BCG. Additionally, promising response rates have been achieved in high risk SBC that were BCG-refractory.

So far, gemcitabine seems to have fulfilled the requirements to be a promising new candidate for standard intravesical therapy in SBC. Moreover, a number of phase II trials are presently ongoing either to confirm the activity of gemcitabine on marker lesions in patients with low, intermediate and high risk SBC or to compare the efficacy of Gemcitabine versus mitomycin or BCG in preventing recurrences in intermediate/high risk patients. The SWOG cooperative

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**Table 2. Phase II marker lesion studies of intravesical Gemcitabine on intermediate risk SBC**

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug concentration</th>
<th>Schedule</th>
<th>Indwell time</th>
<th>Patients No.</th>
<th>Tumours</th>
<th>Type and size of marker lesion</th>
<th>CR*N (%)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[29]</td>
<td>40 mg/ml</td>
<td>weekly for 6 weeks</td>
<td>1 h</td>
<td>39</td>
<td>Ta-T1, G1-G2</td>
<td>Single, 0.5–1 cm</td>
<td>22 (56)</td>
<td>--</td>
</tr>
<tr>
<td>[35]</td>
<td>10–40 mg/ml</td>
<td>weekly for 6 weeks</td>
<td>2 h</td>
<td>27</td>
<td>Ta-T1, G1-G2</td>
<td>1 to 3 marker lesions, 5–15 mm in size</td>
<td>6 (22)</td>
<td>--</td>
</tr>
<tr>
<td>[34]</td>
<td>40 mg/ml</td>
<td>weekly for 6 weeks</td>
<td>2 h</td>
<td>24</td>
<td>Ta-T1, G1-G2</td>
<td>Single, 1 cm</td>
<td>12 (50)</td>
<td>--</td>
</tr>
<tr>
<td>[31]</td>
<td>20 mg/ml (2000 mg in 100 ml)</td>
<td>weekly for 6 weeks</td>
<td>1 h</td>
<td>32</td>
<td>Ta-G1-G2</td>
<td>Single, 1 cm</td>
<td>Overall: (30)</td>
<td>--</td>
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<td></td>
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</tr>
<tr>
<td>[32]</td>
<td>40 mg/ml</td>
<td>weekly for 8 weeks</td>
<td>1 h</td>
<td>42</td>
<td>Papillary Ta, T1</td>
<td>Single, 1 cm</td>
<td>(66.6)</td>
<td>--</td>
</tr>
<tr>
<td>[33]</td>
<td>40 mg/ml</td>
<td>weekly for 4 weeks</td>
<td>1 h</td>
<td>20</td>
<td>Ta, T1 with multiple recurrences</td>
<td>Single, 5–15 mm</td>
<td>(50)</td>
<td>--</td>
</tr>
</tbody>
</table>

*CR, complete response (complete disappearance of the marker lesion with negative urine cytology and biopsy).

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**Table 3. Phase II studies of intravesical Gemcitabine on high risk SBC**

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug concentration</th>
<th>Schedule</th>
<th>Indwell time</th>
<th>Patients No.</th>
<th>Tumours</th>
<th>Type of tumours</th>
<th>CR*N (%)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[29]</td>
<td>5–20 mg/ml</td>
<td>Twice weekly for 3 weeks (with 1 week of rest after each week)</td>
<td>1 h</td>
<td>18</td>
<td>BCG refractory refusing cystectomy (including 3 Tis)</td>
<td>(38)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>[35]</td>
<td>20 mg/ml</td>
<td>Twice weekly for 3 weeks, repeated after a week of rest</td>
<td>1 h</td>
<td>28</td>
<td>BCG refractory refusing cystectomy</td>
<td>16 (57)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>[36]</td>
<td>20 mg/ml</td>
<td>Weekly for 6 weeks after TUR</td>
<td>--</td>
<td>29</td>
<td>Tis-T1</td>
<td>Intermediate and high risk SBC</td>
<td>29 (100)</td>
<td>--</td>
</tr>
<tr>
<td>[37]</td>
<td>40 mg/ml</td>
<td>Weekly for 6 weeks, then maintenance with 3 weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months</td>
<td>1 h</td>
<td>118</td>
<td>Not evaluable</td>
<td>74.6% recurrence free at a median follow up of 12 months</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

*CR, complete response (complete disappearance of the marker lesion with negative urine cytology and biopsy).
Dr Gontero has indicated that he has lectured in symposia on the rationale for comparative phase III trials. Future. These large phase II trials will ultimately provide the rationale for comparative phase III trials.

disclosures

Dr Gontero has indicated that he has lectured in symposia sponsored by Eli Lilly.

references


