Prolonged Versus Standard Gemcitabine Infusion: Translation of Molecular Pharmacology to New Treatment Strategy

STEPHAN A. VELTKAMP,a,b JOS H. BEIJNEN,c,d JAN H.M. SCHELLENSa,b,d

aDivision of Experimental Therapy and bDepartment of Clinical Pharmacology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; cDepartment of Pharmacy & Pharmacology, Slotervaart Hospital, Amsterdam, The Netherlands; dFaculty of Science, Department of Pharmaceutical Sciences, Section of Biomedical Analysis, Division of Drug Toxicology, Utrecht University, Utrecht, The Netherlands

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LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Describe the molecular pharmacology of nucleoside analogues.
2. Explain transport, metabolism, and elimination in relation to the activity of gemcitabine.
3. Describe the clinical pharmacology of gemcitabine in relation to its rate of administration.

ABSTRACT
Gemcitabine is frequently used in the treatment of patients with solid tumors. Gemcitabine is taken up into the cell via human nucleoside transporters (hNTs) and is intracellularly phosphorylated by deoxycytidine kinase (dCK) to its monophosphate and subsequently into its main active triphosphate metabolite 2’,2’-difluorodeoxycytidine triphosphate (dFdCTP), which is incorporated into DNA and inhibits DNA synthesis. In addition, gemcitabine is extensively deaminated to 2’,2’-difluorodeoxyuridine, which is largely excreted into the urine. High expression levels of human equilibrative nucleoside transporter type 1 were associated with a significantly longer overall survival duration after gemcitabine treatment in patients with pancreatic cancer.

Clinical studies in blood mononuclear and leukemic cells demonstrated that a lower infusion rate of gemcitabine was associated with higher intracellular dFdCTP levels. Prolonged infusion of gemcitabine at a fixed dose rate (FDR) of 10 mg/m² per minute was associated with a higher intracellular accumulation of dFdCTP, greater toxicity, and a higher response rate than with the standard 30-minute infusion of gemcitabine in patients with pancreatic cancer.

In the current review, we discuss the molecular pharmacology of nucleoside analogues and the influence of hNTs and dCK on the activity and toxicity of gemcitabine, which is the basis for clinical studies on
FDR administration, and the results of FDR gemcitabine administration in patients. These findings might aid optimal clinical application of gemcitabine in the future. *The Oncologist* 2008;13:261–276

**INTRODUCTION**

Nucleoside anticancer drugs constitute an important class of antimitabolites that are used in the treatment of patients with cancer. The pyrimidine nucleoside analogues cytarabine (cytosine arabinoside [ara-C]) and gemcitabine (2’,2’-difluorodeoxycytidine [dFdC]) are frequently used in the treatment of patients with solid tumors and hematological malignancies [1–4]. The chemical structures of gemcitabine and cytarabine are depicted in Figure 1.

Gemcitabine is applied in the clinic either as a single agent or in combination with chemotherapeutic agents [5] or radiotherapy [6]. It is usually administered i.v. at a dose of 1,000–1,250 mg/m² as a 30-minute infusion on days 1 and 8 of a 21-day cycle or days 1, 8, and 15 of a 28-day cycle. Preclinical studies in human tumor cell lines and xenografts showed that intracellular accumulation of gemcitabine triphosphate (dFdCTP), the active metabolite of gemcitabine, is dependent on the total exposure time and rate of administration of gemcitabine [7–10]. Different gemcitabine dosing schedules have been investigated in the clinic [5]. Standard gemcitabine infusion of 1,000 mg/m² in 30 minutes (~33 mg/m² per minute) was shown to saturate deoxycytidine kinase (dCK) and intracellular formation of dFdCTP. Prolonged gemcitabine infusion at a fixed dose rate (FDR) of 10 mg/m² per minute was investigated to increase the intracellular accumulation of dFdCTP, aiming to enhance the antitumor activity of gemcitabine and the response rate in patients. This FDR approach was derived from earlier studies on cytarabine that showed a greater area under the concentration–time curve (AUC) of cytarabine triphosphate (ara-CTP), the active metabolite of cytarabine, in leukemic cells of patients following prolonged infusion times of cytarabine [11, 12]. The activity and toxicity of gemcitabine depend on the dose and dosing schedule [13, 14]. In various randomized clinical trials, FDR administration was compared with the standard 30-minute infusion of gemcitabine. To date, there are no sufficiently powered studies that demonstrate that FDR administration leads to a significantly better treatment outcome in patients compared with standard gemcitabine infusion.

In the current review, we discuss the molecular pharmacology of nucleoside analogues and the influence of human nucleoside transporters (hNTs) and dCK on the activity and toxicity of gemcitabine that is the basis for preclinical and clinical studies on FDR dosing compared with standard gemcitabine administration, of which trial results are summarized. These findings can be relevant for the optimal use of gemcitabine in patients in the future.

**MOLECULAR PHARMACOLOGY OF NUCLEOSIDE ANTICANCER DRUGS**

**Uptake by hNTs**

The nucleoside anticancer drugs gemcitabine and cytarabine are hydrophilic compounds. Their uptake into cells is largely dependent on the activity of human equilibrative nucleoside transporters (hENTs) and human concentrative nucleoside transporters (hCNTs) [15–18]. The hENTs are capable of transporting pyrimidine and purine nucleosides from outside to inside the cell and vice versa, and are widely distributed in most human cells [19]. The hCNTs transport substrates, such as pyrimidine and purine nucleosides, only from outside to inside the cell, and are highly expressed in liver [20], kidney [21, 22], and intestine [23, 24]. hCNTs generally have a higher affinity for transport of nucleosides than hENTs (e.g., hCNT1 has a tenfold higher affinity for gemcitabine than hENT1).

**Metabolism: Activation and Deactivation**

Gemcitabine and cytarabine are phosphorylated by dCK into their corresponding monophosphate forms, which is the rate-limiting step in the formation of their active triphosphate metabolites, which are incorporated into DNA, thereby inhibiting DNA synthesis and DNA repair. Gemcitabine and cytarabine are extensively deaminated by cytidine deaminase (CDA) [7, 25] in liver, kidney, and plasma to their corresponding uracil metabolites 2’,2’-difluorodeoxyuridine (dFdU) and arabinosyluracil, respectively. These metabolites have a much lower cytotoxicity than their parent compounds. Because of this rapid deami-
nation, the elimination half-life \( (t_{1/2}) \) of gemcitabine and cytarabine is short, in the range of 10–30 minutes.

**MECHANISMS OF ACTION OF GEMCITABINE**

The chemical structures of dFdC, dFdU, and dFdCTP and the metabolic scheme and proposed pharmacological actions of gemcitabine and its metabolites are depicted in Figure 2. dFdC, the main active metabolite of gemcitabine, competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA, thereby competing with dCTP for incorporation. dFdC inhibits RR, which inhibits the conversion of CDP to dCDP and inhibits synthesis of dCTP, leading to an elevation in the intracellular dFdCTP/dCTP ratio and enhanced incorporation of dFdCTP into DNA. Since dCTP inhibits dCK, decreased dCTP pools can result in higher dCK activity and an increase in phosphorylation of dFdC to its active metabolites. dFdC is deaminated by CDA to dFdU. dFdCMP can be dephosphorylated to dFdC by 5'-NT and deaminated to dFdUMP by dCMPD. dFdCTP can inhibit dCMPD, which stimulates its own formation. Thus, dFdC is converted to its active metabolite, dFdCTP, which is incorporated into DNA, competing with dCTP for incorporation.

**PRECLINICAL PHARMACOLOGY OF GEMCITABINE**

**Nucleoside Cytotoxicity**

High intracellular accumulation of dFdCTP and incorporation into DNA are associated with greater sensitivity to gemcitabine in preclinical tumor models [9]. Clonogenic
survival assays demonstrated that the loss of cell viability increased with increasing gemcitabine concentrations and suggested intracellular retention of active gemcitabine metabolites for prolonged periods of time [27, 28]. The elimination kinetics of dFdCTP were found to be dependent on the intracellular concentration of dFdCTP. Elimination of dFdCTP was linear, with a t_{1/2} of about 3.6 hours at lower concentrations (<50 μM), and became biphasic at higher dFdCTP concentrations (>100 μM), with an initial t_{1/2} of about 1 hour, and an apparent terminal t_{1/2} of about 19 hours in leukemic cells [10].

The intracellular accumulation of active metabolites and cytotoxicity of gemcitabine are influenced by multiple factors, such as (a) the dosing schedule, (b) phosphorylation/activation (dCK), (c) cellular transport (hNTs), (d) degradation/inactivation (CDA), and (e) genetic factors (e.g., single nucleotide polymorphisms in dCK and CDA) [29–32]. In this review, we discuss the effect of the dosing schedule and the role of dCK and hNTs on the activity and toxicity of gemcitabine.

**The Importance of dCK**

Phosphorylation of gemcitabine to dFdCMP by dCK was shown to be the rate-limiting step in the formation of dFdCTP [33, 34]. The affinity of dCK is higher for gemcitabine than for cytarabine and other nucleoside antitumor drugs (e.g., cladribine and fludarabine) [35]. The activity of dCK is an important factor in the overall cytotoxicity of gemcitabine. A2780 human ovarian carcinoma cell lines deficient in dCK were resistant to gemcitabine [36]. Greater expression of dCK cDNA in HT-29 human colon carcinoma xenografts in nude mice was positively correlated with enhanced dFdCTP accumulation and with the antitumor activity of gemcitabine [37].

**The Importance of hNTs**

Transport of gemcitabine occurs particularly by hCNT1, hENT1, and hENT2 [18, 38, 39], and is saturable [40]. Sensitivity to gemcitabine positively correlated with the expression of hENT1 [41], and hENT1-deficient cells were highly resistant to cytotoxicity by gemcitabine and cytarabine [42–44]. Inhibitors of nucleoside transporters, such as nitrobenzylmercaptapurine riboside (NBMPR), a specific hENT1 inhibitor at low nanomolar concentrations, and dipyr idamole, a hENT1/2 inhibitor, reduced sensitivity to gemcitabine by 39- and 1,800-fold [18]. hENT1 transports gemcitabine with a high affinity and low capacity, whereas hENT2 transports gemcitabine with a low affinity and high capacity [40]. Restoration of hCNT1 activity in human pancreatic cancer cells positively correlated with the cytotoxicity of gemcitabine [45].

**CLINICAL PHARMACOLOGY OF GEMCITABINE**

Gemcitabine is generally administered as a standard 30-minute infusion at a dose of 1,000 mg/m² once weekly for 3 weeks of a 4-week cycle. Following i.v. administration, gemcitabine has a short t_{1/2} (~8–20 minutes) because of rapid deamination to dFdU [46], which has a long t_{1/2} (~50 hours) and is largely excreted in the urine [47]. dFdCTP peak concentrations were obtained within 30 minutes of the end of the infusion, and dFdCTP elimination was linear at low concentrations, and became biphasic at high concentrations in leukemic and blood mononuclear cells [46, 48, 49]. The long retention time of dFdCTP likely contributes to the fact that gemcitabine has activity against both rapidly proliferating and slowly dividing tumors.

**dCK and Intracellular Levels of Nucleoside Triphosphates**

Gemcitabine was shown to be a good substrate for phosphorylation by dCK, having a Michaelis-Menten constant (Km) value of 5–10 μM [34, 50]. Inhibition of the reaction was shown at higher substrate concentrations [34]. Therefore, it was expected that the rate of phosphorylation became saturated at gemcitabine concentrations >20 μM, with a negative effect on phosphorylation at higher levels. Clinical pharmacokinetic studies strongly suggested that the rate of intracellular accumulation of dFdCTP was saturated at gemcitabine concentrations of 15–20 μM in plasma [46, 51], which were achieved with gemcitabine infusions at a dose rate of 8–10 mg/m² per minute [51]. A standard 30-minute infusion of gemcitabine at doses of 800–2,600 mg/m² generates gemcitabine plasma concentrations of 20–60 μM, which exceed levels at which the formation of dFdCTP becomes saturated [46, 49], and which may also inhibit the process of phosphorylation of gemcitabine [34]. Consequently, cells are not able to phosphorylate a substantial portion of the infused drug and the main portion of gemcitabine is deaminated to dFdU. These findings suggested that dose schedules resulting in gemcitabine plasma concentrations of 15–20 μM were optimal to achieve maximal intracellular dFdCTP levels. Additionally, the maximal accumulation of dFdCTP was likely achieved by more prolonged infusions at a dose rate that resulted in maintenance of a gemcitabine plasma concentration that saturated the formation of gemcitabine nucleotides.

The formation of ara-CTP was also saturable during high-dose cytarabine therapy at cytarabine plasma concentrations >10 μM [52–54]. Exposure to ara-CTP in acute leukemic blasts positively correlated with response following administration of cytarabine either on an intermittent schedule [55] or by continuous infusion. Nonlinear elimination kinetics of ara-CTP were observed at
high dose regimens of cytarabine corresponding to plasma concentrations >100 μM [56–58].

The Role of hNTs in the Cytotoxicity of Nucleosides

In 21 patients with pancreatic cancer treated with gemcitabine, hENT1 expression levels correlated with the median overall survival (OS) time. Patients with high expression levels of hENT1 had a significantly longer OS time of 25.7 months (95% confidence interval [CI], 17.6–33.7 months), compared with the OS time of 8.5 months (95% CI, 7.0–9.9 months) in patients with low levels of hENT1 [59]. Additionally, characterization of gene-expression patterns in tumor specimens of 102 patients with pancreatic cancer revealed that patients with high expression of hENT1 had a significantly longer OS time of 25.7 months, compared with the 12.4-month OS time in patients with low transcription levels (p < .001) [60].

Prolonged infusion of gemcitabine (1,200–2,800 mg/m²) at an FDR of 10 mg/m² per minute was safe and resulted in cumulative myelotoxicity with a lower maximum-tolerated dose (MTD) than with the standard 30-minute gemcitabine infusion [61]. Prolonged gemcitabine infusion at low dose levels (300 mg/m² in 6 hours) was associated with more pronounced nonhematological toxicity (e.g., alanine aminotransferase/aspartate aminotransferase elevations) [62, 63]. This might be a result of more pronounced accumulation of gemcitabine in the liver (high hCNT1 expression) than in other tissues. Because of the higher affinity of hCNT1 than hENT1 for gemcitabine, prolonged infusion of gemcitabine at a low dose level might allow selective uptake of gemcitabine into tumor cells with high expression of hCNT1, while sparing bone marrow cells that predominantly contain hENTs.

Intracellular accumulation of ara-CTP in leukemic cells of patients was limited and directly correlated with the number of membrane nucleoside transporters at low (<1 μM) cytarabine concentrations [17, 64, 65] after low-dose cytarabine therapy (100–200 mg/m² per day) [66, 67]. Concordant with these findings, patients with acute myelogenous leukemia (AML) who did not respond to cytarabine therapy (100–200 mg/m² per day) demonstrated low cytarabine uptake and low numbers of NBMPR binding sites in leukemic blasts [16]. Thus, at low cytarabine plasma concentrations, transport of cytarabine by hNTs is the rate-limiting step, whereas at high cytarabine concentrations, intracellular phosphorylation of cytarabine by dCK becomes the rate-limiting step in the formation of ara-CTP.

Coadministration of an inhibitor of hENT1 to cytarabine enhanced its cytotoxicity toward cells that coexpressed hENTs and hCNTs, which was explained by inhibition of efflux of cytarabine by hENT1, and enhanced intracellular uptake by hCNT1.

The Concept of FDR Dosing of Gemcitabine

Gemcitabine plasma concentrations of 20–60 μM are achieved following a standard 30-minute infusion of gemcitabine at a dose of 1,000–1,200 mg/m², which exceeds the levels of 15–20 μM at which dCK becomes saturated [46, 48–50]. Prolongation of the duration of infusion of gemcitabine at lower dose levels might increase the intracellular concentration of dFdC. In addition, it leads to the maintenance of plasma gemcitabine concentrations at levels at which dCK is saturated for prolonged periods of time, which increases intracellular accumulation of dFdCTP [48, 68]. This strategy was hypothesized to result in a higher antitumor activity of gemcitabine in patients. Clinical studies on the prolonged administration of gemcitabine at an FDR (e.g., 10 mg/m² per minute) compared with the standard 30-minute infusion (e.g., 30 mg/m² per minute) are discussed below.

PHASE II/III DOSE-FINDING STUDIES INVESTIGATING PROLONGED (FDR) AND STANDARD INFUSION OF GEMCITABINE

Grunewald and coworkers demonstrated, in a small subset of patients, that prolongation of the infusion duration of gemcitabine at a dose of 800 mg/m² increased the AUC of dFdCTP in leukemic cells (Table 1) [48]. In a dose-escalation study (10–1,000 mg/m² gemcitabine), they showed that a prolonged 60-minute dosing schedule of 800 mg/m² (~400 mg/m² in 30 minutes), resulting in plasma gemcitabine concentrations of 20 μM, led to a fourfold higher AUC of dFdCTP compared with a 30-minute infusion of 790 mg/m², after which gemcitabine concentrations of 60 μM were obtained [49]. No significant difference in the AUC for dFdCTP was observed at gemcitabine plasma concentrations >20 μM [49]. In a different dose-escalation study with gemcitabine (10–1,000 mg/m²), Abbruzzese and colleagues demonstrated that, after the end of a 30-minute infusion, plasma levels of gemcitabine decreased rapidly (t1/2 ~8 minutes) because of deamination to dFdU [46]. Both the rate of accumulation (μM/hour) and the maximum concentration (μM) of dFdCTP in mononuclear cells increased with the gemcitabine dose up to 350 mg/m², corresponding to gemcitabine plasma concentrations of 15–20 μM, without a further increase at higher dose levels, suggesting saturation of the intracellular formation of dFdCTP [46]. Administration of gemcitabine (1,200–6,400 mg/m²) at an FDR of 10 mg/m² per minute resulted in a linear increase in the AUC of dFdCTP with the infusion time and with the dose [51]. Additionally, inhibition of DNA synthe-
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<th>Tumor type</th>
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<th>Phase</th>
<th>Dose schedule</th>
<th>Intracellular dFdCTP</th>
<th>Toxicity</th>
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<th>Study</th>
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<tr>
<td>Leukemia</td>
<td>4</td>
<td>I</td>
<td>800 mg/m² in 1 hour (13 mg/m²/min); 800 mg/m² in 2 hours (7 mg/m²/min); 800 mg/m² in 3 hours (4 mg/m²/min); days 1, 8, and 15, every 4 wks</td>
<td>Median AUC (range), 140 (66–252) hours · µM (n = 4); 217 (129–1,012) hours · µM (n = 4); 432 (430–435) hours · µM (n = 2)</td>
<td>Thrombocytopenia was observed in 2 patients with chronic lymphocytic leukemia after the first two infusion schedules of 1 and 2 hours (grade not further specified)</td>
<td>NR</td>
<td>NR</td>
<td>Grunewald et al. [48]</td>
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<td></td>
<td>29</td>
<td>I</td>
<td>790 mg/m² in 0.5 hours (26 mg/m²/min); 800 mg/m² in 1 hour (13 mg/m²/min); days 1, 8, and 15, every 4 wks</td>
<td>Median AUC (range), 19 (19–23) hours · µM (n = 3); 98 (55–174) hours · µM (n = 5)</td>
<td></td>
<td></td>
<td>NR</td>
<td>Grunewald et al. [49]</td>
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<td></td>
<td>50</td>
<td>I</td>
<td>22.5, 35, 53, 80, 120, 180, 225, 350, 525, 790, 1,000 mg/m² in 0.5 hours (0.8–33 mg/m²/min); days 1, 8, and 15, every 4 wks</td>
<td>C_{max}, 18–284 µM; C_{max} increased with dose (no statistical significance and no dFdCTP AUC values were reported)</td>
<td>DLT was myelosuppression: G3 or 4 thrombocytopenia, G3 anemia, G3 granulocytopenia at 525, 790, and 1,000 mg/m², with somewhat higher incidences at higher doses; rash (n = 5) occurred at doses ≥525 mg/m²; N/V and anoxia were mild and appeared not to be dose-dependent</td>
<td></td>
<td>790 mg/m²</td>
<td>PR, 2/47 (4%)</td>
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<td>Leukemia</td>
<td>22</td>
<td>I</td>
<td>1,200, 1,500, 2,400, 3,600, 4,800, 6,400 mg/m² (10 mg/m²/min); days 1, 8, and 15, every 4 wks</td>
<td>AUC, 11–7,217 hours · µM; AUC increased with dose (no statistical significance reported)</td>
<td>G3 thrombocytopenia with pulmonary hemorrhage (n = 1) at 2,400 mg/m²; G4 skin ulceration (n = 1) and G4 mucositis (n = 1) at 6,400 mg/m²; G1 or 2 N/V (n = 6); mucositis, and stomatitis seemed to be dose-dependent (n, G, and dose levels not further specified)</td>
<td></td>
<td>4,800 mg/m²</td>
<td>No CR observed</td>
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<td>Solid tumors; various types</td>
<td>31</td>
<td>I</td>
<td>1,200, 1,500, 1,800, 2,250, and 2,800 mg/m² (10 mg/m²/min); days 1, 8, and 15 every 4 wks</td>
<td></td>
<td>G3 or 4 granulocytopenia and G3 thrombocytopenia at dose levels of 1,500–2,800 mg/m², without major differences in incidence and severity;</td>
<td></td>
<td>2,250 mg/m²</td>
<td>CR, 1/30 (3%); PR, 2/30 (7%)</td>
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<th>Tumor type</th>
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<th>MTD</th>
<th>Response</th>
<th>Study</th>
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<td>Soft tissue sarcoma</td>
<td>56</td>
<td>II</td>
<td>1,000 mg/m² in 0.5 hours (33 mg/m²/min); 1,000 mg/m² in 2.5 hours (~6.7 mg/m²/min); days 1, 8, 15, 22, 29, 36, and 42, every 8 wks</td>
<td>Median C&lt;sub&gt;max&lt;/sub&gt; (range), 120 (50–310) μM (n = 9); 170 (65–445) μM (n = 7); median C&lt;sub&gt;max&lt;/sub&gt; 1.4-fold higher after FDR dosing (p = .016)</td>
<td>Mainly G3 or 4 neutropenia (n = 6), G3 or 4 thrombocytopenia (n = 5), G3 anemia (n = 2), G3 ALT elevation (n = 2), and G1 or 2 fatigue (n = 11)</td>
<td>NR</td>
<td>PR, 7/39 (18%); survival, 13.9 mos</td>
<td>Patel et al. [69]</td>
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<tr>
<td>Acute myeloid leukemia</td>
<td>19</td>
<td>I</td>
<td>4,800, 6,000, 7,200, 9,240, 10,800 mg/m² (10 mg/m²/min); day 1 every 3–4 wks</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;, 133–970 μM (high interpatient variability likely because of inability of cells to accumulate dFdCTP because of variation in phosphorylation of gemcitabine to dFdCTP)</td>
<td>G2 or 3 mucositis at all dose levels; G2 diarrhea at 7,200 mg/m²; G2 N/V at 7,200, 9,240, and 10,800 mg/m²; G3 rash at 9,240, 10,800 mg/m²</td>
<td>~7,200–9,240 mg/m²</td>
<td>PR, 1/19 (5%)</td>
<td>Gandhi et al. [70]</td>
</tr>
<tr>
<td>Advanced pancreatic cancer</td>
<td>23</td>
<td>I</td>
<td>3,000–7,000 mg/m² in 5–11.7 hours (10 mg/m²/min); day 1, every 2 wks</td>
<td>NR</td>
<td>G4 mucositis at 7,000 mg/m²; other toxicities were G3 or 4 neutropenia, G3 anemia, G3 thrombocytopenia, G2 diarrhea, G2 fever (n and dose levels not specified)</td>
<td>6,500 mg/m²</td>
<td>CR, 1/18 (6%); PR, 3/18 (17%); SD, 7/18 (39%); TTP, 4.8 mos; OS, 7 mos; 1-yr SR, 1.9%</td>
<td>Bengala et al. [71]</td>
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<td>NSCLC</td>
<td>24</td>
<td>I</td>
<td>10, 20, 40, 80, 120, 180, 210 mg/m² in 24 hours (0.007–0.15 mg/m²/min); days 1, 8, and 15, every 4 wks</td>
<td>NR</td>
<td>G2 or 3 leukopenia, G2 neutropenia, G2 anemia, G3 N/V, G2 ALT elevation, G2 or 3 lethargy, and G2 or 3 mucositis, which seemed to increase in severity and incidence with dose</td>
<td>180 mg/m²</td>
<td>PR, 5/24 (21%)</td>
<td>Anderson et al. [72]</td>
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<tr>
<td>Solid tumors; various types</td>
<td>47</td>
<td>I</td>
<td>300 mg/m² in 0.5, 1, 2, 3, 4.5, and 6 hours; 875 mg/m² in 0.5 and 1 hour (0.8–29 mg/m²/min); days 1, 8, and 15, every 4 wks</td>
<td>NR</td>
<td>DLT, leukopenia with 6-hour infusion schedule, of which the severity increased with duration of infusion; no DLTs; however, incidence of</td>
<td>300 mg/m² in 6 hours</td>
<td>PR, 8/47 (17%)</td>
<td>Pollera et al. [62]</td>
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<tr>
<th>Tumor type</th>
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<th>Phase</th>
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<th>MTD</th>
<th>Response</th>
<th>Study</th>
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<tr>
<td>Breast cancer</td>
<td>16</td>
<td>I</td>
<td>200, 250, and 300 mg/m² in 6 hours (0.56–0.83 mg/m²/min); days 1, 8, and 15 every 4 wks</td>
<td>NR</td>
<td>Leukopenia was higher with the 1-hour than the 0.5-hour schedule; G2 or 3 AST/ALT elevations increased with infusion duration</td>
<td>250 mg/m²</td>
<td>CR, 1/16 (6%); PR, 1/16 (6%); SD, 7/16 (44%)</td>
<td>Akrivakis et al. [75]</td>
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<td>Solid tumors; various types</td>
<td>27</td>
<td>I</td>
<td>300, 400, 450, and 500 mg/m² in 3 hours (1.7–2.8 mg/m²/min); days 1, 8, and 15 every 4 wks</td>
<td>NR</td>
<td>Myelosuppression was generally mild at all dose levels and consisted mainly of neutropenia; AST/ALT elevation was the predominant nonhematological toxicity and tended to occur earlier and with greater intensity at higher dose levels and at higher cumulative doses</td>
<td>450 mg/m²</td>
<td>NR</td>
<td>Maurel et al. [73]</td>
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<tr>
<td>Solid tumors; various types</td>
<td>21</td>
<td>I</td>
<td>350, 400, 450 mg/m² in 4 hours (1.5–1.9 mg/m²/min)</td>
<td>NR</td>
<td>Myelosuppression appeared to be the most common toxicity with an increase in incidence with dose</td>
<td>400 mg/m²</td>
<td>PR, 2/16 (13%); SD, 5/16 (31%)</td>
<td>Schmid et al. [74]</td>
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<tr>
<td>NSCLC</td>
<td>15</td>
<td>I</td>
<td>600 mg/m² in 1 hour (( n = 3 )), 750 mg/m² in 1.25 hours (( n = 6 )), 900 mg/m² in 1.5 hours (( n = 6 )) (10 mg/m²/min plus carboplatin (AUC 5)); days 1 and 8, every 3 wks</td>
<td>NR</td>
<td>600 mg/m², no DLT; 750 mg/m², DLT, G3 neutropenia (( n = 1 )); 900 mg/m², DLTs, G3 liver failure (( n = 1 )), G3 thrombocytopenia (( n = 1 ))</td>
<td>900 mg/m²</td>
<td>PR, 2/10 (20%); SD, 5/10 (50%)</td>
<td>Soo et al. [76]</td>
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<tr>
<td>NSCLC</td>
<td>23</td>
<td>II</td>
<td>1,200 mg/m² in 2 hours (10 mg/m²/min) plus carboplatin (AUC 5); days 1 and 8 every 3 wks</td>
<td>NR</td>
<td>Main toxicities were G3 or 4 thrombocytopenia (( n = 9 )), G3 or 4 neutropenia</td>
<td>NR</td>
<td>PR, 10/21 (48%); SD, 7/21 (33%); TTP, 6 mos; 1-yr SR, 40%</td>
<td>Wang et al. [77]</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>n</th>
<th>Phase</th>
<th>Dose schedule</th>
<th>Intracellular dFdCTP</th>
<th>Toxicity</th>
<th>MTD</th>
<th>Response</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>61</td>
<td>I/II</td>
<td>130–210 mg/m(^2) in 6 hours (n = 21); 250 mg/m(^2) in 6 hours (n = 40) (&lt;0.4–0.7 mg/m(^2)/min) plus cisplatin (75 mg/m(^2)); days 1 and 8 every 3 wks</td>
<td>NR</td>
<td>No DLTs; mainly anemia, neutropenia, and alopecia, of which the incidence and/or severity was higher at the dose level of 250 mg/m(^2) than at lower dose levels</td>
<td>NR</td>
<td>CR, 1/61 (2%); PR, 27/61 (44%); SD, 20/61 (33%)</td>
<td>Zwitter et al. [78]</td>
</tr>
<tr>
<td>Advanced solid tumors and lymphoma</td>
<td>34</td>
<td>I</td>
<td>1, 2, 4, 6, 7, 8, 9, 10, 15, 20, and 25 mg/m(^2)/day as a 96-hour infusion (&lt;0.2 mg/m(^2)/min); day 1, every 2 or 3 wks</td>
<td>NR</td>
<td>Myelosuppression was uncommon; DLTs were dyspnea, mucositis, fever, and hypotension at dose levels of 10–25 mg/m(^2) per day</td>
<td>~24 mg/m(^2) every 2 wks or 32 mg/m(^2) every 3 wks</td>
<td>SD, 6/34 (18%)</td>
<td>Rajdev et al. [79]</td>
</tr>
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</table>

Toxicities of Common Toxicity Criteria (CTC) grade ≥2 are reported. CTC grade is calculated based on CTC version 3.0, when data were given as number of cells/mm\(^3\). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration–time curve; C\(_{\text{max}}\), maximum concentration; CR, complete response; dFdCTP, 2',2'-difluorodeoxycytidine triphosphate (gemcitabine triphosphate); DLT, dose-limiting toxicity; FDR, fixed dose rate; G, CTC grade; MTD, maximum-tolerated dose; NR, not reported; NSCLC, non-small cell lung cancer; N/V, nausea/vomiting; OS, overall survival; PR, partial response; SD, stable disease; SR, survival rate; TTP, time to progression.
sis in circulating blasts increased proportionately with the AUC of dFdCTP. A study by Touroutoglou and colleagues showed that FDR gemcitabine (1,200–2,800 mg/m²) was safe and well tolerated [61]. Once-weekly administration of gemcitabine for 7 weeks of an 8-week cycle and FDR dosing of 1,000 mg/m² in 150 minutes demonstrated that intracellular levels of dFdCTP in peripheral blood mononuclear cells (PBMCs) increased linearly with infusion duration [69]. The maximum concentration (C_max) of dFdCTP was 1.4-fold higher after FDR than after standard gemcitabine. Similarly, Gandhi and colleagues demonstrated that levels of dFdCTP in AML blasts increased linearly with infusion time following FDR gemcitabine dosing [70]. An abrupt decrease in DNA synthesis to values of 5%–20% of the pre-treatment value at 1 hour after the infusion was observed, and DNA synthesis remained inhibited until 24 hours after the start of the infusion. Moreover, dATP pools decreased during gemcitabine infusion up to 24 hours after the start of the infusion. Bengal and coworkers found that FDR gemcitabine infusion in patients with advanced pancreatic adenocarcinoma resulted in a median time to progression (TTP) of 4.8 months, a median OS time of 7 months, and a 1-year survival rate (SR) of 21.9% [71]. The AUC of dFdU, the main deaminated metabolite of gemcitabine, and OS time significantly correlated with the expression and activity of cytidine deaminase (p < .05). Studies on the prolonged infusion of gemcitabine during 3, 4, 6, and 24 hours at low dose levels in patients with advanced solid tumors found low MTD values between 180 and 450 mg/m² [72–75]. Besides treatment with single-agent gemcitabine, FDR infusion of gemcitabine has been investigated in combination with other chemotherapeutic agents, such as carboplatin and cisplatin. Sook and colleagues found that combination therapy with carboplatin (AUC, 5 mg/mlminute) and gemcitabine administered as a 75-minute infusion at a dose of 750 mg/m² was active and tolerable in patients with non-small cell lung cancer (NSCLC) and resulted in plasma gemcitabine concentrations >10 µM [76]. Others found that the combination of carboplatin (AUC, 5 mg/mlminute) with gemcitabine administered as a 120-minute infusion at a dose of 1,200 mg/m² resulted in a median TTP of 7.0 months and an OS time of 12.0 months [77]. The gemcitabine concentration at the end of the infusion was positively correlated with the percentage reduction in leukocytes and platelets. The prolonged infusion of gemcitabine (120–250 mg/m²) over 6 hours with cisplatin (75 mg/m²) had an acceptable toxicity profile [78]. The median TTP was 6 months and the 1-year SR was 40%. Prolonged gemcitabine infusion over 96 hours at doses of 1–25 mg/m² per day resulted mainly in nonhematological toxicities (e.g., mucositis, fever, rash), in contrast to studies with shorter infusion durations (<2 hours), which predominantly resulted in myelotoxicity [79].

**Phase II/III Randomized Trials Comparing FDR with Standard Dosing of Gemcitabine**

A study in 48 Asian patients with unresectable hepatocellular carcinoma treated with first-line single-agent gemcitabine (1,250 mg/m²) either as a 30-minute or FDR infusion in 2 hours resulted in a TTP and median OS time of 46 and 97 days, respectively, without statistically significant differences in response and toxicity between the two treatment schedules [80] (Table 2). A randomized phase II study by Tempo et al. [81] in 92 patients with pancreatic cancer compared standard infusion (2,200 mg/m² in 30 minutes) with an FDR infusion (1,500 mg/m² in 150 minutes) of gemcitabine. The dose levels for each dosing regimen were based on the established MTD for gemcitabine in previous studies [61, 82, 83], which permitted comparison of clinical responses at equitoxic gemcitabine doses between the two dosing schedules. They found that the concentration of dFdCTP in PBMCs increased linearly with the infusion time up to 188 µM at the end of the 150-minute infusion, while infusion of the higher dose in 30 minutes resulted in a plateau in the dFdCTP concentration at 103 µM at 1 hour after the end of the infusion. However, no AUC values of dFdCTP were reported. The 1- and 2-year SRs were significantly higher following FDR than following the standard gemcitabine infusion (p = .007) (Table 2). Furthermore, the OS time was longer for patients in the FDR arm than for those in the standard arm (8.0 versus 5.0 months; p = .013), but the time to treatment failure (TTF), their primary end-point, was similar between the standard and FDR infusions of gemcitabine (1.8 versus 2.0 months; p = .09). The fact that the difference in OS was not statistically significant may be a result of insufficient power of the study. It was surprising that the advantage in survival in the FDR group was not accompanied by a longer TTF. According to the authors, TTF may not be a good predictor of survival benefit, because this endpoint may be influenced by other factors, such as poor tolerance to therapy and clinical deterioration. Furthermore, twice as many patients in the FDR arm as in the standard arm received second-line chemotherapy, which might have influenced survival. On the other hand, it is possible that more patients receiving FDR gemcitabine were able to proceed to second-line treatment based on a better performance status. Patients receiving FDR infusion experienced more hematological toxicities than patients treated with standard gemcitabine: grade 3 or 4 thrombocytopenia, 37.2% versus 10.2%; neutropenia, 48.8% versus 26.5%; and grade 4 anemia, 9.3% versus 2%. In summary, although the results have to be interpreted carefully, the
<table>
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<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic cancer</td>
<td>25</td>
<td>II Randomized</td>
<td>1,250 mg/m² in 0.5 hours (42 mg/m²/min); days 1 and 8 every 3 wks</td>
<td>NR</td>
<td>44% G3 or 4 hematological and 76% nonhematological toxicity</td>
<td>PR, 1/25 (4%)</td>
<td>Guan et al. [80]</td>
</tr>
<tr>
<td>In total, 50 patients were enrolled; 2 patients did not receive study treatment</td>
<td>23</td>
<td>II Randomized</td>
<td>1,250 mg/m² in 2 hours (10 mg/m²/min); days 1 and 8, every 3 wks</td>
<td></td>
<td>35% G3 or 4 hematological and 52% nonhematological toxicity; no statistical differences between the treatment arms</td>
<td>No PR observed; no significant difference in OS between the two schedules</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>49</td>
<td>II Randomized</td>
<td>2,200 mg/m² in 0.5 hours (73 mg/m²/min); days 1, 8, and 15, every 4 wks</td>
<td>Median C&lt;sub&gt;max&lt;/sub&gt; (range), 188 (44–533) μM</td>
<td>G3 or 4 neutropenia (26.5%), G3 or 4 thrombocytopenia (10.2%), G4 anemia (2%)</td>
<td>PR, 2/49 (4%); OS, 5 mos; 1-yr SR, 9%; 2-yr SR, 2%; TTF, 1.8 mos</td>
<td>Tempero et al. [81]</td>
</tr>
<tr>
<td>No reason for the difference in number of patients between the two arms was given</td>
<td>43</td>
<td>II Randomized</td>
<td>1,500 mg/m² in 2.5 hours (10 mg/m²/min); days 1, 8, and 15, every 4 wks</td>
<td>Median C&lt;sub&gt;max&lt;/sub&gt; (range), 398 (111–682) μM</td>
<td>G3 or 4 neutropenia (48.8%), G3 or 4 thrombocytopenia (37.2%), G4 anemia (9.3%)</td>
<td>PR, 1/43 (2%); OS, 8 mos; 1-yr SR, 29%; 2-yr SR, 18%; TTF, 2.1 mos; TTF, p = .09; OS, p = .013; 2-yr SR, p = .007</td>
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</tr>
<tr>
<td>NSCLC</td>
<td>38</td>
<td>II Randomized</td>
<td>1,000 mg/m² in 0.5 hours (33 mg/m²/min); plus carboplatin; days 1 and 8, every 3 wks</td>
<td>Mean AUC (± SD), 585 ± 304 hours · μM</td>
<td>G3 or 4 anemia (31%), G3 or 4 neutropenia (68%), G3 or 4 thrombocytopenia (59%)</td>
<td>PR, 16/38 (42%); OS, 9.6 mos; 1-yr SR, 36%; TTP, 5.2 mos</td>
<td>Soo et al. [84]</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>II Randomized</td>
<td>750 mg/m² in 1.25 hours (10 mg/m²/min); plus carboplatin; days 1 and 8, every 3 wks</td>
<td>Mean AUC (± SD), 537 ± 188 hours · μM</td>
<td>G3 or 4 anemia (33%), G3 or 4 neutropenia (75%), G3 or 4 thrombocytopenia (52%); no significant differences observed</td>
<td>PR, 13/38 (34%); OS, 7.0 mos; 1-yr SR, 32%; TTP, 5.3 mos; no significant differences observed</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>56</td>
<td>II Randomized</td>
<td>1,500 mg/m² in 0.5 hours (50 mg/m²/min); days 1 and 8, every 3 wks</td>
<td>NR</td>
<td>G3 or 4 neutropenia (17.9%), G3 leukopenia (10.7%), G3 anemia (5.4%), pulmonary toxicity (12.5%)</td>
<td>CR, 1/56 (2%); PR, 8/56 (14%); SD, 24/56 (43%); ORR, 16%; TTP, 4 mos; 1-yr SR, 42.6%; OS, 9 mos</td>
<td>Cappuzzo et al. [85]</td>
</tr>
</tbody>
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(continued)
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>n</th>
<th>Phase</th>
<th>Study</th>
<th>Toxicity</th>
<th>Intracellular dFdCTP</th>
<th>Dose schedule</th>
<th>Response</th>
<th>Study</th>
<th>Toxicity</th>
<th>Intracellular dFdCTP</th>
<th>Dose schedule</th>
<th>Response</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>57</td>
<td>II Randomized</td>
<td>1,000 mg/m² in 1.7 hours (10 mg/m²/min); 5 patients completed, 2 patients discontinued</td>
<td>G3 or 4 neutropenia (24%), G3 or 4 thrombocytopenia (18%), G3 or 4 anemia (11%); no significant differences observed</td>
<td>No significant differences were noted in the occurrence and severity of the majority of all toxicities; G2, 3, or 4 vomiting occurred more frequently in the prolonged infusion schedule (28%) than in the standard schedule (18%)</td>
<td>G3 or 4 neutropenia (24%), G3 or 4 thrombocytopenia (18%), G3 or 4 anemia (11%); no significant differences observed</td>
<td>PR, 19/55 (34%); SD, 27/55 (49%); TTP, 8 mos; OS, 13 mos; 1-yr SR, 52%</td>
<td>Gridelli et al. [87]</td>
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</tr>
<tr>
<td>NSCLC</td>
<td>200</td>
<td>III Randomized</td>
<td>1,200 mg/m² in 2 hours; plus cisplatin, days 1 and 8 every 3 wks</td>
<td>CR, 2/200 (1%); PR, 35/200 (17%); SD, 34/200 (17%); TTP, 6 mos; OS, 10 mos; 1-yr SR, 39%</td>
<td>No significant differences were observed</td>
<td>CR, 2/200 (1%); PR, 35/200 (17%); SD, 34/200 (17%); TTP, 6 mos; OS, 10 mos; 1-yr SR, 39%</td>
<td>CR, 2/200 (1%); PR, 35/200 (17%); SD, 34/200 (17%); TTP, 6 mos; OS, 10 mos; 1-yr SR, 39%</td>
<td>Ceribelli et al. [86]</td>
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Table 2. (Continued)

In total, 121 patients were enrolled; 4 patients did not receive study treatment. The response rates and survival data are reported in Table 2. CTC grade ≥ 2 are reported. CTC grade is calculated based on CTC version 3.0, when data were given as number of cells/mm³.

Toxicities of Common Toxicity Criteria (CTC) grade ≥ 2 are reported. CTC grade is calculated based on CTC version 3.0, when data were given as number of cells/mm³.

Abbreviations: ANC, absolute neutrophil count; AUC, area under the concentration-time curve; Cmax, maximum concentration; CR, complete response; CTC, Common Toxicity Criteria; FDR, fixed dose rate; G, CTC grade; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate; OSI, overall survival; P, phase of the study; SD, stable disease; SR, survival rate; TTP, time to progression; TTF, time to treatment failure; TTP, time to progression.
pharmacological and clinical findings of the study supported an FDR infusion strategy for gemcitabine.

A randomized phase II study by Soo and colleagues, investigating combination therapy with carboplatin (AUC, 5 mg/ml-minute) and either the standard 30-minute infusion of gemcitabine or FDR gemcitabine (750 mg/m² over 75 minutes) demonstrated that the mean Cmax of gemcitabine in plasma was significantly lower following FDR infusion (21 μM) than following the standard infusion (41 μM) [84]. The mean AUC of dFdCTP in blood mononuclear cells, however, was comparable between the two dosing schedules (Table 2). Furthermore, the TTP, OS time, 1-year SR, and rate of hematological toxicity were comparable between the two treatment arms (Table 2). A randomized phase II study by Cappuzzo and colleagues demonstrated no significant differences in the response rate and OS time between FDR and standard gemcitabine dosing [85]. However, FDR dosing resulted in a higher incidence of grade 3 or 4 neutropenia than with the standard infusion of gemcitabine (49.2% versus 17.9%; p < .001). A randomized phase II study in patients with advanced NSCLC treated with cisplatin (80 mg/m²) plus gemcitabine resulted in a median TTP of 6 months (range, 1–26 months) and 8 months (range, 2–21 months) following standard and FDR infusion of gemcitabine, respectively [86]. The median OS time was 13 months for both treatment schedules, which were tolerated with cumulative incidences of grade 3 or 4 neutropenia and thrombocytopenia of 27% and 15%, respectively. Recently, a phase III randomized trial assessed whether prolonged infusion of gemcitabine (1,200 mg/m² in 120 minutes) could improve OS in patients with advanced NSCLC over that seen with first-line treatment with cisplatin (80 mg/m²) plus gemcitabine (1,200 mg/m²) as a 30-minute infusion. Prolonged administration of gemcitabine did not result in a longer OS duration, but did result in more pronounced vomiting and fatigue [87].

**DISCUSSION AND FUTURE PERSPECTIVES**

In summary, various clinical studies have shown that prolonged i.v. gemcitabine administration over 1–24 hours at lower rates of infusion (<30 mg/m² per minute) can be safely administered and has remarkable antitumor activity in patients with advanced solid tumors. Overall, there was a trend that prolonged infusion of gemcitabine resulted in a somewhat higher degree of nonhematological toxicity (e.g., elevations in transaminases) than with the standard 30-minute infusion, after which myelosuppression was the most common toxicity. The FDR strategy (e.g., 10 mg/m² per minute) resulted in gemcitabine plasma concentrations at levels at which dCK becomes saturated for prolonged periods of time and led to higher AUC values of dFdCTP in mononuclear and leukemic cells than with the standard gemcitabine infusion (e.g., 33 mg/m² per minute). Concordant with these findings, one would expect FDR gemcitabine to result in higher concentrations of dFdCTP in solid tumors of patients. However, in vivo metabolism and/or transport of gemcitabine might be somewhat different among blood mononuclear, leukemic, and solid tumor cells; for example, as a result of differences in expression of metabolic enzymes and hNTs. Thus far, not many studies have determined dFdCTP concentrations in tumor tissue following gemcitabine therapy. A study in 30 patients with head and neck cancer treated with i.v. gemcitabine (50–300 mg/m²) over 30 minutes resulted in dFdCTP concentrations of 733–3,817 pmol/g tumor biopsy, which was suggested to produce potent radiosensitization based on in vitro studies [88]. In a phase I trial in 52 patients with refractory solid cancers, a 30-minute infusion of gemcitabine (1500 mg/m²) resulted in 70 pmol of dFdCTP per gram wet weight tumor biopsy of patients with head and neck cancer (n = 2) [89].

Overall, clinical studies provide pharmacological evidence for an advantage of prolonged FDR dosing above the standard 30-minute infusion of gemcitabine, based on the increase in dFdCTP exposure in blood mononuclear cells, which could be used to further optimize gemcitabine treatment. Thus far, only the study by Tempero and coworkers demonstrated an advantage for FDR infusion over standard gemcitabine in terms of survival of patients. Recently, a phase III study compared the OS time seen with standard gemcitabine (1,000 mg/m² over 30 minutes weekly for 7 weeks over 56 days then weekly for 3 weeks every 28 days, A) with that seen with FDR gemcitabine (1,500 mg/m² over 150 minutes weekly for 3 weeks for 28 days, B) and with FDR gemcitabine (1,000 mg/m² over 100 minutes on day 1) plus oxaliplatin (100 mg/m² on day 2 every 14 days), C, in 750 patients with advanced pancreatic cancer [90]. An interim analysis showed median OS times of 4.96, 6.01, and 6.47 months for arm A, B, and C, respectively, without significant differences among the three treatment arms. In general, pancreatic cancer is an unresponsive disease, and anticancer drugs other than gemcitabine are needed for the treatment of this type of cancer. New well-powered, randomized clinical studies are warranted to establish the optimal dose and infusion duration of gemcitabine providing the greatest antitumor activity with acceptable toxicity in types of cancer other than pancreatic cancer. Furthermore, future studies should assess relationships between the exposure to dFdCTP in PBMCs and solid tumors following prolonged FDR and following standard gemcitabine therapy. These studies should prove whether prolonged FDR gemcitabine dosing is a better treatment option than standard gemcitabine.
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