Improveing Gemcitabine-Mediated Radiosensitization Using Molecularly Targeted Therapy: A Review

Meredith A. Morgan,1 Leslie A. Parsels,2 Jonathan Maybaum,2 and Theodore S. Lawrence1

Abstract In the last three decades, gemcitabine has progressed from the status of a laboratory cytotoxic drug to a standard clinical chemotherapeutic agent and a potent radiation sensitizer. In an effort to improve the efficacy of gemcitabine, additional chemotherapeutic agents have been combined with gemcitabine (both with and without radiation) but with toxicity proving to be a major limitation. Therefore, the integration of molecularly targeted agents, which potentially produce less toxicity than standard chemotherapy, with gemcitabine radiation is a promising strategy for improving chemoradiation. Two of the most promising targets, described in this review, for improving the efficacy of gemcitabine radiation are epidermal growth factor receptor and checkpoint kinase 1.

Gemcitabine was first introduced into the clinic as a chemotherapeutic agent nearly 3 decades ago. Since then, both laboratory and clinical investigations have shown gemcitabine to be a potent radiation sensitizer. In this review, we will begin with a discussion of gemcitabine biochemistry and its mechanisms of interaction with radiation, highlighting observations that may lead to improving the design of clinical trials combining gemcitabine with radiation. Previous attempts to improve the efficacy of gemcitabine radiotherapy have included the addition of other chemotherapeutic agents (1–3) such as cisplatin (4) and oxaliplatin (5). More recent studies have focused on the addition of molecularly targeted therapies, to gemcitabine, and radiation (6, 7). In this review, we will present our rationale for integrating checkpoint kinase 1 (Chk1)- and epidermal growth factor (EGFR) molecularly targeted agents with gemcitabine radiation therapy.

Gemcitabine Biochemistry and Radiosensitization

The antitumor activity of gemcitabine depends on a series of sequential phosphorylations. In the first rate-limiting step, deoxycytidine kinase converts gemcitabine to the monophosphorylated metabolite, dFdCMP [this has motivated the study of fixed-dose-rate infusion (10 mg/m²/min), which increases intracellular metabolites compared with bolus treatment (8, 9), but in the majority of trials, does not significantly improve survival (10)]. Subsequent phosphorylations lead to the accumulation of gemcitabine diphosphate and triphosphate (dFdCDP and dFdCTP) that are both active metabolites (Fig. 1). Whereas dFdCTP can interfere with DNA synthesis by competing with endogenous dCTP for misincorporation into replicating DNA, dFdCDP is a potent inhibitor of ribonucleotide reductase, reducing the synthesis of deoxynucleoside triphosphates, primarily dATP (in solid tumor cells).3

The inhibition of ribonucleotide reductase by dFdCDP and subsequent depletion of dATP pools caused by gemcitabine suggested that it would be a good radiation sensitizer (Table 1; refs. 12, 13). Early preclinical studies showed that, as anticipated, gemcitabine radiosensitized both solid tumor cell lines (12, 14–16) and mouse sarcoma (17). Subsequent studies showed that cells transduced with the active subunit of ribonucleotide reductase become relatively resistant to gemcitabine-mediated radiosensitization (18). Furthermore, radiosensitization does not correlate with intracellular concentrations of dFdCTP (19), suggesting that dATP pool depletion and not incorporation of dFdCMP into DNA underlies radiosensitization. Although gemcitabine-induced dATP pool depletion is necessary, it alone is not sufficient for radiosensitization. The ability of gemcitabine to cause redistribution of cells into S phase is also required for radiosensitization (20). Although high concentrations of gemcitabine cause near complete dATP pool depletion within just a few hours, cells irradiated at this time are minimally radiosensitized. Maximum sensitization requires both dATP pool depletion and sufficient time to permit redistribution of cells into early S-phase (15, 21). Sensitization is maximized in vivo by a fixed-dose-rate exposure to gemcitabine, compared with a bolus administration (22), presumably due to the production of more intracellular metabolites, as alluded to above.

Cellular Effects of Radiation and Gemcitabine

DNA-directed effects. Based on the inhibition of deoxynucleotide triphosphate synthesis by gemcitabine, it seemed likely
that gemcitabine would have an effect on the repair of radiation-induced DNA damage, which may contribute in part to its radiosensitizing activity. When initial work showed that gemcitabine had no effect on the induction or repair of bulk DNA damage (23–25), individual repair pathways were explored. These studies found that DNA damage induced by ionizing radiation is primarily repaired by the nonhomologous end joining pathway and, to a lesser extent, through base excision repair and homologous recombination repair (HRR; end joining pathway and, to a lesser extent, through base excision repair and homologous recombination repair (HRR; ref. 26). Our hope is that this review will stimulate rationally designed clinical trials combining molecularly targeted agents with gemcitabine radiation with the ultimate goal of improving survival.

**Table 1. Mechanisms of radiosensitization by gemcitabine**

<table>
<thead>
<tr>
<th>Mechanism</th>
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<tr>
<td>Requires dATP pool depletion and S phase redistribution (15)</td>
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<td>Correlates with Chk1 and Chk2 activation (33)</td>
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<td>Interferes with homologous end rejoining (27)</td>
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<td>Increased in mismatch repair deficient cells (19)</td>
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<td>Partially mediated by apoptosis (16)</td>
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**Fig. 1. Gemcitabine mechanisms of action.** After cellular incorporation, gemcitabine (dFdCyd) undergoes a series of sequential phosphorylations mediated by deoxycytidine kinase. dFdCDP is a direct inhibitor of ribonucleotide reductase, which results in inhibition of deoxyribonucleotide triphosphate synthesis, specifically dATP. Depletion of dATP pools is crucial for radiosensitization (19). dFdCTP is incorporated into DNA during synthesis and contributes to cytotoxicity (87–89).
studies assessing the effects of checkpoint inhibition on progression with DNA synthesis, preventing cells with stalled Chk1 activation functions in part to coordinate cell cycle (premature mitosis). Thus, it seems that gemcitabine-induced DNA content (normal mitosis) or a sub-4N DNA content checkpoint, and permitted gemcitabine-treated cells with protein, inhibition of Rad51 focus formation, and increased gemcitabine by Chk1 inhibition and depletion of Rad51 data show a stronger correlation between sensitization to inhibition of Cdc25A degradation and induction of premature mitotic observations led to the hypothesis that Chk1 and/or Chk2 activation were required for gemcitabine-induced early S-phase arrest. Initial studies found, however, that although Chk1 activity was required for gemcitabine-induced Cdc25A degradation, neither Chk1 nor Chk2 inhibition affected the gemcitabine-induced accumulation of cells in early S-phase (33, 35, 36). Instead, Chk1 inhibition abrogated the G2-M checkpoint, and permitted gemcitabine-treated cells with arrested DNA synthesis to enter mitosis with either a 4N DNA content (normal mitosis) or a sub-4N DNA content (prematuration mitosis). Thus, it seems that gemcitabine-induced Chk1 activation functions in part to coordinate cell cycle progression with DNA synthesis, preventing cells with stalled replication from prematurely entering mitosis (33).

The finding that gemcitabine activates Chk1 and Chk2 led to studies assessing the effects of checkpoint inhibition on gemcitabine-induced cytotoxicity. Inhibition of Chk1 by either siRNA-mediated Chk1 depletion (34, 36) or by small molecule Chk1 inhibitors (35) enhanced gemcitabine cytotoxicity. Likewise, inhibition of other members of the Chk1 signaling pathway, such as Rad9, ataxia telangiectasia–mutated Rad3-related kinase, and ataxia telangiectasia–mutated kinase, enhanced gemcitabine cytotoxicity (34). Although, enhancement of gemcitabine cytotoxicity is accompanied by inhibition of Cdc25A degradation and induction of premature mitotic entry in some instances, we have found examples where these markers do not correlate with sensitization. Instead, our recent data show a stronger correlation between sensitization to gemcitabine by Chk1 inhibition and depletion of Rad51 protein, inhibition of Rad51 focus formation, and increased γH2AX. These findings suggest that sensitization to gemcitabine by Chk1 inhibition is mediated by inhibition of the DNA damage response.

Chk1 may also play a role in radiosensitization by gemcitabine. Chk1 inhibitors such as PD-321852 (Pfizer) and AZD7762 (AstraZeneca; ref. 37) increase radiation sensitivity in a variety of model systems (38–41). Based on the ability of Chk1 inhibitors to sensitize to gemcitabine or radiation, we have initiated studies to examine whether Chk1 inhibition might enhance gemcitabine-mediated radiosensitization. PD-321852 (42) enhanced radiation sensitivity (Fig. 4A) as well as gemcitabine cytotoxicity (5) in pancreas tumor cell lines. Likewise, AZD7762 enhanced radiation sensitivity and further enhanced gemcitabine-mediated radiosensitization (Fig. 4B). Chk1 inhibitors have now entered clinical trials (for a review, see ref. 43).

**EGFR signaling.** EGFR is a transmembrane receptor tyrosine kinase that is activated in response to binding of ligands such as EGF, transforming growth factor-α, or amphiregulin (for a review, see ref. 41). Ligand binding results in receptor dimerization and activation of a number of downstream pathways (STAT, AKT, extracellular signal-regulated kinase, PKC), which promote survival, angiogenesis, cell cycle progression, and transformation. A recent phase III clinical trial in metastatic pancreatic cancer showed a statistically significant but clinically modest improvement in overall survival for patients treated with gemcitabine plus erlotinib versus gemcitabine alone (6.2 versus 5.9 months; ref. 44). There are several mechanisms (discussed below) through which EGFR inhibitors might interact with gemcitabine and/or radiation including EGFR activity, cell cycle, and DNA repair.

In addition to nucleotide pool depletion, S-phase arrest, and cell cycle checkpoint activation, gemcitabine stimulates phosphorylation of EGFR both in head and neck cancer cells (45, 46). EGFR is also phosphorylated in response to a variety of other cytotoxic agents (47–50), and it is hypothesized that this phosphorylation may promote survival through stimulation of stress/survival response pathways as illustrated in Fig. 3. This model provides an obvious rationale for the addition of EGFR inhibitors, such as the small molecule tyrosine kinase inhibitor, erlotinib or the anti-EGFR antibody, cetuximab to gemcitabine therapy. Initial studies in head and neck cancer xenografts showed that gefitinib, which blocked gemcitabine-mediated EGFR phosphorylation, enhanced gemcitabine-mediated tumor growth delay (45). In other studies, both cetuximab and erlotinib were found to enhance pancreatic tumor growth delay when combined with gemcitabine and radiation (7, 46).

The ability of EGFR inhibitors to sensitize to gemcitabine is sequence dependent. In head and neck cancer cells as well as xenografts, the combination of gemcitabine followed by gefitinib is superior to the reverse sequence (45). This observation has been supported in pancreatic cancer cells as well where treatment with gemcitabine before gefitinib produced additive to synergistic effects but antagonistic effects in response to the reverse sequence (51, 52). This schedule-dependent cell killing may be attributable to the cell cycle effects of EGFR inhibitors because EGFR inhibitors up-regulate the cyclin-dependent kinase inhibitors, p27 (53, 54) and p21 (55) and, thus, produce G1 cell cycle arrest.

EGFR also plays a role in DNA repair. Ionizing radiation and chemotherapeutic agents produce a variety of types of DNA damage including single- and double-strand DNA breaks, DNA adducts, and DNA crosslinks. EGFR can physically interact with DNA-dependent protein kinase (56). In response to radiation, EGFR translocates to the nucleus, which is associated with increased DNA-dependent protein kinase activity (57, 58). Inhibition of EGFR activation by cetuximab blocks nuclear EGFR import, DNA-dependent protein kinase activity, and
radiation-induced DNA damage repair, and induces radiosensitization (59; for a review, see ref. 60). Together, these results suggest that EGFR inhibitors could potentiate the efficacy of gemcitabine radiation through inhibition of DNA repair.

In addition to kinase activity, EGFR may have important structural functions to inhibit cell death (61). In head and neck cancer, treatment with gemcitabine results in degradation of EGFR (62). EGFR degradation in response to gemcitabine is accompanied by inhibition of downstream EGFR signaling molecules such as AKT and extracellular signal-regulated kinase as well as cell death. In preclinical studies, EGFR degradation in response to gemcitabine correlated with response. In contrast, gemcitabine does not cause EGFR degradation in pancreatic cancer models (46). These differences in EGFR degradation may at least in part account for the greater sensitivity to gemcitabine in head and neck cancer versus pancreatic cancer models.

The finding that EGFR inhibitors produce much greater effects in head and neck versus pancreatic cancer tumor models (46, 63) illustrates the importance of the cellular context of EGFR activation or inhibition. One plausible explanation for the relative insensitivity of pancreatic cancers to EGFR inhibitors is the presence of mutant Ras in >85% of pancreatic cancers (64). Mutant Ras confers resistance to EGFR inhibitor monotherapy and combination EGFR inhibitor chemotherapy, some preclinical models have shown radiosensitization by EGFR inhibitors in Ras mutant cell types, which could be explained by inhibition of EGFR/H-Ras (7, 67–69). Although the role of Ras mutation status in patients treated with radiation and EGFR inhibitor therapies has not yet been determined, the consensus of the existing clinical data are that Ras mutation confers resistance to both EGFR inhibitor monotherapy as well as combination EGFR inhibitor chemotherapy. Recent clinical studies in colorectal cancer and non–small cell lung cancer showed a lack of efficacy of EGFR inhibitors (as monotherapy and in combination with chemotherapy) against tumors with Ras mutations (70–72). Because Ras mutation is present in the majority of pancreatic cancers.

Fig. 3. The effects of gemcitabine and radiation on cell cycle checkpoints and EGFR signaling. Radiation-induced double-strand breaks or gemcitabine-induced replication stress trigger the activation of ataxia telangiectasia – mutated (ATM), and ataxia telangiectasia – mutated and Rad3-related (ATR) kinases, respectively (91). Active ataxia telangiectasia – mutated/ataxia telangiectasia – mutated Rad3-related kinase phosphorylate and activate Chk1 and Chk2 (92–94), which phosphorylate Cdc25 phosphatases, leading to their inactivation through degradation (Cdc25A; ref. 95) or cytoplasmic sequestration (Cdc25C; ref. 92). In the absence of Cdc25 phosphatase activity, cyclin-dependent kinases (Cdk1 and Cdk2) remain bound by inhibitory phosphorylations, resulting in arrest of the cell cycle at G1-S, intra-S, or G2-M. Treatment of cells with gemcitabine before radiation results in radiosensitization that can be attributed to a number of events (Table 1), including dATP depletion and S-phase arrest.

Inhibition of Chk1 sensitizes cells to gemcitabine and radiation by a number of potential mechanisms including abrogation of cell cycle arrest, premature mitotic entry, and inhibition of Ras signaling resulting in impaired HRR. EGFR is phosphorylated in response to radiation or gemcitabine by an unknown mechanism(s) (96). Radiation triggers translocation of EGFR into the nucleus (57, 59). This process coincides with transport of Ku70/80 and protein phosphatase1 into the nucleus, resulting in increases in DNA-dependent protein kinase activity, repair of DNA-strand breaks (nonhomologous end joining), and cell survival. Activation of EGFR in response to gemcitabine can also result in activation of the survival signal AKT (45). Activating Ras mutations can result in activation of Ras-dependent pathways, such as PI3K/AKT, even in the presence of EGFR inhibitors. EGFR inhibitors prevent gemcitabine and/or radiation-mediated EGFR signaling and are thought to impair cell survival signals and DNA repair. EGFR inhibition blocks nuclear transport of EGFR and DNA-dependent protein kinase activity (59, 97). In some instances, phosphorylation of EGFR by gemcitabine promotes ubiquitination of the receptor leading to degradation along a proteosome/lysosome pathway (62). EGFR degradation results in down-regulation of the survival signal pAKT, leading to apoptosis. Blocking EGFR degradation at various steps of this pathway reduces gemcitabine-mediated cytotoxicity. Whether an EGFR-activating insult leads to cell survival or cell death may ultimately be determined by the severity and duration of the stress. Colored arrows, effects mediated by gemcitabine (red) versus radiation (blue). Dotted lines, less pronounced effects.
Gemcitabine and radiation have been used in combination to treat a variety of solid tumors types including lung, head and neck, cervix, bladder, and breast (for a review see refs. 73, 74). Based on its two distinct mechanisms of action (incorporation into DNA and ribonucleotide reductase inhibition), gemcitabine has been used clinically both as a chemotherapeutic agent and as a radiation sensitizer, effects separable by concentration. For example, early clinical trials in pancreatic cancer investigated low-dose gemcitabine concurrent with standard radiation (50.4 Gy in 1.8-Gy fractions) in patients with locally advanced pancreatic cancer (75) and determined the maximum tolerated dose of gemcitabine to be ~ 40 mg/m² given twice a week. In latter trials, patients treated with 350 to 500 mg/m² gemcitabine weekly and 30 to 33 Gy in 3-Gy fractions (76) experienced unacceptable toxicities (fatigue, anorexia, vomiting, etc.). It has been speculated that the relatively large standard radiation fields including clinically uninvolved regional lymph nodes increased the toxicity of the combination therapy. Our study used a standard chemotherapeutic dose of gemcitabine (1,000 mg/m²), which should maximize systemic control, with dose-escalated three-dimensional conformal radiotherapy administered to the gross disease only, with exclusion of clinically uninvolved regional lymph nodes (77). We found this treatment was tolerable and produced a favorable objective response rate (10 of 33 patients) and median survival (11.6 months). The great majority of the recurrences were systemic, suggesting that the most important need was better systemic therapy. Subsequent preclinical and clinical trials have been carried out adding cisplatin or oxaliplatin to gemcitabine-radiation (4, 5, 78, 79). Unfortunately, neither cisplatin-gemcitabine nor oxaliplatin-gemcitabine significantly prolong survival compared with gemcitabine alone in the treatment of metastatic disease (80, 81), suggesting that these combinations will only modestly improve the treatment of locally advanced, nonmetastatic disease. Likewise, adding capecitabine to gemcitabine marginally improved the survival of patients with metastatic disease in one study (median, 6-7.4 months; ref. 82) but not in another (83).

Therefore, we have turned to integrating targeted agents with gemcitabine-radiation with the goal of improving systemic disease control while maintaining or improving local radiosensitization. This has led us to combine EGFR or Chk1 inhibitors with gemcitabine radiation. Because both preclinical and clinical studies have shown that erlotinib plus gemcitabine is superior to gemcitabine alone, we have initiated studies combining EGFR inhibitors with gemcitabine and radiation. Although clinical trials combining Chk1 inhibitors with gemcitabine are under way, a variety of preclinical models have shown enhanced gemcitabine-mediated radiosensitization as well as cytotoxicity in response to Chk1 inhibitors (Fig. 4). These studies have prompted our ongoing investigation of Chk1 inhibitors in combination with gemcitabine radiation.

**Looking into the future.** One of our current goals in gemcitabine radiation therapy for pancreatic cancer is to integrate a third agent to gemcitabine radiation therapy that improves systemic disease control (cytotoxicity) without reducing local tumor control (radiosensitization). In the previous decade, we have successfully added other standard chemotherapeutic agents (i.e., cisplatin, oxaliplatin) to gemcitabine radiation therapy. However, trials combining agents such as oxaliplatin, cisplatin, irinotecan, and 5-fluorouracil have not significantly improved survival (although capecitabine may). Likewise, targeted therapies such as marimastat (matrix metalloproteinase inhibitor) and tipifarnib (farnesyltransferase inhibitor) with gemcitabine have not produced significant survival improvements over gemcitabine alone (84). Thus, the finding that the addition of erlotinib to gemcitabine produced a significant (yet modest) improvement in survival (0.3 months) compared with gemcitabine alone is of interest (44).

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**Fig. 4.** The effects of Chk1 inhibition on radiation and chemoradiation sensitivity. MiaPaca-2 cells were treated with 30 nmol/L PD-321852 for 24 h preirradiation and postirradiation (0-10 Gy; A) or for 2 h with gemcitabine (50 nmol/L) and then with AZD7762 (100 nmol/L) for 1 h preirradiation and 24 h postirradiation (B). Cells were then plated at cloning densities and grown for 10 d to determine the surviving fraction, which represents the fraction of cells surviving radiation treatment relative to unirradiated controls. Cell survival curves were then fitted using the linear quadratic equation, and the mean inactivation dose was calculated according to the method of Fertil et al. (98). The radiation enhancement ratio was calculated by dividing the mean inactivation dose under control conditions by the mean inactivation dose of Chk1 inhibitor – treated cells.

**Combining Molecularly Targeted Agents with Gemcitabine Radiotherapy in the Clinic**

Gemcitabine and radiation have been used in combination to treat a variety of solid tumors types including lung, head and neck, cervix, bladder, and breast (for a review see refs. 73, 74). Based on its two distinct mechanisms of action (incorporation into DNA and ribonucleotide reductase inhibition), gemcitabine has been used clinically both as a chemotherapeutic agent and as a radiation sensitizer, effects separable by concentration. For example, early clinical trials in pancreatic cancer investigated low-dose gemcitabine concurrent with standard radiation (50.4 Gy in 1.8-Gy fractions) in patients with locally advanced pancreatic cancer (75) and determined the maximum tolerated dose of gemcitabine to be ~ 40 mg/m² given twice a week. In latter trials, patients treated with 350 to 500 mg/m² gemcitabine weekly and 30 to 33 Gy in 3-Gy fractions (76) experienced unacceptable toxicities (fatigue, anorexia, vomiting, etc.). It has been speculated that the relatively large standard radiation fields including clinically uninvolved regional lymph nodes increased the toxicity of the combination therapy. Our study used a standard chemotherapeutic dose of gemcitabine (1,000 mg/m²), which should maximize systemic control, with dose-escalated three-dimensional conformal radiotherapy administered to the gross disease only, with exclusion of clinically uninvolved regional lymph nodes (77). We found this treatment was tolerable and produced a favorable objective response rate (10 of 33 patients) and median survival (11.6 months). The great majority of the recurrences were systemic, suggesting that the most important need was better systemic therapy. Subsequent preclinical and clinical trials have been carried out adding cisplatin or oxaliplatin to gemcitabine-radiation (4, 5, 78, 79). Unfortunately, neither cisplatin-gemcitabine nor oxaliplatin-gemcitabine significantly prolong survival compared with gemcitabine alone in the treatment of metastatic disease (80, 81), suggesting that these combinations will only modestly improve the treatment of locally advanced, nonmetastatic disease. Likewise, adding capecitabine to gemcitabine marginally improved the survival of patients with metastatic disease in one study (median, 6-7.4 months; ref. 82) but not in another (83).

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How can laboratory studies help us improve on these results? One obvious strategy is better patient selection. For example, it is conceivable that the efficacy of the combination of gemcitabine with EGFR inhibitors could be improved upon by identifying populations of patients most sensitive to EGFR inhibition, such as those who lack Ras activation (70–72) or who develop a rash in response to EGFR inhibitor therapy (85). Another approach to improve the clinical efficacy of molecularly targeted agents in combination with gemcitabine or gemcitabine radiation is through preclinical determination of the optimal response of gemcitabine, radiation and a molecular targeted agent. For instance, in the aforementioned clinical trial, EGFR inhibitor was given concurrently with gemcitabine and produced a modest survival advantage. It seems possible that survival might have been improved if the most effective preclinical schedule (gemcitabine before EGFR inhibitor) had been used. Other targets, such as Chk1, need to be explored in combination with gemcitabine radiation therapy. The use of better preclinical models such as tumor xenografts derived from primary human tumors will be crucial to translate results directly to the clinic. In addition, the effects of therapy combinations on tumor stem cells versus gross tumor (86) may provide insight into potential therapeutic efficacy. This decade will focus on preclinical studies in the best available model systems, combining molecularly targeted therapies with gemcitabine radiation with the goal of producing better patient responses.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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