Expert Opinion on Investigational Drugs

ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: informahealthcare.com/journals/ieid20

Nucleoside and nucleobase analogs in cancer treatment: not only sapacitabine, but also gemcitabine

Franco Muggia, Isabela Diaz & Godefridus J Peters

To cite this article: Franco Muggia, Isabela Diaz & Godefridus J Peters (2012) Nucleoside and nucleobase analogs in cancer treatment: not only sapacitabine, but also gemcitabine, Expert Opinion on Investigational Drugs, 21:4, 403-408, DOI: 10.1517/13543784.2012.666236

To link to this article: https://doi.org/10.1517/13543784.2012.666236

EXPERT OPINION

Nucleoside and nucleobase analogs in cancer treatment: not only sapacitabine, but also gemcitabine

Franco Muggia†, Isabela Diaz & Godefridus J Peters
†*NYU Langone Medical Center, NY, USA*

Nucleoside analogs are widely used for treatment of various malignancies. Benchmark drugs are cytarabine for acute myeloid leukemia and gemcitabine for pancreatic and lung cancer. Sapacitabine is a novel cytidine analog currently in development. This editorial focuses on the potential of new nucleoside analogs and on novel possibilities of gemcitabine. Gemcitabine is a nucleoside analog with many faces, which shows a remarkable activity in a variety of cancers, most likely because it has a unique metabolism, a so-called self-potentiation. Gemcitabine is taken up by nucleoside transporters, is activated by deoxycytidine kinase and incorporated into both RNA and DNA. Inhibition of ribonucleotide reductase and dCMP deaminase enhances its activation, while cytidine deaminase converts gemcitabine to its presumably inactive metabolite 2′,2′-difluorodeoxyuridine, which in its nucleotide form may inhibit thymidylate synthase. Gemcitabine is widely used in combination, predominantly with a platinum analog, with other combinations less frequently used or being explored. Standard administration of gemcitabine is with a 30-min weekly infusion at 1000 mg/m^2, but alternatives are being explored such as prodrugs (e.g., CO-1.01, which can bypass transport deficiency), the fixed-dose rate infusion (10 mg/m^2/min), and local routes of administration by a 24-h hepatic artery infusion, by instillation in the bladder or by intraperitoneal administration to treat advanced ovarian cancer. Other alternatives for combinations of gemcitabine in ovarian cancer consist of increasing the inhibition of ribonucleotide reductase with triapine or hydroxyurea. Gemcitabine's action on signaling also provides a rational concept for combination with signal transduction pathways.

Keywords: cancer, nucleoside, nucleoside base analogs, sapacitabine

Expert Opin. Investig. Drugs (2012) ***21****(4):403-408*

The article 'Sapacitabine for cancer' serves as a reminder that much remains to be learned about this class of agents. Their tabular description of 'Diversity of mechanisms of action and clinical activities of nucleoside and nucleoside base analogs' represents a wake-up call. Not only do we have incomplete information on the mechanism of action for many of these drugs, but most remarkable is the diversity of mechanisms and disease targets. Moreover, this listing must be regarded as incomplete, considering mechanisms of action and disease types. For example, several oral prodrugs such as capecitabine, UFT and S-1 have a different activity profile [1], while 5-fluoro-2′-deoxyuridine because of both pharmacologic and pharmacodynamic (PD) reasons seems to have selective activity via hepatic artery infusion (HAI) [2]. Furthermore, depending on dose-scheduling and other unknown factors, the extent of the RNA incorporation varies with unclear implication on drug effects. While studies overwhelmingly supports that

informa
healthcare

10.1517/13543784.2012.666236 © 2012 Informa UK, Ltd. ISSN 1354-3784

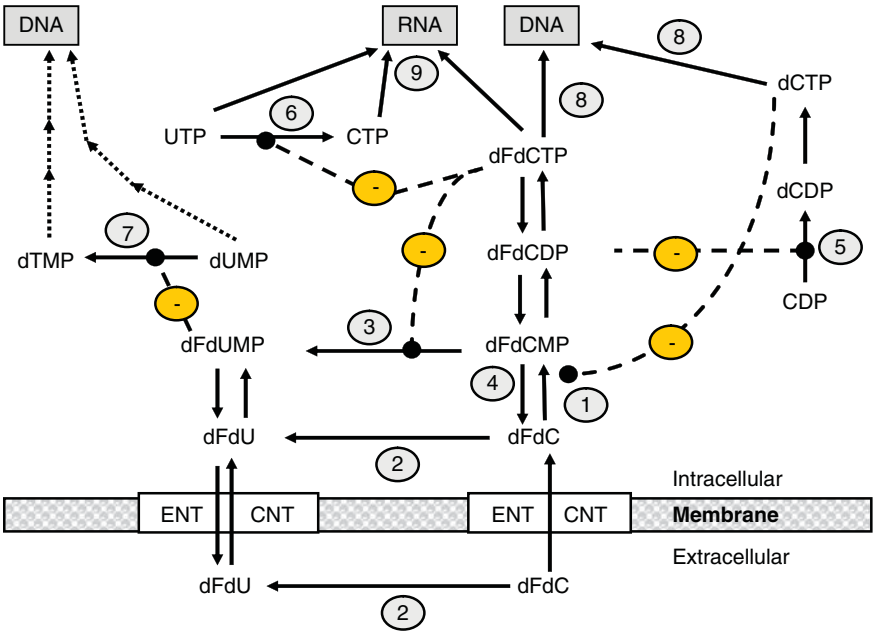

Figure 1. Self-potentiation of gemcitabine. hNTs (hENT and hCNT) transports dFdC into the cell. dFdC is intracellularly phosphorylated by dCK to its monophosphate dFdCMP [1] and subsequently into its active dFdCDP and dFdCTP metabolites by ribonucleotide mono- and diphosphate kinases, respectively. DNA polymerase (8) catalyzes the incorporation of dFdCTP into DNA, competing with dCTP. dFdCDP inhibits RNR (5), which inhibits the conversion of dinucleotides to deoxynucleotides, including CDP to dCDP and inhibits synthesis of dCTP. The feedback inhibition of dCK by dCTP is reduced, leading to an increase in the phosphorylation of dFdCTP. This will elevate the intracellular dFdCTP/dCTP ratio and enhance incorporation of dFdCTP into DNA.CDA deaminates dFdC to dFdU (2), which can occur in and outside the cell. dFdCMP can be dephosphorylated to dFdC by 5′-NT (4) and be deaminated to dFdUMP by dCMPD (3). dFdCTP can inhibit dCMPD, which stimulates its own formation. dFdCMP can also inhibit CTP synthetase (6) leading to a reduction in CTP, which has a dual effect, less competition of CTP with dFdCTP for incorporation into RNA (9), while the decrease in CTP will also decrease CDP, leading to an additional decrease in the reduction to dCDP. Finally, the deaminated product dFddUMP can inhibit thymidylate synthase (7), which will decrease dTTP pools but increase dUTP pools, leading to additional DNA damage. dFdUMP can also be formed from intra- and extracellularly produced dFdU, which can be taken up by hNTs, and subsequently phosphorylated to dFdUMP. This phosphorylation may be catalyzed by dCK, since dCK-deficient cells are also resistant to dFdU. However, dFdU is also a substrate for the mitochondrial thymidine kinase 2.

CDP: Cytidine diphosphate; dCDP: Deoxycytidine diphosphate; dCK: Deoxycytidine kinase; dCMPD: Deoxycytidylate deaminase; dCTP: Deoxycytidine triphosphate; dFdC: 2′,2′-difluorodeoxycytidine; dFdCDP: DFdC diphosphate; dFdCMP: DFdC monophosphate; dFdCTP: DFdC triphosphate; dFdU: 2′,2′-difluorodeoxyuridine; dFdUMP: 2′,2′-difluorodeoxyuridine monophosphate; hNTs: Human nucleoside transporters; RR: Ribonucleotide reductase.

the incorporation of 5-fluorouracil (5-FU) into RNA is associated with toxicity [3], the impact of gemcitabine incorporation into RNA is unknown [4]. To add to the complexity of factors influencing specific drug actions, prodrugs of cytarabine and gemcitabine, CP-4055 and CP-4126 (now CO-1.01), respectively, may bypass transport and seem sequestered in intracellular organelles [5]. Finally, a nucleoside–alkylating moiety complex, bendamustine, after years of clinical development, has recently emerged as a drug with a very favorable therapeutic index against many lymphoid malignancies. What this 'rediscovery' tells us, is that drug developers have neglected this area for some time. This Editorial expands on some newer aspects of gemcitabine's development, to encourage further research on antimetabolites for solid tumors and not confined to sapacitabine.

Gemcitabine's mechanism of action in the Expert Opinion paper is listed as causing inhibition of ribonucleotide reductase (RNR) and DNA replication. This list is incomplete: although many antimetabolites have multiple mechanisms of action, gemcitabine has a unique mode of self-potentiation. Its uptake via the equilibrative nucleoside transporters (ENT1-4), the role of activation by deoxycytidine kinase (dCK) and inactivation via dCMP deaminase (dCMPD) play a key role in this self-potentiation (**Figure 1**) [6-8], which is possibly responsible for the enhanced selectivity of gemcitabine by preferential intracellular retention and accumulation of its di- and triphosphates in solid tumor cell lines and tumor samples [9]. The self-potentiation occurs as follows: after phosphorylation dFdCTP competes with the natural substrate,

dCTP, to be incorporated into DNA while dFdCDP inhibits RNR, the enzyme responsible for producing the four key deoxynucleotides required for DNA synthesis and repair, leading to blockade of these cellular functions [7]. Moreover, the diminished dCTP level does not exert its feedback inhibition on dCK, with the consequent increase of gemcitabine phosphorylation. Also, since dFdCTP negatively regulates dCMPD, dFdCMP is not only not deaminated but is further phosphorylated contributing to enhance dFdCTP and dFdCDP concentrations.

Moreover, dFdCTP is also an inhibitor of CTP synthetase, thus decreasing CTP synthesis as well, which will further deplete dCTP and as a consequence more dFdCTP will be incorporated into DNA. Furthermore, in contrast to other deoxynucleoside analogs, the presence of two fluorine atoms in the sugar apparently gives gemcitabine some ribonucleoside properties enabling its incorporation into RNA, which is further enhanced by CTP depletion [10,11]. Finally, intracellular formation of dFdUMP has been demonstrated by several groups [6,12]; dFdUMP can inhibit thymidylate synthase [4]. The implication of this finding is not clear, but this phenomenon leads to an increase in dUTP synthesis which may be misincorporated into DNA, adding to the DNA damage already caused by dFdCTP incorporation [12]. Plunkett's group demonstrated that dFdCTP incorporation led to a so-called 'masked chain termination', which means that after incorporation into DNA, one more deoxynucleotide may be incorporated [13]. However, in cellular systems, incorporation into DNA seems to continue over a prolonged period [10]. The dFdCTP incorporation into DNA and the deoxynucleotide depletion seem important features in the interaction with other drugs, such as cisplatin, since this decreases DNA repair enhancing the cisplatin effect [14]. Furthermore, these features also lead to decreased repair of radiation-induced damage, making gemcitabine one of the most potent radiosensitizers studied clinically [15].

Mechanistic considerations have not been sufficiently utilized in the clinical development of gemcitabine. In the 1990s, Plunkett and clinical co-workers at MD Anderson worked out relevant PD parameters of gemcitabine activation in leukemia patients leading to testing the 'fixed-dose-rate' (i.e., 10 mg/m^2/min) administration of its most 'tumor-selective' weekly schedule. With a dose of 1500 mg/m^2 this led to an infusion of 150 min, during which dFdCTP continued to accumulate in lymphocytes (as a surrogate tissue) with a twofold higher C_{max} compared with the 30-min schedule [16]. While initial clinical studies supported this hypothesis in patients with pancreatic cancer [16] and uterine sarcoma [17], a subsequent larger Phase III study in pancreatic cancer failed to meet its end point [18]. Nevertheless, an extensive PD study of these two schedules supports that a 'carryover-effect' of one dose to the subsequent one is stronger when the fixed dose rate is utilized [19]. With the standard 30-min weekly infusion no carryover of plasma gemcitabine or lymphocyte dFdCTP was observed, although dFdU was still present in the low µM range after 1 week [20]. Based on the cell-cycle properties of gemcitabine and experience with other antimetabolites it can be argued whether this infusion was long enough. In an animal study, the most efficacious schedule was a weekly 24-h infusion [21]. This was further investigated in order to determine whether gemcitabine would be a suitable agent for therapy of localized hepatic disease. Gemcitabine given as HAI was well tolerated [22]. At the recommended Phase II dose of 135 mg/m^2, the hepatic extraction rate was 0.75 which is comparable with that of 5-fluoro-2′-deoxyuridine; plasma levels at i.v. administration were 263 nM compared with 80 nM at HAI. This study underlines the potential of gemcitabine for localized treatment, not only as HAI, but also for bladder instillation or intraperitoneal infusions. Since gemcitabine is active in advanced bladder cancer (with cisplatin), a bladder instillation for localized treatment is a logical step and the first clinical studies clearly demonstrated the feasibility [23]. During bladder instillation no systemic gemcitabine or its metabolite dFdU were measured. Another form of localized treatment is intraperitoneal administration, which has been studied in Phase I trials for gemcitabine as a single agent in patients who had chemotherapeutically unresponsive malignancies [24] or in combination with cisplatin [25] in patients with microscopic or macroscopic disease after initial surgical cytoreduction and adjuvant platinum-based chemotherapy. The mean peritoneal advantages (AUC-ip/AUC-plasma) were 847 and 759, respectively, confirming an increase in local dose intensity with acceptable side effects. Hence, these studies demonstrate that using appropriate pharmacokinetics (PK) and PD gemcitabine administration can further be optimized, possibly with disease-specific adjustments, based on pharmacogenetic (PG) features. An example of relevant new PG information includes the prolonged progression-free survival (PFS) of pancreatic cancer associated with a low miR-21 expression, which regulates the PI3K pathway [26]. However, miR-21 does not seem to play the same role in lung cancer [27]. Another example includes decreased cytidine deaminase activity (CDA), which increases toxicity [28]. An integrated PK/PD/PG approach may improve current therapeutic expectations, especially when the drug is used to treat more sensitive tumors such as ovarian cancer.

Recurrent ovarian cancer is a major target of gemcitabine treatment, whether given by itself in platinum-resistant disease or in combination with carboplatin in the platinum-sensitive population. More recently, a Phase III placebo-controlled study sponsored by Genentech, (OCEANS, Dic, South San Francisco, CA, USA) [29] documented a hazard ratio (HR) of 0.48 (95% confidence interval 0.39 – 61) for gemcitabine + carboplatin + bevacizumab relative to the cytotoxic doublet + placebo, and this HR compares favorably with other control or experimental regimens (**Table 1**). It is unfortunate that there has been little follow-up using PG to improve the PD of gemcitabine in these combinations, or suggestions that platinums given together with gemcitabine alter its PD [36] or alter platinum resistance [37]. Future studies should aim to bypass potential resistance mechanisms to gemcitabine, which consists

Table 1. Outcome in patients with platinum-sensitive ovarian cancer recurrence.

Eligibility (months)	Control regimen	Patient number	Comparator	Comments outcome (months)
Platinum sensitive (> 6) [30]	Carboplatin + epirubicin	190	Carboplatin	Powered for response differences; OS 17 vs 15
Platinum sensitive (≥ 12) [31]	Cisplatin + doxorubicin + cyclophosphamide	97	Paclitaxel	PFS 15.7 vs 9; OS 34.7 vs 25.8
Platinum sensitive (> 6) [32]	Carboplatin + gemcitabine	356	Carboplatin	PFS 8.6 vs 5.8; OS 18 vs 17
Platinum sensitive [29]	Carboplatin + gemcitabine + placebo	484	Carboplatin + gemcitabine + bevacizumab	HR PFS: 0.48 (95% CI 39.0 – 61.9%, p < 0.0001)
Platinum sensitive (> 6) [33]	Cisplatin or carboplatin + paclitaxel	802	Single or non-taxane + platinums	PFS 11 vs 9; OS 24 vs 19
Platinum sensitive (> 6) [34]	Carboplatin + PLD	976	Carboplatin + paclitaxel	Median PFS 11.3 vs 9.4; median OS not assessed
Platinum partially sensitive (> 6 & < 12) [35]	PLD	672	Trabectedin + PLD	Subset analysis

Adapted from PDQ.

CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; PLD: Pegylated liposomal doxorubicin.

predominantly of impaired uptake, decreased activation, increased inactivation by CDA or increased RNR [4,28]. The novel gemcitabine prodrug CO-1.01, with an elaidic acid attached to the 5′-carboxy position, has shown similar activity in cells with inhibited transporter function and also showed oral activity against xenografts [1]. CP-4126 seems sequestered in cell lines leading to a longer intracellular retention and enhanced formation and retention of dFdCTP [5], hence bypassing multiple resistance parameters. In advanced pancreatic cancer the drug is currently compared with gemcitabine, using companion diagnostics for ENT. A similar prodrug for ara-C, CP-4055 [38] has recently shown activity in acute myeloid leukemia (AML) independent of the ENT expression [39].

Since RNR overexpression is a potential resistance mechanism, RNR inhibition is an attractive way to enhance gemcitabine activity, which should be exploited further in the clinic. A sequence-dependent interaction between the RNR inhibitor triapine [40] or hydroxyurea [41] and gemcitabine has been demonstrated and linked to a transient lowering of dCTP pools favoring dFdCTP formation and its incorporation into DNA [40]. Clinical studies of such PD-based doublet (either triapine or hydroxyurea) did not advance beyond Phase I [42]. We have added pretreatment with hydroxyurea in some gemcitabine-responding patients to extend waning responses (reflected by rises in their tumor markers) in patients with ovarian cancer, clinically obvious evidence of modulation ensued (such as sudden development of total alopecia and in some instances marker improvements; ([43] and I Diaz, unpublished). Unfortunately, a randomized Phase II study of hydroxyurea → gemcitabine versus gemcitabine alone in platinum-resistant recurrences of ovarian cancer is difficult to realize in the current investigator-initiated clinical trials environment that is focused exclusively on 'novel targets'. Hopefully, knowledge of signaling pathways will also further enhance gemcitabine's activity when this agent is combined with some tyrosine and/or serine–threonine kinases inhibitors [44].

Taken within this broad context, the renewed interest generated by sapacitabine may catalyze additional questions in these neglected areas of therapeutic research. Nucleoside analogs, in particular gemcitabine, are likely to be more active when the administration route is changed, while its action on signaling provides a rational concept for combination with anti-signaling targeted drugs.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

1. Adema AD, Bijnsdorp IV, Sandvold ML, et al. Innovations and opportunities to improve conventional (deoxy)nucleoside and fluoropyrimidine analogs in cancer. Curr Med Chem 2009;16:4632-43
2. Cohen AD, Kemeny NE. An update on hepatic arterial infusion chemotherapy for colorectal cancer. Oncologist 2003;8:553-66
3. Peters GJ, Backus HHJ, Freemantle S, et al. Induction of thymidylate synthase as a 5-fluorouracil resistance mechanism. Biochim Biophys Acta 2002;1587:194-205
4. Bergman AM, Pinedo HM, Peters GJ. Determinants of resistance to 2',2'-difluorodeoxycytidine (gemcitabine). Drug Resist Updat 2002;5:19-33
5. Adema AD, Losekoot N, Smid K, et al. Differential metabolism and accumulation of the lipophilic deoxynucleoside analogs elacytarabine and CP-4126. Invest New Drugs 2011; In press
6. Heinemann V, Hertel LW, Grindey GB, Plunkett W. Comparison of the cellular pharmacokinetics and toxicity of 2',2'-difluorodeoxycytidine and 1-beta-D-arabinofuranosylcytosine. Cancer Res 1988;48:4024-31
7. Heinemann V, Xu YZ, Chubb S, et al. Inhibition of ribonucleotide reduction in CCRF-CEM cells by 2',2'-difluorodeoxycytidine. Mol Pharmacol 1990;38:567-72
8. Mackey JR, Mani RS, Selner M, et al. Functional nucleoside transporters are required for gemcitabine influx and manifestation of toxicity in cancer cell lines. Cancer Res 1998;58:4349-57
9. Heinemann V, Xu YZ, Chubb S, et al. Cellular elimination of 2',2'-difluorodeoxycytidine 5'-triphosphate: a mechanism of self-potentiation. Cancer Res 1992;52:533-9
10. Ruiz van Haperen V, Veerman G, Vermorken JB, Peters GJ. 2',2'-Difluorodeoxycytidine (gemcitabine) incorporation into RNA and DNA of tumour cell lines. Biochem Pharmacol 1993;46:762-6
11. Ruiz van Haperen VW, Veerman G, Boven E, et al. Schedule dependence of sensitivity to 2',2'-difluorodeoxycytidine (gemcitabine) in relation to accumulation and retention of its triphosphate in solid tumour cell lines and solid tumours. Biochem Pharmacol 1994;48:1327-39
12. Honeywell R, Giovannetti E, Peters GJ. Determination of the phosphorylated metabolites of gemcitabine and of difluorodeoxyuridine by LCMSMS. Nucleosides Nucleotides Nucleic Acids 2011;30:1203-13
13. Huang P, Chubb S, Hertel LW, et al. Action of 2',2'-difluorodeoxycytidine on DNA synthesis. Cancer Res 1991;51:6110-17
14. Peters GJ, Van Moorsel CJ, Lakerveld B, et al. Effects of gemcitabine on cis-platinum-DNA adduct formation and repair in a panel of gemcitabine and cisplatin-sensitive or -resistant human ovarian cancer cell lines. Int J Oncol 2006;28:237-44
15. Pauwels B, Korst AE, Lardon F, Vermorken JB. Combined modality therapy of gemcitabine and radiation. Oncologist 2005;10:34-51
16. Tempero M, Plunkett W, Ruiz van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 2003;21:3402-8
17. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol 2008; 109(3):329-34
18. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27:3778-85
19. Grimison P, Galletis P, Manners S, et al. Randomized crossover study evaluating the effect of gemcitabine infusion dose rate: evidence of auto-induction of gemcitabine accumulation. J Clin Oncol 2007;36:5704-9
20. De Lange SM, Van der Born K, Kroep JR, et al. No evidence of gemcitabine accumulation during weekly administration. Eur J Clin Pharmacol 2005;61:843-9
21. Veerman G, Ruiz van Haperen VWT, Vermorken JB, et al. Antitumor activity of prolonged as compared with bolus administration of 2',2'-difluorodeoxycytidine in vivo against murine colon tumors. Cancer Chemother Pharmacol 1996;38:335-42
22. van Riel JM, Peters GJ, Mammatas LH, et al. A phase I and pharmacokinetic study of gemcitabine given by 24-h hepatic arterial infusion. Eur J Cancer 2009;45:2519-27
23. Witjes JA, Van der Heijden AG, Vriesema JLJ, et al. Intravesical gemcitabine: a phase 1 and pharmacokinetic study. Eur Urol 2004;45:182-6
24. Morgan RJ Jr, Synold TW, Xi B, et al. Phase I trial of intraperitoneal gemcitabine in the treatment of advanced malignancies primarily confined to the peritoneal cavity. Clin Cancer Res 2007;13:1232-7
25. Sabbatini P, Aghajanian C, Leitao M, et al. Intraperitoneal cisplatin with intraperitoneal gemcitabine in patients with epithelial ovarian cancer: results of a phase I/II trial. Clin Cancer Res 2004;10:2962-7
26. Giovannetti E, Funel N, Peters GJ, et al. MicroRNA-21 in pancreatic cancer: correlation with clinical outcome and pharmacological aspects underlying its role in the modulation of gemcitabine activity. Cancer Res 2010;70:4528-38
27. Voortman J, Goto A, Mendiboure J, et al. Small cell lung carcinoma - resection of non treated with adjuvant chemotherapy after complete MicroRNA. Cancer Res 2010;70:8288-98
28. Ciccolini J, Mercier C, Dahan L, Andre N. Integrating pharmacogenetics into gemcitabine dosing-time for a change? Nat Rev Clin Oncol 2011;8:439-44
29. Aghajanian C, Finkler NJ, Rutherford T, et al. OCEANS: a randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with

platinum-sensitive recurrent epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC). J Clin Oncol 2011;29:abstract LBA5007

30. Bolis G, Scarfone G, Giardina G, et al. Carboplatin alone vs carboplatin plus epidoxorubicin as second-line therapy for cisplatin- or carboplatin-sensitive ovarian cancer. Gynecol Oncol 2001;81:3-9

31. Cantu MG, Buda A, Parma G, et al. Randomized controlled trial of single-agent paclitaxel versus cyclophosphamide, doxorubicin, and cisplatin in patients with recurrent ovarian cancer who responded to first-line platinum-based regimens. J Clin Oncol 2002;20(5):1232-7

32. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24(29):4699-707

33. Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003;361(9375):2099-106

34. Pujade-Lauraine E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 2010;28(20):3323-9

35. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010;28(19):3107-14

36. van Moorsel CJ, Kroep JR, Pinedo HM, et al. Pharmacokinetic schedule finding study of the combination of gemcitabine and cisplatin in patients with solid tumors. Ann Oncol 1999;10:441-8

37. Nagourney RA, Brewer CA, Radecki S, et al. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. Gynecol Oncol 2003;88(1):35-9

38. Bergman AM, Kuiper CM, Voorn DA, et al. Antiproliferative activity and mechanism of action of fatty acid derivatives of arabinofuranosylcytosine in leukemia and solid tumor cell lines. Biochem Pharmacol 2004;67:503-11

39. Rizzieri D, Vey N, Schlenck N, et al. A phase II study of elacytarabine/idarubicin as second course remission-induction in patients with acute myeloid leukemia who failed cytarabine/anthracycline, and evaluation of the impact of the nucleoside transporter hENT1 on response. Blood Proc ASH 2011;abstract #42825

40. Sigmond J, Kamphuis JA, Laan AC, et al. The synergistic interaction of gemcitabine and cytosine arabinoside with the ribonucleotide reductase inhibitor triapine is schedule dependent. Biochem Pharmacol 2007;73:1548-57

41. Yen Y, Chow W, Leong L, et al. Phase I pharmacodynamic study of time and sequence dependency of hydroxyurea in combination with gemcitabine: a California Cancer Consortium Trial. Cancer Chemother Pharmacol 2002;50(5):353-9

42. Traynor AM, Lee JW, Bayer GK, et al. A phase II trial of triapine (NSC# 663249) and gemcitabine as second line treatment of advanced non-small cell lung cancer: eastern Cooperative Oncology Group Study 1503. Invest New Drugs 2010;28:91-7

43. Muggia FM, Hazarika M. Ovarian cancer: rationale and strategies beyond first-line treatment. In: Angioli R, Kavanagh JJ, Pecorelli S, Penalver M, editors. Chemotherapy for Gynecological Neoplasms: Current Therapy and Novel Approaches. Marcel Dekker; New York: 2004. p. 471-82

44. Arlt A, Gehrz A, Muerkoster S, et al. Role of NF-kappaB and Akt/P13K in the resistance of pancreatic carcinoma cell lines against gemcitabine-induced cell death. Oncogene 2003;22:3243-51

Affiliation

Franco Muggia[†1], Isabela Diaz[2] & Godefridus J Peters[3]
[†]Author for correspondence
[1]NYU Langone Medical Center, NY, USA
E-mail: franco.muggia@nyumc.org
[2]Galdakao-Usánsolo Hospital, Department of Medical Oncology, Basque Country
[3]VU University Medical Center, Veotry Medical Center, Department of Medical Oncology, PO Box 7057, 1007 MB Amsterdam, The Netherlands