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Strategic Perspectives on Improved Anti-Tumor Drug Effects in Combination with Clinically Equivalent or Lower Concentrations of Epigenetic Modifiers, DNA Methyltransferase Inhibitors, and Histone Deacetylase Inhibitors

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Abstract

The aim of this research is to facilitate the pursuit of improved chemotherapeutic drugs in combination with epigenetic modifiers. Both *in vitro* studies and a clinical study have described the combinations of DNA methyltransferase inhibitors with irinotecan and histone deacetylase inhibitors with 5-fluorouracil or gemcitabine to enhance their anti-cancer activities. The molecular mechanisms involved in the potentiation of anti-tumor activities were apoptosis regulation, cellular metabolism, DNA topoisomerase-I upregulation, cell-cell adhesion, regulation of transcription (DNA-templated), DNA repair, and the PI3K/AKT signaling pathway. More importantly, the priming effects and long-lasting effects induced by DNA methyltransferase inhibitors, when applied as a pretreatment, sensitized cancer cells to subsequent anti-cancer drug treatments. The combinations of 5-fluorouracil and gemcitabine with histone deacetylase inhibitors (depsipeptide and valproic acid, respectively), increased the expression of major histocompatibility complex class II, which may warrant further investigation for possible accurate biomarkers and therapeutic targets. As valproic acid downregulated histone deacetylase in patients recruited in a clinical phase I/II study, the activity of valproic acid may be associated with the enhanced anti-tumor activity in combination with 5-fluorouracil. This research provides a positive perspective on the combination therapy of anti-cancer drugs with epigenetic modifiers.

Keywords: DNA Methyltransferase inhibitor; 5-aza-2′-deoxycytidine; Histone deacetylase inhibitor; Depsipeptide; Valproic acid; Irinotecan; 5-fluorouracil; Human colon cancer cell lines.

Abbreviations: CPT-11: Irinotecan; CRC: Colorectal Cancer; DAC: 5-aza-2′-deoxycytidine; 5-Aza-C: 5-azacytidine; DNMT: DNA Methyltransferase; SN-38: 7-ethyl-10-hydroxycamptothecin; HDAC: Histone Deacetylase

Introduction

As reported by the World Health Organization, cancer is a leading cause of death and accounted for 8.8 million deaths worldwide in 2015; among these, 0.77 million deaths were attributed to colorectal cancer [1]. The current first-line treatments for metastatic CRC include the following cytotoxic combinations: 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI); 5-FU, leucovorin, and oxaliplatin by infusion (FOLFOX); capecitabine and oxaliplatin (XELOX); and 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) [2]. Our research group studies the genetically determined individual differences in the capacities of drug metabolism and disposition, with a focus on anti-cancer drugs [3]. There are two classes of drug metabolizing enzymes: phase I enzymes, such as cytochrome P450 (CYP), which catalyze the oxidation of various drugs and phase II enzymes, including a number of conjugation enzymes, which catalyze the conjugation reactions of drugs with various endogenous substrates to inactivate or detoxify drugs, including UDP-glucuronosyltransferase (UGT) and sulfotransferases. In an irinotecan pharmacogenetic study of 195 Japanese patients with cancer with different UGT1A1 alleles, the subjects without any known variant alleles showed the widest variation in blood SN-38 glucuronide/SN-38 ratios (and index of UGT1A1 metabolic capacity) [4]. This may indicate that the individual variability in the drug metabolism and disposition capacities involved individual difference in the epigenetic regulatory mechanisms. From the perspective of molecular mechanisms in cancer development, genetic alterations, together with epigenetic alterations, are important molecular events in which malignant cells acquire higher grade malignancy. Local hypermethylation of CpG islands in the promoter region of tumor suppressor genes make them transcriptionally inactive. Epigenetic modifiers, histone deacetylase (HDAC) inhibitors, and DNA methyltransferase (DNMT) inhibitors are used for their intrinsic anti-cancer activities to re-activate tumor suppressor genes. Another application of epigenetic modifiers is their combined use with existing anti-cancer agents. With regard to the epigenetic regulation of drug metabolism, we have reported epigenetically silenced genes through promoter methylations and their re-activation by the application of the DNMT inhibitor, 5-aza-2′-deoxycytidine (DAC). Habano et al. reported the re-activation of CYP1B1 [5] and pregnane X receptor (PXR) [6] by DAC in human CRC lines (SW48, Caco-2, HT29, HCT116, LS180, and LoVo). The epigenetics of genes that encode phase II drug metabolizing enzymes have been investigated. Among them, the epigenetically silencing of the UDP-glucuronosyltransferase gene (UGT1A1) in human CRC cells through promoter methylation was demethylated by DAC treatment

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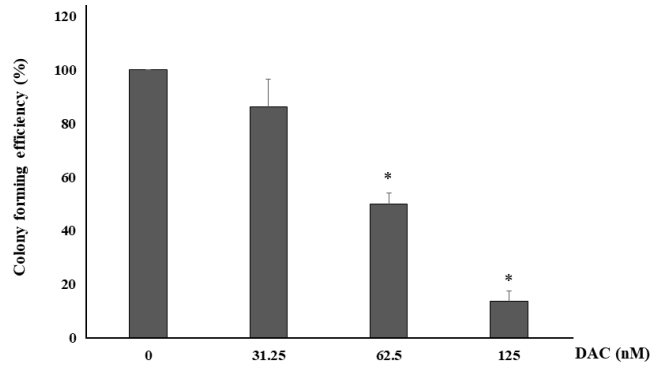
and re-activated; thus, UGT1A1 expressed levels were markedly increased in HCT116 (UGT1A1-promoter methylated), but not HT29 (UGT1A1-promoter unmethylated) cells [7]. These results led us to speculate that DNA methyltransferase inhibitors may render cancer cells resistant to anti-cancer agents through the demethylation of hypermethylated UGT1A1 promoter regions. In order to demethylate the promoter regions of CYP1B1 and PXR, human CRC cells were exposed to DAC (0.5 μM or 5 μM) for up to 24 h. In the case of UGT1A1, the DAC treatment was 5 μM for 72 h. We attempted to evaluate the changes in the chemosensitivity of HCT116 cells and other human CRC cells in response to irinotecan and its active metabolite, SN-38, by the co-administration of DAC. We found that 0.5 μM DAC was too cytotoxic to allow the evaluation of cell viability by colony forming ability (generally, a 10-day culture period). We tested lower concentrations of DAC and found that 31.25 nM DAC showed low cytotoxicity (Figure 1). This DAC concentration was at least 10-fold lower than the clinically achieved plasma concentrations (approximately 360 nM to 660 nM) in a phase I clinical trial study (1 h infusion of 45 mg/m^2) when used in combination with carboplatin in solid tumors in a study conducted in the United Kingdom [8] and a phase I/II study of DAC (1 h infusion of 15 mg/m^2 to 20 mg/m^2) in patients with myelodysplastic syndrome in a study conducted in Japan [9]. Although lower cytotoxicity and a much lower concentration was obtained in comparison with clinically achieved plasma concentrations, this concentration of DAC potentiated the anti-tumor activities of irinotecan (91% colony forming ability relative to control at 62.5 nM irinotecan without DAC and 74% in the presence of a low concentration of DAC, $p<0.05$, unpublished) and SN-38 (57% at 0.7 nM SN-38 without DAC and 36% with the in the presence of a low cytotoxic of DAC, $p<0.05$, unpublished). We also examined the possible enhancement of the anti-tumor activity of 5-FU by DAC and other HDAC inhibitors. Depsipeptide (1 nM; Dep, romidepsin, or ISTODAX), which was 700-fold lower than the clinical Cmax and 7-fold lower than the clinical Cmin after a 4 h infusion of 14 mg/m^2 (ISTODAX (romidepsin) Label-US FDA) [10], potentiated the anti-tumor effect of 5-FU (1.75 μM). A single dep treatment reduced the colony forming ability of HCT116 cells by approximately 50%, whereas 1 nM Dep plus 1.75 μM 5-FU further reduced the colony forming ability to 30% ($p<0.05$) [11]. These results prompted us to examine whether preclinical studies on the combination therapy of epigenetic modifiers with existing anti-cancer agents required relatively lower concentrations of DNMT inhibitors and HDAC inhibitors. We were also prompted to draw conclusions as to whether low concentrations of epigenetic modifiers were clinically significant for development of good combination therapies with existing anti-cancer agents. In the present research, we review a considerable number of studies on these preclinical combination studies and discuss the significance of combination therapies of epigenetic modifiers and existing anti-cancer agents, especially irinotecan and 5-FU.



* indicates a significantly lower colony forming efficiency than the control: $p<0.05$ (Student's *t*-test).

Figure 1: Effect of various concentrations of DAC on the colony forming efficiency in the human colon cancer cell line HCT116. The cells were cultured for 10 days. The data are expressed as the mean ± standard deviation.

Materials and Methods

Cell lines and culture conditions

The human colon carcinoma cell line HCT116 (No. CCL-247) was obtained from DS Pharma Biomedical, Ltd (Osaka, Japan). The cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Hyclone, South Logan, VT, USA) and 1% antibiotic-antimycotic (Gibco) at 37°C in a 5% CO_2 incubator.

Reagents

5-Aza-2′-deoxycytidine (DAC) was obtained from Sigma-Aldrich (St. Louis, MO, USA) and dissolved in milli-Q water.

Drug exposure and colony forming assay

Were plated at density of 20,000 cells per 60 mm dish. After incubation with DAC for 10 days, the colonies were stained by 0.04% crystal violet and counted. The colonies were only scored if they contained more than 50 cells. The DAC concentrations used for the colony forming assay were 31.25 nM, 62.5 nM, and 125 nM. HCT116 cells.

Combination with DNMT inhibitors

The combination of low-concentration DNMT inhibitors, DAC, or 5-Aza-C with irinotecan has been investigated by a number of research groups in human CRC cell lines, xenograft models using CRC cells, and cervical cancer cells (Table 1) [12-19]. These combinations sensitized the CRC cells used with the modification of the expression of various genes related to apoptosis regulators, DNA topoisomerase-I (upregulation) coupled to p16 demethylation and Sp1 upregulation, cell-cell adhesion, regulation of transcription (DNA-templated), and DNA repair. A single treatment of 5-Aza-C treatment resulted in a reduction in AKT phosphorylation, which was supposed to be involved in the long-lasting effects of 5-azanucleosides on the sensitization of CRC cells to the combination of 5-Aza-C and etoposide [19]. In the case of cervical cancer cells, the combination of irinotecan and DAC resulted in epigenetic upregulation (promoter demethylation) of the WRN gene, which conferred chemotherapeutic resistance to the cervical cancer cells [16]. These results clearly indicated that the epigenetic modifications of the anti-tumor activity of irinotecan was dependent on the type of malignant tissues. In a CRC cell xenograft model, DAC plus 5-FU effectively retarded the tumor growth of 5-FU resistant cells [13]. Another important aspect of the augmentation of anti-tumor activities of irinotecan by DNMT inhibitors is the "priming effects" that sensitize CRC cells to irinotecan therapy. These effects result in the sensitization of cancer cells to subsequent irinotecan therapy. Although its molecular mechanisms are presently unclear, chemosensitization through these priming effects caused by DNMT inhibitors is dependent on treatment schedules. Thus, systematic investigations are required to establish the combination therapy of DNMT inhibitors with irinotecan and other existing anti-cancer drugs.

Combination with HDAC inhibitors

Experimental chemosensitization of 5-FU in combination with

Anti-cancer drug (Exposure protocol)	DNMT inhibitor (Exposure protocol)	Cells/patients	Target gene/protein (Expression change)	Consequences	Reference
CPT-11 (62.5 nM, 10 days)	DAC (31.25 nM, 10 days)	Human CRC cell-line, HCT116	Bcl-2 downregulated	Sensitization to CPT-11 in the presence of little toxic dose of DAC	This paper (Unpublished results)
SN-38 (0.7 nM, 10 days)	DAC (31.25 nM, 10 days)	Human CRC cell-line, HCT116	Bcl-2 downregulated	Sensitization to SN-38 in the presence of little toxic dose of DAC	This paper (Unpublished results)
SN-38 (5 nM, 72 h after DAC exposure)	DAC (500 nM, 72 h)	Human CRC cell-line, HCT-15	$p14^{ARF}$, $p16^{INK4a}$, XAF1	Marked suppression of tumor growth *in vitro*	Ishiguro et al. [12]
CPT-11 (400 mg/kg, i.p., × 3 times	DAC (1 mg/kg, i.p., × 3 times)	Xenograft (HCT-15)	$p14^{ARF}$	Far smaller HCT-15 tumor volumes in xenograft model was observed only in the CPT-11 plus DAC. This treatment resulted in no body weight loss.	Ishiguro et al. [12]
5-FU (Friday, 50 mg/kg, i.p., one or two courses)	DAC (Tuesday, Wednesday, and Thursday, 0.5 mg/kg, i.p., one or two courses)	Xenograft (human CRC cell-line, HCT-8 and its 5-FU-resistant subline)	Uridine monophosphate kinase	HCT-8 parental cell xenograft responded single and combined treatments. Its 5-FU resistant cell xenograft showed a significant delay in tumor growth only in the 5-FU plus DAC treatment.	Humeniuk et al. [13]
CPT (3 μM, 24 h after DAC exposure)	DAC (1 μM, 72 h)	HCT116	DEXI	DAC exerted synergistic effects in combination	Miyaki et al. [14]
5-FU (7.5 μM, 5 days after DAC exposure)	DAC (1 μM, 72 h)	HCT116		No effect	
CPT-11 (2.6 μM, 72 h)	DAC (1.7 μM, 72 h)	HCT116	Not investigated	Synergism (CI=0.43)	Ikehata et al. [15]
CPT-11 (44 nM, 24 h)	DAC (1 μM, 24 h)	Cervical cancer cells, SKG-II and TCO-1	WRN (Werner gene)	Became resistant in combination with DAC	Masuda et al. [16]
SN-38 (0.1 fM to 1 μM) for 48 h, 1 μM DAC for 7 days, and 1 nM SN-38 for 24 h)		Human CRC cell lines, HT29, SW620, and WiDr	DNA topoisomerase-I upregulation, coupled to p16 demethylation and Sp1 upregulation	20-fold, 10-fold, 3-fold sensitization to SN-38, respectively, in the presence of less toxic dose of DAC	Crea et al. [17]
CPT-11 (0.01 nM-100 μM, 72 h after 5-Aza-C treatment	5-Aza-C (500 nM, 72 h): Important new concept of this 5-aza-C treatment preceding CPT-11. This 5-aza-C pretreatment exerts "priming" effects to sensitize CRC cell lines.	Human CRC cell lines, Caco-2 and SW480	CHMP5, and S100B (cell-cell adhesion), MED23, and HOXD3 (regulation of transcription [DNA-templated]), FANCA1, FEN1, and MSH3 (DNA repair)	16-fold, 62-fold sensitization to CPT-11, respectively, after treatment with slightly (<20%) cytotoxic 500 nM 5-Aza-C. This 500 nM 5-Aza-C caused decrease (>25%) in tumor burden in these CRC cell line xenografts.	Sharma et al. [18]
CPT-11 (5 μM to 75 μM, 2 or 3 days with DAC), Etoposide (5 μM to 50 μM, 2 or 3 days with DAC) after the initial DAC treatment	DAC (1 μM, 48 h, initial treatment)	HCT116 DLD-1 HT29	DAC and 5-Aza-C exerted long-lasting effects reducing apoptosis and cell viability, and affecting PI3K/AKT signaling pathway through the reduction in AKT phosphorylation	Sensitization to CPT-11 in the presence of 10-40% growth inhibitory concentration of DAC.	Pawlak et al. [19]
CPT-11, Etoposide (same as above)	5-Aza-C (4 μM, 48 h, initial treatment)			All effectively sensitized	
CPT: camtothecin; CPT-11: irinotecan; DAC: 5-aza 2'-deoxycytidine; SN-38: 7-ethyl-10-hydroxycamptothecin, the active metabolite of irinotecan; 5-Aza-C: 5-azacytidine.					

Table 1: *In vitro* and tumor cell xenograft studies on chemosensitization of irinotecan or SN-38 in combination with DNA methyltransferase inhibitors.

histone deacetylase inhibitors, including depsipeptide and valproic acid, has been investigated (Table 2) [11,20,21]. Although not much has been clarified, the S-1 clinical study showed a marked decrease in HDAC activities 4 weeks after valproic acid administration. As the levels of valproic acid in blood are 40 μg/mL to 120 μg/mL (0.28 mM to 0.83 mM), the concentrations of valproic acid used in cancer cell-line studies were within the clinically achieved blood concentration levels [22]. As some HDAC inhibitors are used as anti-cancer agents, this decrease in HDAC activity is probably associated with the augmentation of S-1 anti-tumor activity. Another point to be clarified was the elevated expression of MHC class II members in studies of 5-FU plus depsipeptide and gemcitabine plus valproic acid. These results were reported from two different research groups. Therefore, the consequences of elevated anti-tumor activities from 5-FU plus gemcitabine should be fully investigated with regard to changes in gene/protein expression related to anti-tumor activities.

Clinical Studies

Subdural hematoma (n=1), elevated blood glucose (n=1), and pulmonary hypertension (n=1) were recorded. The conclusion of this study was that DAC was safe and demonstrated efficacy in Japanese patients with high-risk myelodysplastic syndrome. A clinical study of the sirtuin inhibitor niacinamide, which comprised escalating doses of 20 mg/kg, 40 mg/kg, 60 mg/kg, 80 mg/kg, and 100 mg/kg once-daily for 14 days of a 21. A phase I study of DAC was performed with the DAC doses of 20 mg/m^2/day, 30 mg/m^2/day, and 40 mg/m^2/day by continuous infusion over 72 h of a 28-day cycle [23]. In this clinical study, grade 4 vomiting (20 mg/m^2/day, n=1), and grade 4 granulocytopenia (30 mg/m^2/day and 40 mg/m^2/day, n=2 and n=1, respectively) were reported as dose-limiting toxicities. This study concluded that DAC was tolerated and that changes in methylation occurred. A phase I/II study of DAC was performed with DAC doses of 15 (n=3) and 20 (n=34) mg/m^2/day administered intravenously for 5 days of a 28-day cycle [9]. In this Phase I/II study, grade 3 or greater non-hematologic toxicities, including cerebral infarction day cycle) plus vorinostat (400 mg, days 1-14 of a 21-day cycle) (n=25) [24], reported the following adverse events: one grade 3 infection (400 mg vorinostat, and 80 mg/kg niacinamide) and two dose-limiting toxicities (400 mg vorinostat, and 100 mg/kg

Anti-cancer drug (Exposure protocol)	DNMT inhibitor (Exposure protocol)	Cells/patients	Target gene/protein (Expression change)	Consequences	Reference
5-FU (1.75 μM, 7 days)	Depsipeptide (Romidepsin, ISTODAX, 1 nM, 7 days)	Human CRC cell-line, HCT116	Major histocompatibility complex class II upregulated and p21 downregulated	Enhanced 5-FU anti-tumor activity in the presence of little toxic dose of depsipeptide	Okada et al. [11]
Gemcitabine (5 nM, 72 h)	Valproic acid (500 μM, 72 h)	Human cholangiocarcinoma cell-line, HuCCT1	Genes related to "Cellular development" network relevant to the cancer cell differentiation were identified by the comparison between gemcitabine vs. combination with valproic acid. Major histocompatibility complex class II were upregulated.	Enhanced anti-tumor activity of gemcitabine with little toxic dose of Valproic acid	Iwahashi et al. [20]
5-FU (1.0 μM, 72 h)	Valproic acid (500 nM, 72 h)	Human cholangiocarcinoma HuCCT1 and pancreas cancer cell-line, SUIT-2	Not investigated	HuCCT1: No effect by single 5-FU or valproic acid, and 30% inhibition of cell proliferation SUIT-2: No effect by single 1.0 μM 5-FU; 13% inhibition of cell proliferation by 500 nM valproic acid treatment, and 19% inhibition by 5-FU plus valproic acid	Iwahashi et al. [21]
S-1 (a daily dose of 80 mg/m^2 for 28 days) followed by 14-day recovery period	Oral dose of Valproic acid (a daily dose of 15 mg/kg, twice daily)	Clinical study phases I/II: Advanced pancreatobiliary tract cancers (n=12)	A marked decrease in the histone deacetylase expression after 4 weeks of valproic acid administration	Partial response: one patient; Stable disease: ten patients; Progressive disease: one patient; Clinically significant drug-related adverse events: eight patients	Iwahashi et al. [22]

Table 2: *In vitro* and clinical studies on chemosensitization of 5-FU and gemcitabine in combination with histone deacetylase inhibitors.

niacinamide), grade 4 transaminitis, and grade 4 hypotension. The conclusion of this niacinamide plus vorinostat study were that 24% of patients with relapsed or refractory lymphoma achieved a response to niacinamide and vorinostat and 57% attained stable disease.

Conclusion

In the present research, we presented a positive perspective on the combination therapy of DNMT inhibitors plus irinotecan, DNMT inhibitors plus 5-FU, and HDAC inhibitors plus 5-FU. The DNMT inhibitor plus irinotecan therapy involved both priming effects and long-lasting effects induced by DNMT inhibitors to exert more potent anti-cancer activity, which leads to more successful cancer chemotherapy. The study of HDAC inhibitors plus 5-FU highlighted a reduction in HDAC activities and MHC class II upregulations as potential biomarkers and therapeutic targets to be established after combination therapies of valproic acid or depsipeptide (romidepsin) plus S-1, 5-FU, or gemcitabine. Thus, epigenetic modifiers warrant intensive investigation with respect to the potentiation of the anti-cancer activities of existing drugs, as the concentrations of DNMT and HDAC inhibitors were comparable or lower than the clinically achieved concentrations, which hopefully achieved negligible toxicity through an optimized regimen for DNMT inhibitors and HDAC inhibitors. The clinical trials of DAC revealed that DAC was tolerated, safe, and effective in patients with myelodysplastic syndrome. The combination of vorinostat plus niacinamide revealed that 24% of patients with relapsed or refractory lymphoma responded to vorinostat plus niacinamide and that 57% experienced disease stabilization.

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Declaration of Conflict of Interest

The authors have no conflicts of interest to declare associated with the publication of this manuscript.

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