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Review Article

A Concise Overview of Chemotherapeutic Drugs in Gastrointestinal Cancers: Mechanisms of Action and Resistance

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Abstract

Gastrointestinal (GI) cancers are malignancies of the gastrointestinal tract and accessory organs of the digestive system including the esophagus, pancreas, stomach, colon, rectum, anus, liver, gallbladder, biliary system, and small intestine. These account for 28% of global cancer incidence and 35% of cancer-related mortalities. The most common type of GI cancers: colorectal and gastric cancers, rank among the top five cancers. Surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy are available options for GI cancer treatment. With surgery being the first-line of choice, pre or post-operative chemotherapy is the second most-often used. Nevertheless, the long-term survival rate in GI cancer patients is modest due to the development of drug resistance, which can be overcome by administering various combinations of chemotherapeutic and targeted therapeutic drugs. The classic example is fluoropyrimidine, a class of cytotoxic drug used in combination with irinotecan, gemcitabine, and docetaxel to increase overall and progression-free survival in colorectal, pancreatic, and gastric cancers, respectively. Although in-depth expert reviews on select chemotherapies for the most common GI cancer types can be found, a concise overview of different drugs approved for all GI

cancers is not available. In this review, we have compiled a list of the most common chemotherapeutic drugs used for GI cancers and summarized their major modes of action, intrinsic/adaptive resistance, and a few pre-clinical/clinical approaches to overcoming such resistance. We hope this manuscript will be useful for non-expert readers interested in a general overview of GI cancer chemotherapies.

Keywords: Chemotherapy drugs; Resistance mechanisms; Gastrointestinal cancers

1. Introduction

Cancers of the organs that constitute our digestive system are collectively known as the gastrointestinal (GI) cancers. Oesophageal, liver, stomach, gallbladder and biliary tract, pancreatic, small bowel, anal cancers as well as gastrointestinal stromal tumors (GISTs) and neuroendocrine tumors (NETs), all fall into the broad category of GI cancers (https://gicancer.org.au/gi-cancer-explained/). According to Globocon 2018 report (www.uicc.org/news/new-global-cancer-data-globocan-2018), GI cancers represent one of the greatest public health issues worldwide, with the colorectal and stomach cancers alone being among the top five cancer types in terms of newly diagnosed cases (1.8 and 1.0 million, respectively) and overall mortality rates (881,000 and 783,000, respectively) [1]. In the USA, the prevalence and fatality rate of GI cancers have now surpassed that of lung cancers (333,680 and 167,790 versus 228,820 and 135,720) [2]. Treatment modality of GI cancers depends on the type of cancer, stage, and other general health factors. Although, early-stage GI cancers are amenable to surgery, their five-year relapse rate is quite high, which only marginally improves after the addition of chemo or radiation therapies. Unfortunately, about 25% of GI cancer patients are diagnosed at advanced stages and the other 25-50% of patients develop metastatic disease during treatment. In the last decade or so, the introduction of various molecularly targeted drugs including cetuximab, panitumumab, bevacizumab, regorafenib, sorafenib, irinotecan has improved the prognosis of metastatic GI cancers, however, the death rate continues to be quite high. Since the success of immunotherapy in melanoma, genitourinary, non-small cell lung, and hematological cancers, numerous clinical trials have been launched for GI cancers, especially with gastric, gastroesophageal junction, oesophageal, hepatic, and colorectal cancers. However, many of these are still in clinical development [3].

Until the 1990s, before the advent of molecular targeted therapies, cytotoxic drugs, especially fluoropyrimidine-based agents were the standard of care for GI cancers. Many of these drugs are still being used for GI cancer treatment but in combination with targeted therapies. For instance, in metastatic colorectal cancer, anti-angiogenic drugs (example, bevacizumab or aflibercept) are used in combination with fluoropyrimidines (5-FU or capecitabine) or irinotecan or oxaliplatin. A similar combination is also used in oesophageal and gastric cancers. However, the poorly vascularized pancreatic ductal adenocarcinomas are relatively resistant to a combination of chemotherapy (gemcitabine) and antiangiogenic therapies. More recently, anti-angiogenic therapies have been replaced by drugs targeting EGFR (like cetuximab or erlotinib) or multi-kinase inhibitors (like sorafenib or sunitinib or regorafenib) [4].

Drug resistance (against chemo or targeted therapy) is an inevitable problem in cancer treatment and emergence of therapeutic resistance in GI cancers is no exception to this phenomenon. Tumor drug resistance can be intrinsic

(primary) or adaptive (secondary) and may be contributed by one or more of the following mechanisms including altered drug transport, mutations to drug target, enhanced DNA damage repair, rewiring of signalling pathways, changes in drug metabolism, resistance to apoptosis, enrichment of cancer stem cells and transformed tumor microenvironment. Several comprehensive reviews discussing these general mechanisms of anti-cancer drug resistance are available [5, 6]. In this review, we will summarize the most well-known mechanisms of action and resistance of common chemotherapeutic drugs against different GI cancer types. We will also briefly mention alternate therapeutic strategies that have been proposed or adapted in the clinic to avoid and/or overcome GI cancer chemoresistance. Our goal is to make a concise overview of GI cancer chemotherapies available to non-expert readers.

Drug Name	**Used in Cancer types**	**Broad Mode of action**
5-Fluorouracil	Stomach, colon and anal	Anti-metabolite
Capecitabine	Colorectal, Esophageal, hepatobiliary, neuroendocrine, pancreatic	Anti-metabolite
SI	Gastric and pancreatic	Anti-metabolite
Tegafur-uracil	Colorectal	Anti-metabolite
Irinotecan	Colorectal, gastric, pancreatic	Topoisomerase I inhibitor
Oxaliplatin	Colorectal	DNA damage
Cisplatin	Esophageal and stomach	DNA damage
Gemcitabine	Pancreatic	Anti-metabolite
Trifluridine/tipiracil	Esophageal and stomach	Anti-metabolite
Docetaxel	Stomach	Microtubule inhibitor
Leucovorin	Esophageal and colorectal	Anti-metabolite
Etoposide (VP-16)	Stomach	Topoisomerase II inhibitor

Table 1: List of chemotherapies, their most common uses, and broad modes of action in GI cancers.

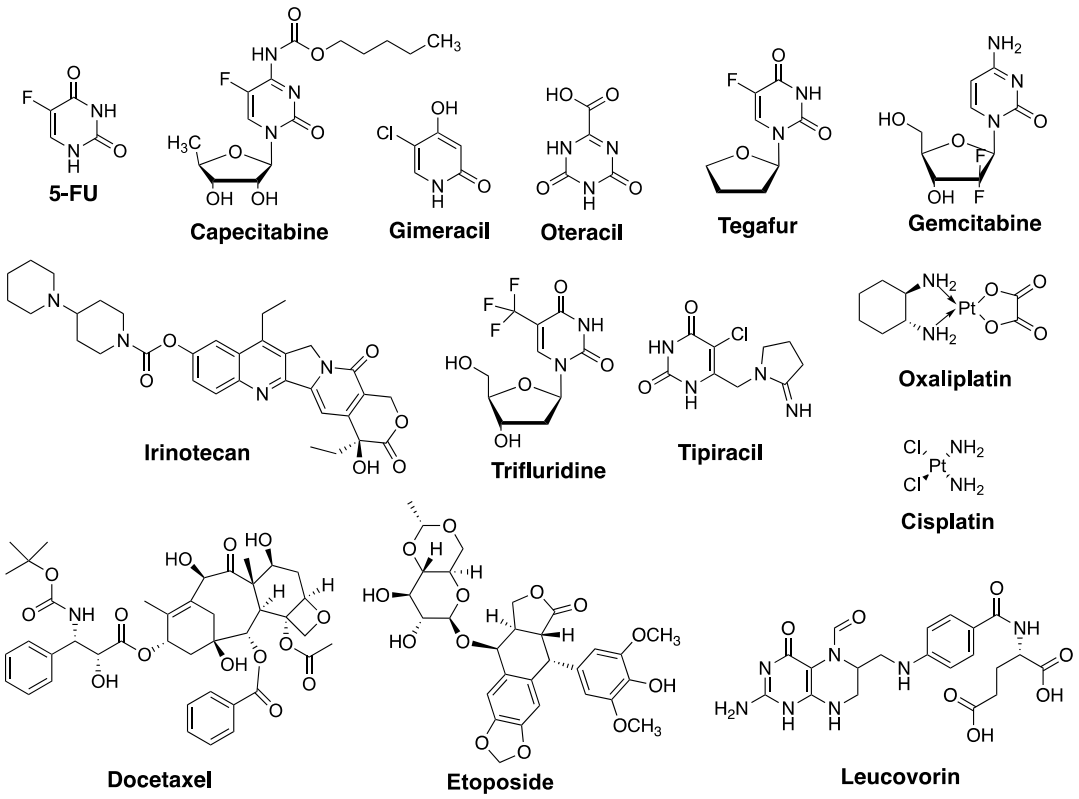

Figure 1: Structures of chemotherapeutic drugs discussed herein.

2. Fluoropyrimidine

5-Flurouracil (5-FU) and its prodrug capecitabine, known as fluoropyrimidines (FPs) kill tumor cells by creating imbalances in the nucleotide pool, resulting in inhibition of DNA replication, transcription, and repair [7]. Although used in several cancer types, FPs exerts the most impact on colorectal cancer treatment [8]. Below, we will briefly discuss their mechanisms of action and resistance.

2.1 5-FU

5-FU, a prototypical FP, one of the first chemotherapeutic drugs reported to have anti-cancer activities is a synthetic fluorinated analog of pyrimidine base. Administered intravenously, 5-FU's cellular import relies on the same facilitated transport mechanism used by uracil. When inside the cell, it is readily converted into several active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP), and fluorouridine triphosphate (FUTP). The primary metabolite FdUMP inhibits thymidylate synthase (TS), an important enzyme involved in the generation of DNA nucleotide dTMP (deoxythymidine monophosphate). This impairs DNA replication and repair. Other 5-FU metabolites FUTP and FdUTP are incorporated into DNA as false nucleotides, interfering with transcription. Collectively, these result in apoptotic cell death. The majority (80%) of the 5-FU is catabolized into dihydrofluouracil (DHFU) in the liver that abundantly expresses the enzyme dihydropyrimidine dehydrogenase (DPD). This decreases the bioavailability of the drug [9].

One of the most well-known modes of 5-FU resistance involves overexpression of its target enzyme TS. In fact, TS expression level has long been recognized as a primary predictor of 5-FU therapy success. Either copy number variation or alteration in the promotor region of the gene encoding TS, *TYMS* results in intrinsic resistance to 5-FU. Free TS controls its expression level by binding to its mRNA and constituting a negative feedback control on its translation. In 5-FU-treated tumor cells, TS binding to FdUMP disrupts this feedback loop, increasing the TS level, and decreasing the sensitivity to 5-FU. This plays an important role in the emergence of adaptive resistance to 5-FU [10]. Formation of an inactive ternary complex between FdUMP and 5,10-methylenetetrahydrofolate (MTTHF) is required for the inhibitory effect of FdUMP on TS. An elevated level of MTHF is important for appropriate inhibition of TS, which is regulated by the enzyme methylenetetrahydrofolate reductase (MTHFR). Therefore, along with TS, MTHFR activity is also a determinant of 5-FU sensitivity in patients. Genetic polymorphisms affecting expression levels and activities of both TS and MTHFR have been reported. Another mechanism of 5-FU resistance is associated with the activities of three enzymes thymidine phosphorylase (TP), uridine phosphorylase (UP), and orate phosphoribosyl transferase (OPRT), necessary for the conversion of 5-FU to 5-FdUTP and 5-FUTP metabolites. However, multiple studies have produced mixed results and require further confirmation [11-16]. Conversion of 5-FU to DHFU by the enzyme DPD is required for increasing its solubility and urinary excretion of the drug. Higher DPD expression in tumor cells has been associated with intrinsic 5-FU resistance. However, definite proof for the same mechanism leading to adaptive 5-FU resistance is lacking.

2.2 Capecitabine

Capecitabine, an orally bioavailable FP was developed to mimic the continuous infusion of 5-FU. It is bioactivated when inside the tumor cells. Capecitabine is a prodrug that is metabolized to 5-FU in different steps. Thymidine phosphorylase (TP), one of the enzymes involved in this process is abundantly expressed in the tumor compared to healthy tissues. This led to the expectation that this drug would have less systemic toxicity. However, in clinical settings this has not been proven correct [17]. Since capecitabine is converted into 5-FU within the tumor, these two drugs share several common mechanisms of resistance. Specifically, DPD expression has been associated with capecitabine resistance [18]. TP, the enzyme that converts capecitabine into 5-FU, is expressed in the tumor microenvironment, rather than the tumor cells themselves. High TP expression correlates with better response to capecitabine, while its loss of function is associated with capecitabine resistance. This could happen by abnormal splicing of TP mRNA due to increased expression of the splicing factors [19, 20].

2.3 S1 and tegafur-uracil

S1, consisting of tegafur (UFT), gimeracil (5-chloro-2, 4-dihydroxypryridine), and oteracil (potassium oxanate) is a fourth-generation oral FP. Tegafur is a prodrug that is converted into FU within tumor cells, while gimeracil interferes with its metabolism by inhibiting DPD and oteracil reduces the toxic side effect of 5-FU by reducing its phosphorylation in the GI tract through inhibition of the enzyme orate phosphoribosyl transferase [21]. Tegafur-uracil consists of tegafur attached to uracil that blocks DPD-mediated catabolism. It is metabolized by the cytochrome P-450 CYP2A6 gene product. Tegafur's high systemic toxicity in white patients than in East Asian patients is likely associated with its altered metabolism due

to polymorphism in the cytochrome P-450 CYP2A6 gene. This is caused by the different extent of conversion of tegafur into 5-FU, responsible for its cytotoxic effects [22].

This drug is not approved in the USA because of its high toxicity [23].

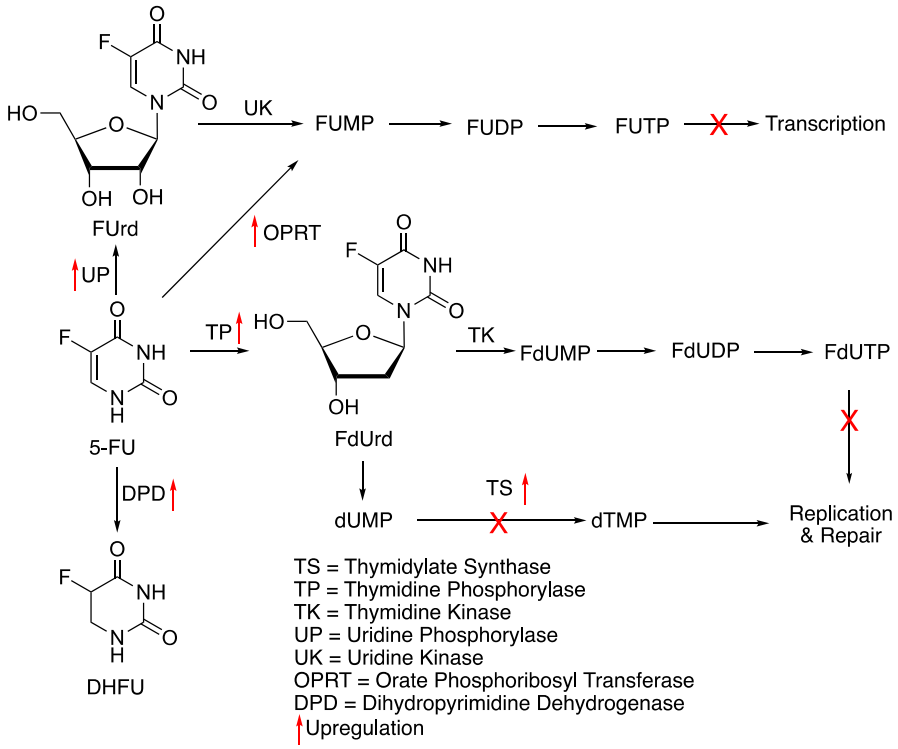

Figure 2: Schematics of 5FU mechanisms of action and resistance. Red arrows indicate altered expression leading to resistance.

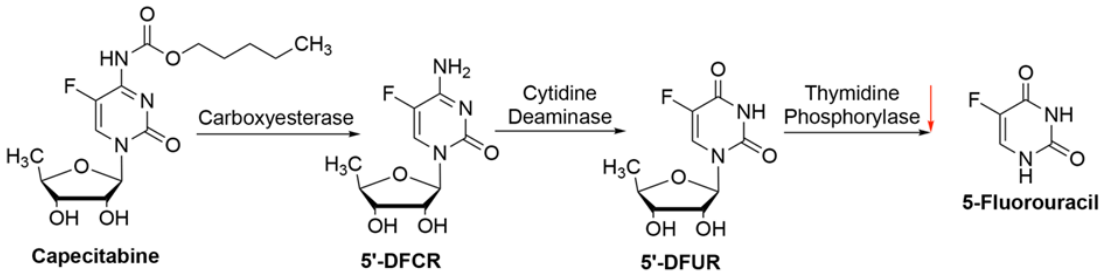

Figure 3: Schematics of capecitabine conversion to FP and its resistance mechanisms. The red arrow indicates altered expression leading to resistance.

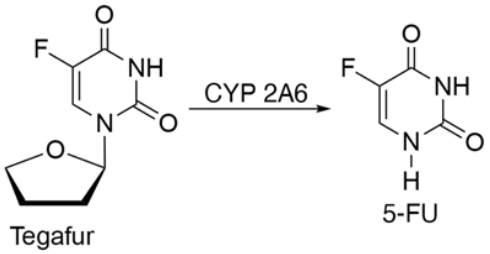

Figure 4: Schematics of tegafur conversion into FP.

3. Irinotecan

Irinotecan is a semi-synthetic derivative of natural DNA-topoisomerase inhibitor camptothecin. DNA topoisomerase-I cleaves one strand of a double-stranded DNA relaxing its supercoiled structure and further re-ligates it. Camptothecin, by forming a complex with topoisomerase I, prevents the re-ligation step causing DNA strand breakage and ultimately, cell death [24]. Irinotecan must be converted to its active metabolite SN-38 by the enzyme carboxylesterase, which reversibly binds to DNA topoisomerase-I, stabilizing it. Irinotecan causes obstruction in DNA synthesis and transcription and works more effectively in combinatorial therapy with FPs, 5-FU and capecitabine, and/or oxaliplatin than as a single agent [25].

Overexpression of the ABC-family of transporter proteins such as multidrug resistance protein (MRP) and P-glycoprotein (Pgp) plays a crucial role in the emergence of resistance by decreasing the intracellular concentration of irinotecan and its metabolite SN-38 [26]. The active involvement of Pgp and MRP in the efflux of SN-38 and irinotecan has been shown in several human epidermoid carcinoma KB-3-1-derived cell lines overexpressing the said transporter proteins, implying their role in the development of intrinsic resistance [27]. SN-38 is converted to SN-38 glucuronosyl (SN-38G) by the action of uridine diphosphate glucuronosyl transferase (UGT) in the liver. This is a step in the drug detoxification process. Enhanced clearance through UGT confers irinotecan resistance by reducing SN-38 concentration in the tumor cells [28]. Another mode of adaptive resistance to irinotecan is the alterations identified in the gene encoding DNA topoisomerase I enzyme. Point mutations within this gene decrease the binding affinity of SN-38 to the enzyme [29, 30]. More specifically, these mutations include changes in the catalytic tyrosine which renders the enzyme catalytically inactive [31, 32]. Insufficient levels of the topoisomerase gene expression, a result of transcriptional silencing due to hypermethylation could attribute to intrinsic resistance. This diminished yield of the enzyme stems from a rearrangement in the Topo-1 genome [20, 25]. Lastly, a lower level of acetylated histone H4K16 is associated with the resistance to irinotecan. H4K16 acetylation is inversely linked to the levels of p53-binding protein (53BP1) repair factor which is responsible for regulating the repair mechanisms of DNA double-stranded breaks. A diminished amount of acetylation implicates dysregulation of H4K16Ac steady levels and a greater accumulation of 53BP1 factor, resulting in mitigating irinotecan's anti-cancer effects [33].

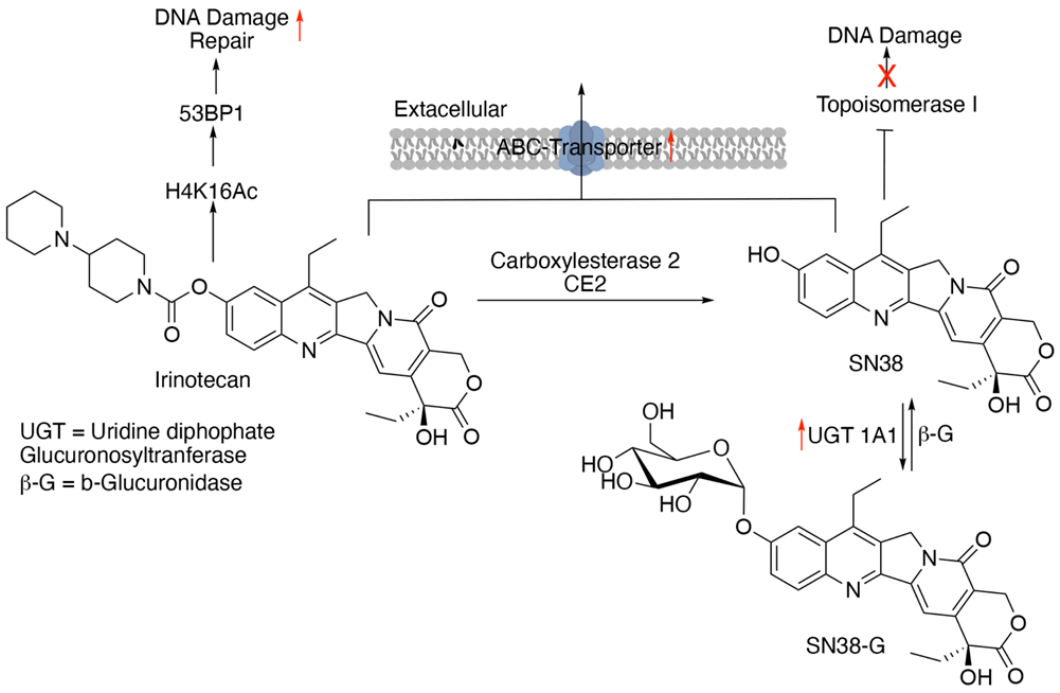

Figure 5: Schematics of conversion of irinotecan to SN-38, their mechanism of action, and resistance. Red arrows indicate altered expression leading to resistance.

4. Oxaliplatin

Oxaliplatin is a third-generation platinum-based chemotherapeutic drug which contains a bidentate (chelating) ligand 1,2-diamniocyclohexane. It has shown about 50% higher progression-free survival (PFS) and overall survival (OS) when given in combination with 5-FU and leucovorin (folinic acid) [34]. Oxaliplatin induces apoptosis by cross-linking (both inter and intra) DNA strands, preventing DNA replication and transcription [35].

Glutathione (GSH) is one of the most potent endogenous antioxidants that prevents the binding of reducing agents such as free radicals and electrophiles to DNA and proteins, thereby preventing them from causing cellular damage. Cancer cells often express increased levels of GSH which is essential for their survival and cell cycle progression [36]. Platinum based compounds like oxaliplatin form conjugates with GSH which facilitates their efflux from the cells via the ABC transporter proteins [37]. Hence, certain tumor cells could become resistant due to the excess GSH levels, in oxaliplatin-based therapy [38]. Nucleotide excision repair (NER) mechanism is responsible for eliminating DNA-Pt adducts particularly the intra-strand cross-links, which are responsible for the antitumor effects of oxaliplatin. Upregulation of genes encoding excision repair cross-complementation group 1 and 2 (ERCC1 and 2) proteins, X-ray cross-complementing group 1 (XRCC1), and xeroderma pigmentosum group D (XDP), primarily involved in the NER pathway are also contributing factors for oxaliplatin acquired resistance [39,

40]. Elevated mRNA expression of ERCC1 in oxaliplatin-resistant tumours and SNPs identified in ERCC1 (354C>A) along with XRCC1 (1196A>G) have been recorded in retrospective analyses of tumor samples [41, 42]. However, forthcoming studies of analyses are still awaited. The breast cancer gene 1, BRCA1 and its interacting partner SRBC (Serum-deprivation response factor-related gene product that binds to c-kinase) are involved in the homology-directed repair (HDR) of double-stranded breaks. Oxaliplatin-induced double-stranded breaks are repaired by these two proteins. Inactivation or depletion of BRCA1 interactor SRBC as a result of methylation is associated with oxaliplatin resistance in colorectal cancer cells [41, 43]. In fact, hypermethylation of SRBC1 has been linked to poor outcome of oxaliplatin treatment [43]. Concrete evidence for the involvement of epigenetic changes specifically in CRC resistance is however, lacking. Finally, cytokine transforming growth factor β1 (TGF-β1), secreted abundantly by tumor cells and known to promote epithelial to mesenchymal transition (EMT) has also been associated with the emergence of oxaliplatin resistance [44].

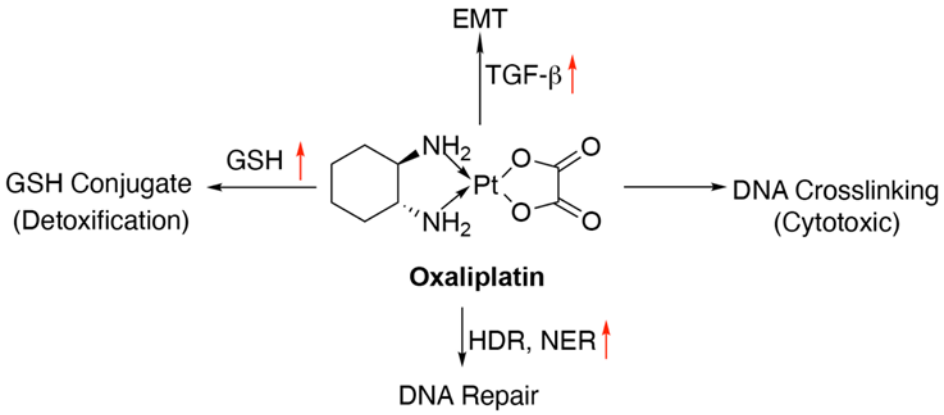

Figure 6: Schematics of oxaliplatin mode of action and resistance mechanisms. Red arrows indicate altered expression leading to resistance.

5. Cisplatin

Cisplatin is a well-known platinum-based chemotherapeutic drug used for the treatment of several GI cancers including oral and oropharyngeal, gall bladder and biliary duct cancer (https://www.cancer.net/cancer-types). Its mode of action is associated with altering DNA repair mechanisms once it is absorbed into the cell leading to DNA damage by the formation of DNA strand cross-linking, which ultimately results in apoptotic cell death [45]. It binds to the N7 atoms of purines (mainly guanine) and form a complex called as the 1,2-intrastand adduct.

DNA repair pathway alterations modulate cisplatin efficacy. Expression of ERCC1, a key player in the NER pathway is enhanced by cisplatin, via the MAPK signalling [46, 47]. This leads to an increased recognition of DNA lesions, counteracting the drug's effect. Dual Specificity Phosphatase-1 (DUSP1) is one of many chemotherapy

resistance-associated genes, and a potential therapeutic target to enhance the cisplatin treatment efficacy in gall bladder cancer. Overexpression of DUSP1 is associated with attenuation of p38 MAPK signalling, preventing tumor cell apoptosis by cisplatin [48]. Cisplatin resistance has also been associated with EMT induction in tongue squamous cell carcinoma (TSCC) cells along with a decrease in the expression of microRNAs miR-200b and miR-15b. These microRNAs functions in metastasis inhibition by obstructing EMT [41, 49].

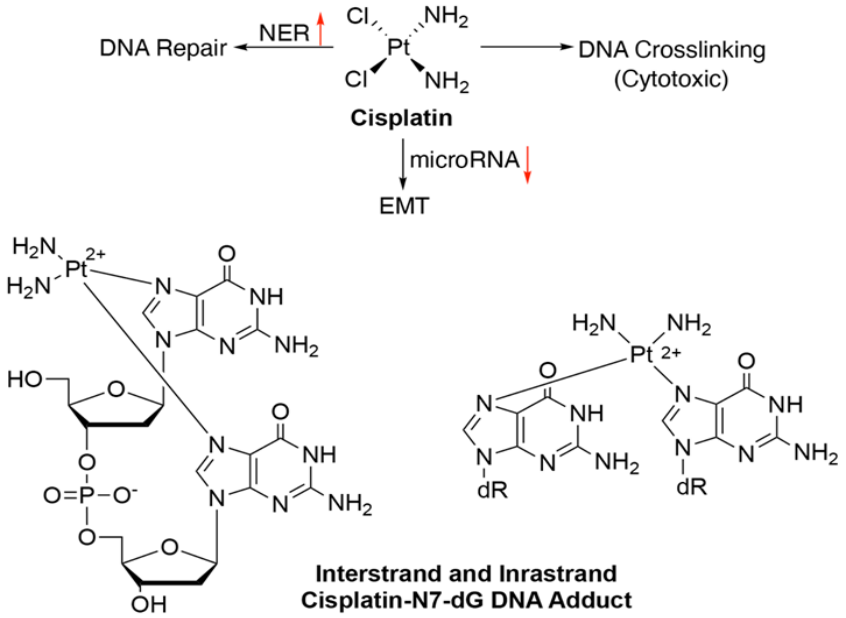

Figure 7: Schematics showing the mechanisms of action and resistance for cisplatin. Structure of cisplatin intra- and inter-strand N7-guanine DNA adducts. Red arrows indicate altered expression leading to resistance.

6. Gemcitabine

Gemcitabine, also referred to as dFdC or 2',2'-difluorodeoxycitidine is the standard choice of treatment for locally advanced and metastatic pancreatic cancers [50]. It is also used in advanced gallbladder cancers [51]. Being a deoxycytidine nucleoside analogue it hinders DNA synthesis and cell cycle at the G1/S-Phase junction [52]. Once imported into the cells by the nucleoside transporters (NTs), it is converted into three metabolites by sequential phosphorylation-first to gemcitabine monophosphate (dFdCMP), then to gemcitabine diphosphate (dFdCDP) and finally to gemcitabine triphosphate (dFdCTP) by the action of deoxycytidine kinase (dCK), pyrimidine nucleoside monophosphate kinase (NMPK) and nucleoside diphosphate kinase (NDPK), respectively [53, 54]. During replication, dFdCTP competes with deoxycytidine triphosphate (dCTP) to integrate into DNA, blocking DNA synthesis and ultimately resulting in cell death [55].

Bioavailability of gemcitabine or dFdC is highly reduced by cytidine deaminase (CDA) that deaminates dFdC to produce less active metabolite-2',2'-diflurodeoxyuridine (dFdU) [56]. Even the phosphorylated metabolites of gemcitabine are converted into their inactivated forms, for

example: dFdCMP is converted to 2'-deoxy-2',2'-difluorouridine monophosphate (dFdUMP) by deoxycytidylate deaminase (DCTD) [54]. Inadequate expression of NTs such as human equilibrative nucleoside transporters (hENT1) in pancreatic cancer cells have been associated with gemcitabine resistance due to insufficient transport into the cells [57, 58]. Deoxycytidine kinase (dCK) is the major rate limiting enzyme in the intracellular activation pathway of gemcitabine's metabolites [59]. Inactivation of dCK gene has also been exhibited in human pancreatic cancer cell lines with acquired resistance [60]. Increase in the concentration of dFdU, the inactive metabolite of Gemcitabine is another main cause of diminished effect of dFdC activity [59]. It was successfully demonstrated in *in vitro* studies that overexpression of CDA which generates such metabolites is responsible for emergence of gemcitabine resistance [61-63].

Similar to cisplatin resistance, DUSP1 overexpression is also associated with gemcitabine insensitivity through modulation of p38 MAPK in pancreatic ductal carcinoma cells and DUSP1 inhibition can enhance gemcitabine sensitivity [64]. The enzyme ribonucleotide reductase (RR) is crucial for DNA synthesis [65]. It regulates the concentration of NTP pool and is responsible for converting CDP to dCDP, followed by its phosphorylation to dCTP, which finally gets incorporated into the DNA. The gemcitabine metabolite, dFdCDP inhibits RR leading to a disruption in the nucleotide pool and facilitating the addition of dFdCTP in place of dCTP into the DNA. Moreover, reduced concentration of dCTP fails to activate the deaminase DCTD, rendering it unable to degrade dFdCMP to dFdUMP [53, 66, 67]. Therefore, RR inhibition or activation plays a vital role in determining gemcitabine sensitivity. It has been reported that enhanced expression of the catalytic subunit of RR, RRM1 is linked to poor overall survival (OS) in pancreatic cancer patients, implying its role in intrinsic resistance to gemcitabine [68-70].

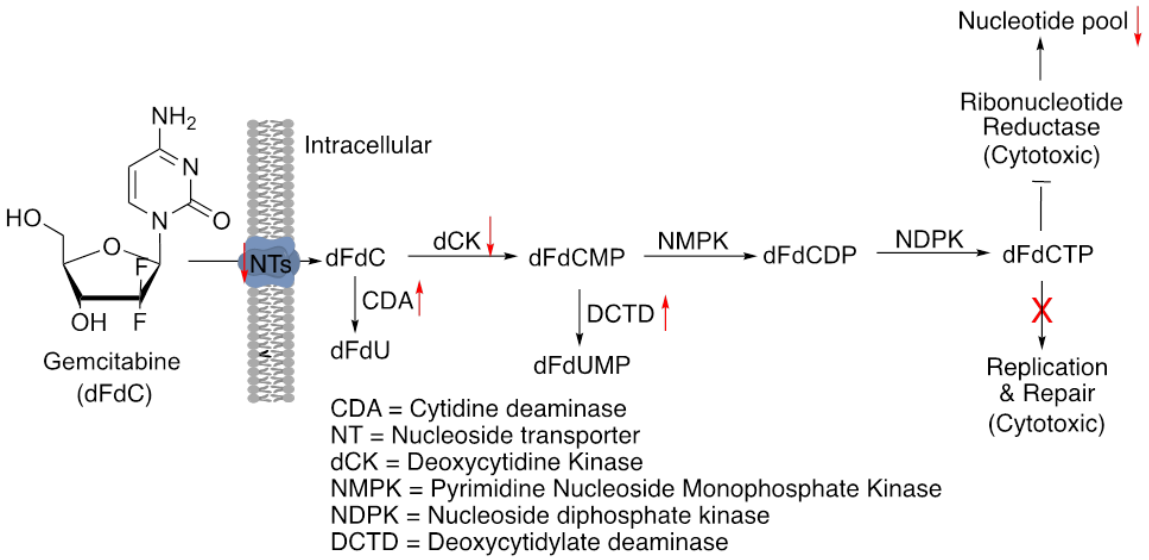

Figure 8: Schematics of gemcitabine's mechanisms of action and resistance. Red arrows indicate altered expression leading to resistance.

7. Trifluridine/tipiracil

Trifluridine (FTD) is a novel drug used to treat patients with metastatic colorectal cancer who have developed resistance to standard chemotherapies such as fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, and also to EGFR and VEGFR targeted therapies [71]. It is also approved for advanced gastric cancers refractory to several lines of treatments [72]. More recently, it is being tested with immune checkpoint inhibitor in microsatellite-stable (MSS) refractory metastatic colorectal cancers [73]. Trifluridine is a thymidine analogue which acts in combination with tipiracil, a thymidine phosphorylase inhibitor [74]. Trifluridine is incorporated into the DNA as its phosphorylated metabolite, triflourothymidine-5'-triphosphate (F_3dTTP) in place of thymidine, obstructing DNA synthesis and tumor cell growth. However, it is also rapidly degraded by the enzyme thymidine phosphorylase (TPase), which is prevented by tipiracil, resulting in the increased bioavailability of trifluridine [72]. This unique feature of trifluridine/tipiracil combination compared to other FPs has rendered it a preferred choice against most 5-FU/FP-resistant GI cancer cell lines and clinical samples [73].

Absence of a functional thymidine kinase 1 (TK1) protein in human colorectal cancer cell lines was shown as an adaptive mechanism of FTD resistance. TK1 is responsible for the conversion of FTD to F_3dTMP [75]. Downregulation of Let-7, a famous tumor suppressor microRNA has been correlated with FTD-induced acquired resistance in the colorectal adenocarcinoma cell line DLD-1. There is an inverse relationship between expression of Let-7d-5p miRNA from chromosome 9 and FTD-induced anti-proliferative effects [74].

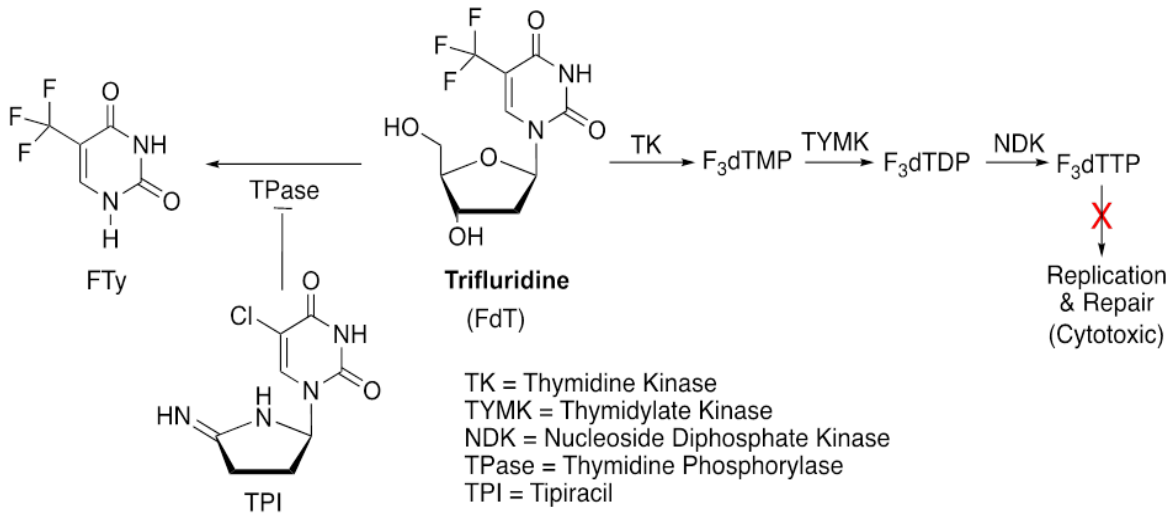

Figure 9: Schematics for the mode of action of trifluridine/tipiracil (TPI).

8. Docetaxel

Chemotherapies for gastric cancer patients include different combinations of 5-FU, platinum based agents like cisplatin and oxaliplatin, irinotecan and taxanes such as docetaxel and paclitaxel (https://www.cancer.net/cancer-types/stomach-cancer/types-treatment). Docetaxel is a second generation taxane that arrests cell cycle by inhibiting mitosis. It stimulates the polymerisation of tubulin by stabilizing the binding of the microtubules to β-actin. As a result, microtubule depolymerisation is inhibited and cell division is arrested at the G_2-M Phase, ultimately inducing apoptosis [76].

With an increase in the efficacy of docetaxel as a third-line treatment for refractory gastric cancer, there is also an increasing emergence of resistance against this drug. Forkhead box protein M1 (FOXM1) is a transcription factor that plays an important role in cell cycle progression from the G1 to S phase and promotes the cell's transition into mitosis [77, 78]. Overexpression of FOXM1 has been associated with acquired resistance to docetaxel in gastric cancers via the direct upregulation of the microtubule-destabilising protein Stathmin [79]. Stathmin overexpression promotes microtubule depolymerisation, counteracting docetaxel action and preventing tumor cell apoptosis [80-83]. Low ratio of soluble to polymerized tubulin was observed in cells overexpressing FOXM1 which is a prominent indication of decreased docetaxel sensitivity [80]. Overexpression of class III β-tubulin (TUBB3) has been studied in depth in non-small cell lung cancer (NSCLC) as a contributor to taxane resistance [84, 85]. However, its significance in gastric cancer is unclear. In a small cohort of advanced gastric cancer patients, enhanced TUBB3 expression was associated with a lack of the desired clinical effect of (preoperative) docetaxel-based treatment [86]. Using cell line models of docetaxel-resistant gastric cancer, expression levels of CXCR4, a chemokine receptor for stromal cell-derived factor-1/SDF-1 was found as a predictor of docetaxel sensitivity. This was verified in gastric cancer specimens as well. In this study, a CXCR4 antagonist, AMD3100 was used to restore docetaxel sensitivity [87]. In another study with gastric cancer cell lines and patient samples, BAK (a proapoptotic member of the BCL2 family) expression was found as a strong predictor of docetaxel sensitivity. Patients with BAK index (as measured by immunohistochemical analysis) equal to or more than 3 had better progression-free and overall survival [88]. In a number of gastric cancer cell lines, docetaxel sensitivity was correlated with the miRNA Let-7a expression level, with lower expression found in the drug-resistant line [89].

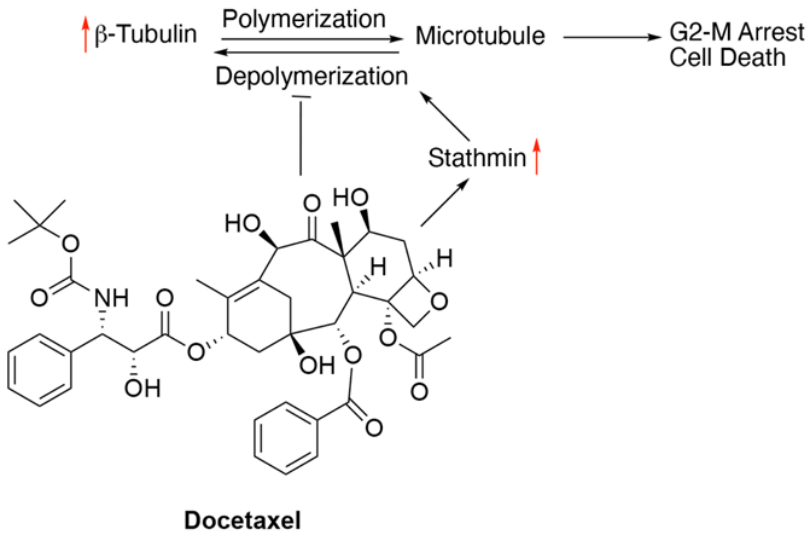

Figure 10: Schematics of docetaxel's mechanism of action and resistance. Red arrows indicate alteration of expression leading to resistance.

9. Leucovorin

Leucovorin (LV) is a 5-formyl derivative of tetrahydrofolic acid (THF) and is best known to facilitate the action of 5-FUs and its derivatives, which inhibit the enzyme TS responsible for DNA synthesis and repair. Administration of LV leads to an increase in the intracellular concentration of 5,10-methylene tetrahydrofolate (CH_2THF) which is responsible for an improved stabilisation of the ternary complex of CH_2THF with TS and FdUMP, via its polyglutamation [90]. LV is used as an adjuvant for many first-line treatments for metastatic colorectal cancer, including FOLFOX (5-FU, LV and oxaliplatin) [23].

In their proteomic studies, Carloni, V. *et al* demonstrated that in metastatic colon cancer cells, ADAM metallopeptidase domain 10 (ADAM10), GTP-binding protein α13 (Gα13) and Ras homolog family member A (RHOA) promote tumor cell fusion, which increases in cells resistant to both 5-FU and oxaliplatin [91]. Therefore, this phenomenon was implicated in the development of multidrug resistance to FOLFOX and poor prognosis. In another study with a large number of advanced gastric cancer clinical samples roles of oncogenes encoding the RAS and β-catenin in the resistance and recurrence following FOLFOX treatment was indicated. In patient-derived xenografts (PDX) from the same clinical samples, resistance to FOLFOX was further correlated with increase in cancer stem cell (CSC)-specific marker expression in addition to enhancement of RAS and β-catenin levels. Treatment with KYA1797K, a small molecule capable of degrading both RAS and β-catenin suppressed the PDX tumors with acquired resistance to FOLFOX and reduced CSC marker expression [92]. In advanced colorectal cancer, another mechanism of poor sensitivity to 5-FU plus LV is associated with p53 overexpression [93]. This could be due to the effect of TS on p53 expression. However, the exact nature of the relationship between these two is still

ambiguous. Multiple studies have demonstrated contrasting roles of ABC family drug transporters in FOLFOX resistance in colorectal cancers. While some correlated high expression levels of ABC family members with reduced drug sensitivity, others did not find a significant association between the two. It is possible that the biological role of ABC transporters in FOLFOX response may vary with cancer stages [94].

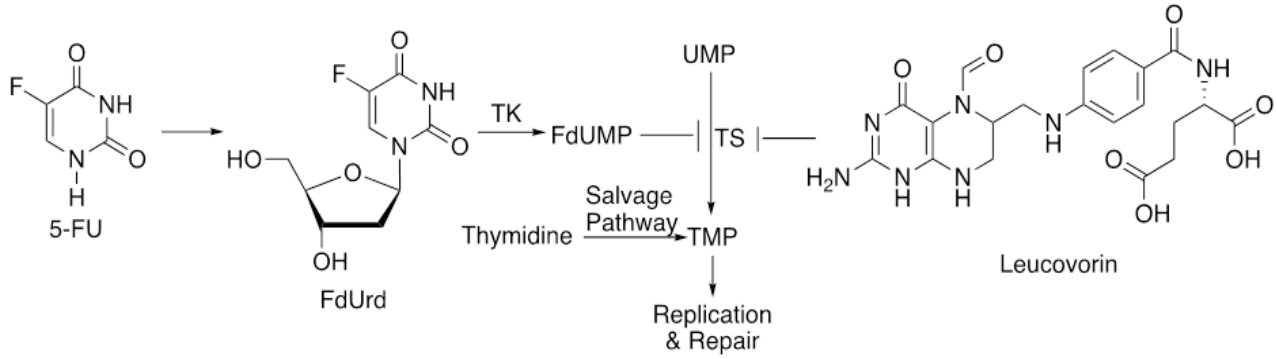

Figure 11: Schematics of leucovorin's mechanism of action.

10. Etoposide (VP-16)

Etoposide is an eukaryotic topoisomerase-II inhibitor which stabilizes the TopoII cleavage complexes and inhibits DNA re-ligation during DNA replication, repair, transcription and chromatin remodelling [95]. The primary mechanism of etoposide resistance is the decrease in the expression level of its target enzyme, TopoII [96]. Additionally, the altered expression of the multidrug resistance protein 1 (MRP1), a transporter protein encoded by *ABCC1* gene which serves multiple functions such as carrying out efflux of drugs, organic anions and several lipid-derived mediators from cells, is implicated in developing etoposide resistance [97]. An increased expression of MRP1 protein is directly correlated with etoposide resistance in stomach cancer cell lines as well oral squamous cell carcinoma (OSCC) [46, 98]. Furthermore, as demonstrated *in vitro*, down regulation of pro-apoptotic proteins, Bid and/or Bax contributed to lower sensitivity to etoposide in a hypoxic (low oxygen) environment, which decreased with further reduction in oxygen level [99].

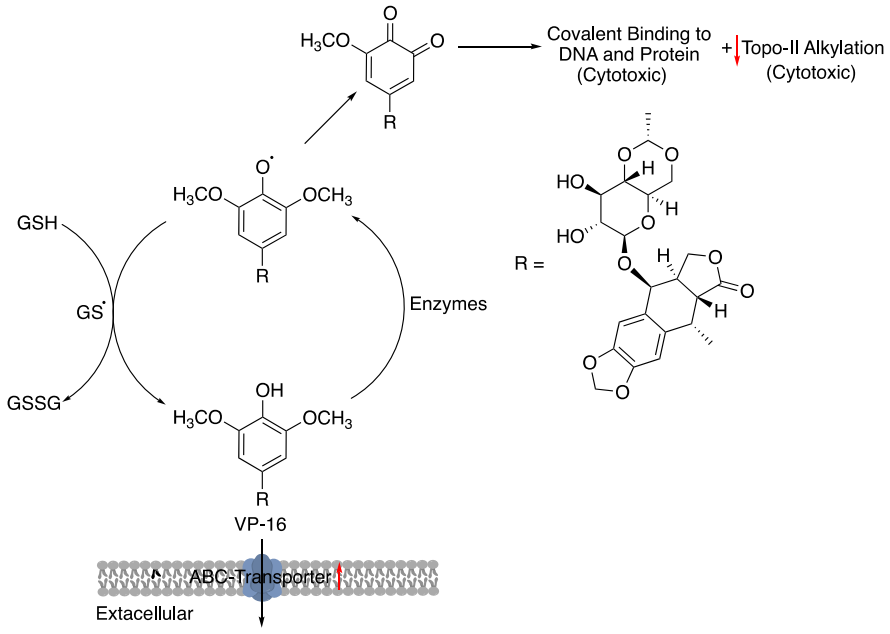

Figure 12: Schematics of etoposide mechanism of action and resistance. Red arrows indicate alteration of expression leading to resistance.

11. Strategies of Overcoming Chemotherapy Resistance

Development of chemoresistance is a major clinical challenge for managing any cancer type. In the previous section, we have discussed several modes of resistance mechanisms of various drugs used for GI cancer treatment and the molecular players involved in these processes. Several of these have been the focus of clinical studies and trials since many years. Some of these have even been adapted in clinic for overcoming chemoresistance in GI cancers. Below, we will briefly mention a handful of strategies that according to us are quite interesting.

DPD-inhibitory fluoropyrimidines (DIF) have been in use as neoadjuvant and/or adjuvant chemotherapy in cases of advanced gastric carcinoma [100] to combat high DPD level-induced 5-FU resistance. Melatonin, a hormone involved in regulating the 24-hour internal clock (circadian rhythm), has been proposed to enhance anticancer effects of 5-FU by downregulating the expression of TYMS via upregulation of the microRNA miR-215-5p, making it a promising therapeutic agent to overcome chemoresistant CRC [101]. Quantifying the expression of OPRT in patients using sandwich ELISA has been suggested to help monitor the efficacy and sensitivity of S-1 based chemotherapy and predict the need of reversal of resistance strategies in advanced gastric carcinomas [102]. Combination treatment with histone deacetylase (HDAC) inhibitor is a an FDA approved clinical strategy to mechanistically overcome irinotecan chemoresistance by enriching H4K16Ac levels and thus maintaining optimum concentrations of 53BPI [36]. A recent study has shown to enhance the effect of gemcitabine in argininosuccinate synthetase-1 negative ($ASS1^-$) tumors of pancreas and few

other cancer cell lines, such as sarcoma and melanoma. Starving the tumor cells of arginine deiminase (ADI-PEG20) and priming it with docetaxel treatment leads to the transport of c-MYC into the nucleus resulting in the increased expression of hENT1, thereby counteracting one of the factors which confers resistance, by increasing the uptake of gemcitabine by tumor cells [103]. As gemcitabine resistance is associated with overactivation of the NF-κB signaling pathway, use of melatonin to block this pathway and overcome drug resistance has been proposed in pre-clinical setting (https://doi.org/10.1111/jpi.12285). Pre-clinical and clinical studies also tested the efficacy of blocking the tyrosine kinase receptor c-Met signaling in gemcitabine-resistant pancreatic cancer, based on the effect of this pathway on CSC population [104]. Over expression of TOP2A to increase the sensitivity to TopoII inhibitory agents like etoposide has been extensively studied [105-107]. However, it requires further investigation to achieve its full therapeutic potential. There is also evidence that MK571, an MRP inhibitor restores etoposide sensitivity of MRP1-expressing stomach cancer cell lines by enhancing the cell-to-medium ratio of etoposide [97]. Since the discovery of the first pgp inhibitor in 1980's, many other inhibitors have been developed and some of those even been tested in clinic for reversal of multidrug resistance. Lack of selectivity and potency, high toxicity are some of the reasons why none of these have yet been approved for patient use [108]. Majority of chemotherapeutics drugs exert cytotoxicity by inducing apoptosis and apoptosis suppression is a common feature of most drug-resistant cancer cells. Reversal of apoptosis resistance by reactivating apoptotic signaling pathways and/or activating alternate cell death pathways are popular approaches for overcoming chemoresistance in GI cancers. For example, several of the therapeutic agents among BH3 mimetics, EGFR inhibitors, autophagy inducers have already been introduced in clinic for treatment of advanced colorectal cancers [108].

12. Conclusion

In this review, we have discussed the major chemotherapeutic drugs used in the treatment of GI cancers, namely 5-FU, capecitabine, S1 (tegafur-uracil), irinotecan, oxaliplatin, cisplatin, gemcitabine, trifluridine, docetaxel, leucovorin and etoposide as well as some of their most noteworthy modes of resistance. We have also touched upon a few approaches of overcoming resistance to some of these drugs. Since the discovery of several targeted therapies and their proven efficacies in clinic for GI cancers such as metastatic CRC, pancreatic cancer and hepatocellular carcinoma (HCC), a majority of chemotherapeutic drugs have been replaced by or used in combination with the anti-EGFR therapies cetuximab [109, 110], panitumumab [111, 112] and erlotinib [113, 114] or anti-angiogenic therapies bevacizumab [115, 116], regorafenib [117, 118], aflibercept [119, 120] and ramucirumab [110] or multi-kinase inhibitors sorafenib [121] and sunitinib [122]. Recently, the success of immunotherapy in lung cancer [123] and melanoma [124, 125] has prompted scientists and oncologists to deploy the use of the same in GI cancers. We believe that the next generation therapy for GI cancer will be a combination of chemotherapy and targeted therapy or immunotherapy. In conclusion, exciting discoveries will continue to pave the way for more effective treatment options to improve the survival rate in GI cancer patients.

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Authors' contribution

SS, AC and GC wrote the manuscripts.

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Conflicts of Interest

The authors declare no conflict of interest.

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