New Anticancer Agents in Clinical Development

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By John Eckardt, MD [2], S. Gail Eckhardt, MD [3], Miguel A. Villalona-calero, MD [4], and Ronald Drengler, MD [5]

A better understanding of the biology and biochemistry of the cancer cell has led to the development of various promising new antineoplastic compounds that are now undergoing phase I, II, and III clinical testing. These drugs include topoisomerase I inhibitors, such as camptothecin and its analogs 9-aminocamptothecin, irinotecan, and topotecan; the paclitaxel analog docetaxel; gemcitabine, an antimetabolite structurally related to cytarabine; and fluorouracil prodrugs and other thymidylate synthase (TS) inhibitors.

Introduction

The 1990s is an exciting decade for oncologists. Intensive research and development programs during the 1980s and 1990s have resulted in new anticancer agents with unique mechanisms of action and significant clinical activity. Recently, three such agents were approved by the FDA: paclitaxel (Taxol), all-trans-retinoic acid, and vinorelbine (Navelbine). These agents have shown significant clinical activity in patients with refractory tumors, such as non-small-cell lung cancer, platinum-refractory ovarian cancer, and anthracycline-refractory breast cancer.

This article will review other promising compounds currently in clinical development. These drugs, which include topoisomerase I inhibitors, docetaxel (Taxotere), gemcitabine (Gemzar), and thymidylate synthase (TS) inhibitors, have significant preclinical activity and are now undergoing phase I, II, and III clinical testing. The hope is that these novel compounds represent the first of a long line of new agents developed as a result of our better understanding of the biology and biochemistry of the cancer cell.

Topoisomerase I Inhibitors

Topoisomerase I inhibitors are an exciting new class of antineoplastic agents currently undergoing clinical testing. These compounds are structurally related to camptothecin, a natural product isolated from the Chinese plant Camptothecin accuminata [1].

Topoisomerase I is a cellular enzyme involved in maintaining the topographic structure of DNA during translation, transcription, and mitosis [2]. The double helix structure of DNA creates torsional strain in a cell that must be overcome in order for replication and translation to proceed. DNA topoisomerases control and modify the topological state of DNA by creating a transient break in a single strand (topoisomerase I) or both complementary strands (topoisomerase II) of the DNA backbone [3]. These enzymes are capable of catalyzing many types of interconversions between DNA topological isomers. Examples of interconversions include catenation (interlocking of DNA circles) and decatenation, and knotting (passing one double strand of DNA through another strand) and unknotting [3].

It is now established that transient breakage of the DNA backbone by topoisomerases is accompanied by the formation of a covalent enzyme-DNA intermediate called the cleavable complex [4]. Inhibition of topoisomerase I by camptothecin and its analogs is accomplished by stabilization of the enzyme-DNA cleavable complex. This occurs after the cleavage step and causes the DNA and topoisomerase to be trapped in the cleavable complex. When camptothecin is removed, the DNA is reannealed (ie, the DNA backbone is resealed), and replication can proceed. Thus, inhibition of topoisomerase I blocks cellular RNA and DNA synthesis. The mechanism by which topoisomerase I inhibitors cause cell death is presently unknown [5].

Camptothecin

During extensive screening of random plant products by the Cancer Chemotherapy National Service Center in the late 1950s, a crude extract of C accuminata was found to have anticancer activity [1]. In 1966, Wall and coworkers [1] isolated this extract, camptothecin (Figure 1), which demonstrated significant anticancer activity in L1210 leukemia and Walker 256 carcinosarcoma [6,7]. In preclinical
studies, hemorrhagic enterocolitis was the major dose-limiting toxicity [8].

**Phase I and II Trials**—In the late 1960s and early 1970s, camptothecin sodium underwent phase I and phase II testing. Phase I studies were performed using various dosing schedules: single-dose [8], daily [9], weekly [9], and daily for 5 days [10]. Although 5 of 18 patients demonstrated objective tumor responses to the drug in one phase I trial, phase II studies in patients with melanoma [11] and adenocarcinoma of the colon [12] were limited by severe hemorrhagic cystitis and unpredictable myelosuppression. As a result, further clinical development of camptothecin sodium was halted.

**Development of Analogs**—It wasn’t until the 1980s, when inhibition of topoisomerase I was identified as the mechanism of action of camptothecin, that interest in this class of compounds was rekindled. In addition, it was found that the lactone ring (E-ring, which is pH labile) was critical to the activity of camptothecin, and thus the sodium salt used in earlier trials (which mainly comprised the carboxylate [inactive] form) might have been the reason for the lack of antitumor activity observed [13]. Structure-activity studies [14] revealed that modification of the A-ring improved water solubility and reduced protein binding. Therefore, analogs of camptothecin with increased water solubility and decreased protein binding were developed, with the anticipation that such modifications would enhance activity while decreasing the hemorrhagic cystitis and unpredictable myelosuppression. Currently, camptothecin and four of its analogs are in clinical development: 9-aminocamptothecin (Figure 1), GI147211, irinotecan (CPT-11), and topotecan.

**Oral Camptothecin**—Camptothecin is undergoing evaluation as an oral preparation. Giovanella and Natelson reported the preliminary results of a trial with oral camptothecin in which the dose-limiting toxicity was gastrointestinal [15]. In the 52 patients treated, 5 partial responses and 1 complete response were noted.

9-Aminocamptothecin
9-Amino-20(S)-camptothecin (9-AC) has demonstrated significant preclinical activity. In studies conducted at the National Cancer Institute that measured DNA strand breaks and cytotoxicity against HT-29 cell lines, 9-AC was found to be slightly more potent than topotecan and significantly more potent than CPT-11, but slightly less potent than SN-38 (the active metabolite of CPT-11) and camptothecin.

Clinical development of 9-AC has proceeded slowly due to its relative water insolubility. In a phase I study of 9-AC administered as a 72-hour continuous infusion in patients with solid tumors, dose-limiting neutropenia occurred at 59 mcg/m²/h [16]. Other toxicities (all grade 2) included nausea, vomiting, mucositis, and diarrhea. Further dose escalation in combination with granulocyte colony-stimulating factor (G-CSF, filgrastim; Neupogen) is currently under study.

**GI147211**
GI147211 is a new water-soluble analog of camptothecin. In human tumor xenograft models HT-29 and SW-48 (colon), PC-3 (prostate), and MX-1 (breast), GI147211 was 1.5 to 1.8 times more active than topotecan in suppressing growth. GI147211 has also been found to be 2.3 to 4.3 times more potent in inhibiting topoisomerase I activity than topotecan [17]. Based on its preclinical activity, GI147211 has recently undergone clinical testing with two dosing schedules: daily doses for 5 days and a 72-hour continuous infusion every 21 days. Reversible grade 3 and 4 neutropenia and thrombocytopenia have been observed with both schedules [18]. Phase II trials are underway using the daily for 5 days schedule.

**Irinotecan**
The initial preclinical and clinical development of irinotecan (CPT-11) was conducted primarily in Japan. In preclinical testing, irinotecan was found to be active against a broad spectrum of tumor models [19]. However, the decarboxylated metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin; Figure 1) plays a major role in the antitumor activity of irinotecan in vivo [20]. The maximum tolerated dose (MTD) of irinotecan depends on the dose and schedule, with diarrhea and neutropenia being the major toxicities. Schedules employing a daily dosing schedule have demonstrated more neutropenia, whereas intermittent schedules have been associated with significant diarrhea [21]. The dose intensity on all the schedules has been approximately 100 mg/m²/wk [21]. However, in a recently published study from France [22], escalation of the irinotecan dose was accomplished by means of aggressive treatment of the diarrhea with antimotility agents. An MTD of 600 mg/m² given over 90 minutes every 3 weeks was reported, with neutropenia being dose-limiting.

**Diarrhea**—Irinotecan has been associated with two forms of diarrhea. The first type occurs during or just after the infusion and has a cholinergic mechanism. The use of atropine at the onset of this early diarrhea is an effective treatment.
The second type of diarrhea begins 3 to 5 days after the irinotecan infusion and may be moderate to severe in 20% of patients. Aggressive treatment at the onset with antimotility agents may obviate its severity. If late diarrhea is not treated early, it usually runs a 5- to 7-day course. The mechanism of this type of diarrhea is unknown, but it may be secondary to the biliary excretion of SN-38, the active metabolite of irinotecan [23].

Other Toxicities--In addition to dose-limiting myelosuppression and diarrhea, other toxicities reported with irinotecan include anemia, transaminasemia, anorexia, alopecia, malaise, flushing, stomatitis, pneumonitis, nausea, and vomiting. These toxicities are mild to moderate in severity and reversible [21].

Antitumor Activity--Single-agent activity of irinotecan has been evaluated in a number of tumor types, including non-Hodgkin's and Hodgkin's lymphoma, acute leukemia, colon cancer, non-small-cell and small-cell lung cancer, ovarian cancer, cervical cancer, breast cancer, pancreatic cancer, and gastric cancer (Table 1). The encouraging activity of this agent seen in patients with refractory tumors, such as cervical cancer and colon cancer, has stimulated large phase II trials now being conducted in the United States and abroad.

Irinotecan Combinations--Because of the novel mechanism of action and clinical activity of irinotecan, investigators have explored its use in combination with other cytotoxic agents. In vitro and in vivo testing of camptothecin analogs has demonstrated synergistic activity when combined with topoisomerase II inhibitors, alkylating agents, platinum compounds, and radiation [24]. Phase I trials of several irinotecan combinations have been initiated. Impressive activity has been demonstrated when irinotecan is combined with cisplatin (Platinol) or etoposide (VePesid) in patients with non-small-cell lung cancer. In untreated patients with non-small-cell lung cancer, response rates to irinotecan-cisplatin have ranged from 43% to 45% [44,45]. These results have prompted further investigation of this combination.

Topotecan

Topotecan is a semisynthetic analog of camptothecin that incorporates a stable basic side chain at the 9-position of the A-ring of 10-hydroxycamptothecin (Figure 1). This basic side chain affords water solubility without requiring hydrolysis of the E-ring lactone.

Based on the preclinical activity seen with topotecan, several phase I clinical studies were initiated. To date, 18 phase I studies using nine different schedules of topotecan have been reported [21].

Cytopenias--The dose-limiting toxicity observed with all schedules of topotecan (except in leukemia, for which mucositis was dose-limiting) has consisted of neutropenia and thrombocytopenia. Neutropenia and mild thrombocytopenia were seen with the short infusion schedules, whereas schedules with longer infusion times resulted in both dose-limiting neutropenia and thrombocytopenia. The neutropenia and thrombocytopenia have generally been short-lived (less than 7 days) and rarely associated with fever.

Other toxicities observed have included mild nausea and vomiting, anorexia, diarrhea, alopecia, fatigue, and skin rash. Unlike camptothecin, hemorrhagic cystitis has not been observed with topotecan, and unlike irinotecan, diarrhea has not been a significant problem.

Efforts at Dose Escalation--Because the major toxicities of topotecan are hematologic, the use of G-CSF to permit further dose escalation of this camptothecin analog has been explored. Unfortunately, no significant dose escalation has been possible with colony-stimulating factors as a result of the development of dose-limiting thrombocytopenia [47].

Use in Hepatic or Renal Dysfunction--Topotecan also has been evaluated in patients with hepatic or renal dysfunction. Patients with renal insufficiency had significantly decreased topotecan clearance requiring dose reduction. Patients with hepatic dysfunction did not exhibit altered drug clearance and were able to tolerate doses similar to those used in patients with normal hepatic function [48].

Antitumor Activity--The phase II activity of topotecan is summarized in Table 2. Encouraging activity in patients with previously treated small-cell lung cancer and ovarian cancer has stimulated phase III trials in these patient populations. Like irinotecan, topotecan has been combined with various antineoplastic agents and with radiotherapy. Phase I studies of the combination of topotecan and etoposide, doxorubicin, cisplatin, paclitaxel, and radiation have been reported (Table 3).

Oral Preparation--Topotecan has recently undergone testing as an oral preparation. The oral route has the potential advantage of ease of administration. In addition, the acidic pH of the stomach should maintain topotecan in the active closed lactone form. Creemers et al reported their experience with topotecan given orally on day one followed by an intravenous dose on day two [66]. They found that the oral form exhibited 32% bioavailability and was not affected by first-pass metabolism.
**Docetaxel**

Docetaxel (N-debenzoyl-N-tert-butoxycarbonyl-10-deacytlyl taxol, RP56976 [Taxotere]) is a semisynthetic analog of paclitaxel prepared from a noncytotoxic precursor extracted from the needles of the European yew tree *Taxus baccata* (**Figure 2**). Docetaxel was synthesized in 1986 and was selected for clinical development in 1987 due to its preclinical activity and a formulation that allowed for shorter infusion schedules than paclitaxel. Early preclinical testing demonstrated that docetaxel is 2.5-fold more potent than paclitaxel [67]. Like paclitaxel, docetaxel binds to tubulin, promotes the assembly of microtubules, and inhibits depolymerization [67].

**Phase I Testing**

In 1990, phase I testing of taxotere began in Europe and the United States. Six dosing schedules have been explored, with neutropenia being the dose-limiting toxicity on all schedules [67]. Studies that have utilized longer schedules or repeated-dose schedules have found both mucositis and neutropenia to be dose-limiting. Mucositis was not found to be a significant problem on 1- and 2-hour dosing schedules.

**Hematologic Toxicity**—The neutropenia associated with docetaxel is dose-dependent, with a median time to neutrophil nadir of 9 days and recovery by day 21. At the recommended phase II dose, approximately 70% of patients develop grade 4 neutropenia; of these patients, only 18% have grade 4 neutropenia lasting for more than 7 days, and 15% have fever associated with the neutropenia. Anemia and thrombocytopenia are generally mild (grade 2) and seen only in a minority of patients (20%).

**Hypersensitivity**—In the phase I studies, none of the patients received premedication for hypersensitivity to docetaxel. In 15% of patients, a reaction characterized by localized or generalized flushing, rash, chest pain or heaviness, back pain, dyspnea, and fever was observed [68]. Such reactions occurred within 3 to 10 minutes after the infusion was begun and resolved within a few minutes after it was interrupted. Treatment with diphenhydramine and hydrocortisone allowed the infusion to be restarted. Severe symptoms associated with hypotension and/or bradycardia were seen in only 2% of patients. Premedication with antihistamines and steroids reduced the incidence of the hypersensitivity reaction [69]. Patients who developed the hypersensitivity reaction did so in the first or second cycle of therapy [68].

**Other toxicities** reported for docetaxel have been generally mild (grade 1 and 2) and include alopecia (100% of patients), mucositis (49% on the longer infusion schedules), skin reactions (69%), edema (40%), weakness (27%), and neuropathy (31%) [70]. The edema has been associated with the development of pleural effusions and ascites. The etiology of this fluid collection syndrome is unknown but may be related to increased capillary permeability [71]. Edema appears to occur after a total dose of approximately 400 to 500 mg/m² and can be delayed by premedication with steroids, antihistamines, and the use of diuretics. The neuropathy is a sensory neuropathy that is generally mild (grade 1 or 2), with symptoms of numbness and dysesthesias. It resolves slowly when docetaxel is discontinued [72].

**Pharmacokinetics**

Population pharmacokinetics of docetaxel have been determined. Bruno et al [73], using a three-compartment model, found docetaxel to have a half-life of 11.1 hours with a clearance of 21.2 L/h/m² and a volume of distribution of 69 L/m². Metabolism studies have demonstrated that 80% of docetaxel is recovered in the feces over 7 days, with only 5% recovered in the urine [74].

**Antitumor Activity**

In view of the activity noted in phase I trials, docetaxel underwent broad phase II testing (**Table 4a** and **Table 4b**). Clinical activity has been documented in patients with a number of tumor types, including breast cancer, non-small-cell lung cancer, ovarian cancer, head and neck cancer, soft-tissue sarcomas, and gastric cancer. The major activity of docetaxel observed in the treatment of patients with breast cancer and non-small-cell lung cancer has sparked intense interest.

**Breast Cancer**—Docetaxel has demonstrated objective responses in both untreated and treated patients with metastatic breast cancer, with response rates reported to be between 44% and 58% in both of these groups [75-79]. This activity is comparable to the most active single agents in breast cancer, including doxorubicin and paclitaxel.

**Non-Small-Cell Lung Cancer**—In non-small-cell lung cancer, responses to docetaxel have been documented in both chemotherapy-naive patients and in those whose disease has progressed after a platinum-containing regimen. Published response rates range from 21% to 33% [80-85]. This activity
in platinum-refractory patients is notable when compared to that of other agents in this population. For example, paclitaxel, cisplatin, etoposide, epirubicin (Epirubicin), and vindesine (Eldisine) all have published response rates ranging from 2% to 10% when used as second-line treatment. **Ongoing Studies** Various studies of docetaxel are currently underway. These include: phase I studies of the combination of docetaxel with cisplatin and with fluorouracil; phase II trials in paclitaxel-resistant breast cancer, hormone-refractory prostate cancer, and cholangiocarcinoma; a phase III trial of docetaxel vs best supportive care as second-line treatment for patients with non-small-cell lung cancer; and a phase III trial of docetaxel vs paclitaxel in anthracycline-refractory breast cancer. **Gemcitabine** Gemcitabine (2’2’-difluorodeoxycytidine; dFdC [Gemzar]) is a synthetic pyrimidine antimetabolite structurally related to cytarabine. Gemcitabine differs from the endogenous nucleoside, deoxycytidine, by the presence of two fluorine atoms in its deoxyribofuranosyl ring (Figure 1). Gemcitabine inhibits both RNA and DNA viruses in cell culture and was originally synthesized as an antiviral agent. Its narrow therapeutic index during in vivo evaluation, however, precluded further development as an antiviral drug [101]. Gemcitabine was subsequently found to have excellent in vitro antineoplastic activity in tumor cell lines, as well as broad-spectrum activity against a panel of murine solid tumors and human tumor xenografts [101]. **Mechanism of Cytotoxicity** Gemcitabine's cytotoxic activity is due to the inhibition of DNA synthesis and repair. It is a prodrug requiring intracellular metabolic activation to its phosphorylated forms by deoxycytidine kinase. Gemcitabine triphosphate competes with deoxycytidine triphosphate (dCTP) as a substrate for incorporation into DNA. Once incorporated into DNA, gemcitabine triphosphate causes a profound inhibition of DNA elongation and chain termination. Gemcitabine diphosphate is an inhibitory substrate for ribonucleotide reductase (RbNR), an enzyme required for the production of deoxynucleotides used for DNA synthesis and repair. Cell death associated with these events exhibits the morphologic and biochemical characteristics of apoptosis. **Self-Potentiation** Gemcitabine appears to have the ability to enhance its own activity (self-potentiation). Inhibition of RbNR causes lowering of intracellular dCTP levels. Through feedback mechanisms, low dCTP levels activate deoxycytidine kinase and inactivate deoxycytidine monophosphate (dCMP) deaminase, leading to increased phosphorylation (activation) and decreased deamination (elimination) of gemcitabine. Low intracellular levels of dCTP also enhance gemcitabine triphosphate's incorporation into DNA, due to competition for DNA poly merase. These mechanisms may explain the increased cellular accumulation and increased activity of gemcitabine seen in solid tumors, as compared with cytarabine. **Phase I Trials** Toxicities of gemcitabine observed in phase I trials have included myelosuppression, reversible skin rash, fever, mild nausea and vomiting, alopecia, lethargy, a flu-like syndrome, peripheral edema, and reversible elevations in liver function tests. Cumulative toxicity has not been observed. In phase I trials, dose-limiting toxicity of gemcitabine has been found to be particularly schedule dependent; ie, there is a marked difference in the minimum tolerated dose (MTD) depending on the schedule of administration. Dose-limiting lethargy and flu-like syndrome were seen on the daily doses for 5 days schedule, whereas myelosuppression was dose-limiting on the every other week schedule. **Antitumor Activity** Clinical activity was demonstrated in patients with non-small-cell lung, pancreatic, breast, head and neck, bladder, renal cell, and colon cancer. Among the dosing schedules studied (daily doses for 5 days, twice a week, weekly, and biweekly), the weekly schedule was chosen for phase II trials due to adequate dose intensity and preclinical data suggesting schedule-related efficacy [102]. Based on the activity profile seen in phase I trials, broad phase II testing with gemcitabine is being conducted in a wide variety of malignancies. As summarized in Table 1, activity has been confirmed in patients with non-small-cell lung and small-cell lung cancers, breast cancer, ovarian cancer, pancreatic cancer, and squamous cell carcinoma of the head and neck. **Pharmacokinetics** The pharmacokinetics of gemcitabine have been extensively studied. Gemcitabine undergoes intracellular phosphorylation by deoxycytidine kinase to its active metabolites. Deamination to its
uridine metabolites (dFdU[difluorodeoxy-uridine]) by cytidine deaminase is the principal mechanism involved in the elimination of gemcitabine. Following a 30-minute intravenous infusion, gemcitabine has a short terminal half-life ranging from 4 to 20 minutes [121]. The deaminated metabolite (dFdU), however, has a much longer half-life (4 to 24 hours). Gemcitabine clearance is lower in women than in men, perhaps related to differences in the activity of cytidine deaminase [122].

**Ongoing Trials**
A determination of gemcitabine's clinical benefit, as assessed by changes in pain, performance status, and weight, is the primary objective of two ongoing clinical trials in patients with advanced pancreatic cancer [123]. Gemcitabine's favorable toxicity profile makes it an attractive candidate for combination therapy with other antineoplastic agents. Several trials utilizing gemcitabine combined with other agents, such as cisplatin (Platinol), carboplatin (Paraplatin), paclitaxel (Taxol), and hydroxyurea (Hydrea) are currently underway.

**TS Inhibitors and Fluorouracil**

**Prodrugs**
Fluorouracil was the first agent specifically synthesized to exploit an observed metabolic difference between normal and tumor cells [124]. It has been used either alone or in combination with other antineoplastic drugs for the treatment of a wide variety of tumors.

Fluorouracil is metabolized through different biochemical pathways, producing different cytotoxic metabolites, and is eliminated through urinary excretion (15% to 20%) or by the liver and extrahepatic tissues (80%). Three different mechanisms of action are thought to be responsible for its cytotoxicity:

1. Inhibition of the enzyme thymidylate synthase (TS) by its metabolite fluorodeoxyuridine monophosphate (FdUMP);
2. Incorporation of another metabolite, fluorouridine triphosphate (FUTP), into cellular RNA; and
3. Incorporation of fluorodeoxyuridine triphosphate (FdUTP) into cellular DNA (Figure 2).

**Modulation of Fluorouracil Metabolism**—Enhancement of the action of fluorouracil through modulation of its metabolic pathways has been pursued avidly for several years. The best known of these modulations is achieved by the use of 5-formyl-tetrahydrofolate (leucovorin), which stabilizes the TS-FdUMP-folate complex (Figure 2).

Other drugs have also been shown to enhance the cytotoxicity of fluorouracil. Dipyridamole inhibits the uptake of thymidine, decreasing the salvage pathway to overcome FdUMP inhibition of TS. Phosphonacetyl-L-aspartate (PALA) decreases intracellular uridine triphosphate and increases incorporation of FUTP into RNA. Methotrexate, when given before fluorouracil, increases intracellular phosphoribosyl pyrophosphate (PRPP), a substrate necessary for the enzyme-dependent conversion of fluorouracil to fluorouridine monophosphate (FUMP) (Figure 2). Interferons increase the conversion of fluorouracil to FdUMP, reduce levels of TS, and inhibit thymidine salvage pathways. Hydroxyurea, through inhibition of RbNR, depletes endogenous levels of deoxyuridine monophosphate (DUMP) and impairs FdUMP binding to TS (Figure 2). Thymidine and uracil have also been explored as fluorouracil-enhancing agents; these agents inhibit fluorouracil catabolism.

Given the multiple targets of fluorouracil and its complicated metabolism, attempts to create a more efficient drug with similar targets have been the focus of research over the last few years.

**Fluorouracil Prodrugs**
Several analogs of fluorouracil have been tested in clinical trials. These include 5-fluoro-2¢-deoxyuridine (floxuridine, FdUrd [FUDR]) and 5-deoxy-5-fluorouridine (dFUrD). Rapid degradation of floxuridine and the significant neurotoxicity produced by dFUrD have limited their use.

**Tegafur (Ftorafur)** is fluorouracil linked to a furan-ring dehydroxylated ribose sugar. Hydroxylation of tegafur by hepatic microsomal enzymes releases fluorouracil, leading to a slow but sustained level of fluorouracil in tumor cells.

Tegafur has exhibited considerable central nervous system (CNS) and gastrointestinal toxicity with no significant clinical benefits when compared to fluorouracil [125]. These findings halted studies in the United States; however, studies abroad have shown that fractionation of the daily dose, when given either intravenously or orally, produces considerably fewer side effects and improved clinical
benefit [126].

**Neurotoxicity** has been a significant obstacle to the development of fluorouracil prodrugs and related oral compounds. Histopathologic studies in necropsies of humans and animals that received these drugs have shown vacuolization and necrosis/softening-like changes in the CNS. These alterations are thought to be produced by two fluorouracil catabolites, monofluoroacetic acid and, especially, alpha-fluoro-beta-alanine. The mechanism of this effect is not well understood [127].

### Inhibitors of Fluorouracil Catabolism

**Dihydropyrimidine dehydrogenase (DPd)** is the initial and rate-limiting enzyme in the catabolism of fluorouracil, uracil, thymine, and other 5-substituted pyrimidines. More than 80% of administered fluorouracil is rapidly degraded by this enzyme. Fluorouracil half-life is approximately 5 to 20 minutes in individuals with normal levels of this enzyme, whereas persons with an inherited deficiency of DPd have a 10-fold longer half-life of the drug. Effective inhibition of this enzyme would theoretically increase the serum levels, half-life, and, possibly, efficacy of fluorouracil (Figure 2).

**UFT**—Two approaches have taken advantage of inhibition of this enzyme. The first approach, known as UFT, consists of an oral form of tegafur with uracil in a 1:4 molar concentration. Uracil inhibits the hepatic activity of DPd, thereby increasing the plasma levels of fluorouracil resulting from tegafur metabolism. The ease of administration of UFT and preliminary studies in Japan have stimulated interest in this drug. A phase II study showed response rates comparable to intravenous fluorouracil in patients with colorectal and gastric carcinomas [128].

Modulation of UFT with oral leucovorin has been attempted as a way to enhance its efficacy [129]. Pazdur et al recently reported a phase II trial using this combination in 45 colon cancer patients (42 of whom were previously untreated and 3 of whom had received adjuvant chemotherapy) [130]. Both drugs were given in three divided doses daily (300 to 350 mg/m² of UFT plus 150 mg/d of leucovorin) for 28 days, followed by a 7-day rest period. After two courses of therapy, 18 patients had a partial response and 1 patient had a complete response (42% response rate).

**5-Ethynyluracil**—The second approach is 5-ethynyluracil (776C85), which binds to and irreversibly inactivates DPd. This drug has been demonstrated to markedly increase the area under the curve, oral bioavailability, and therapeutic index of fluorouracil in animals [131]. Recent data in animals suggest that this compound is considerably more effective than high-dose uracil in sustaining plasma fluorouracil generated from tegafur [132]. In addition, 776C85 has been shown to protect against fluorouracil-induced neurotoxicity in dogs. This may occur through inhibition of the formation of neurotoxic catabolites or through the protection conferred by high serum levels of uracil [133]. Phase I trials testing 5-ethynyluracil in combination with fluorouracil, with or without leucovorin modulation, are currently underway in San Antonio and at the University of Chicago.

### New TS Inhibitors

Thymidylate synthase catalyzes the conversion of DUMP by reductive methylation into deoxythymidine monophosphate (dTMP) and dihydrofolate. This reaction requires the presence of a reduced folate cofactor and provides the precursor of deoxythymidine triphosphate (dTT), one of the deoxyribonucleotides necessary for DNA synthesis. Inhibition of this enzyme is probably the most important mechanism of action of fluorouracil and related compounds (Figure 2). Total TS activity, as measured by a catalytic assay (ie, the capacity to convert DUMP to dTM) and TS inhibition have been shown to correlate with response to fluorouracil [134]. An array of new agents has been developed to produce more effective inhibition of this enzyme.

**CB3717** is a quinazoline-based TS inhibitor that competes with reduced folates, producing potent inhibition of the enzyme. Unfortunately, it has poor aqueous solubility and produces life-threatening nephrotoxicity and dose-independent hepatotoxicity.

**Tomudex**—As an alternative to CB3717, Tomudex (ZD1694, ICI D1694) was synthesized. Tomudex has the advantage of water solubility and rapid intracellular polyglutamation. Its polyglutamate derivatives are more active against TS and are retained longer within the cell, giving this compound more efficacy in vivo [135].

Phase I trials of Tomudex in Europe recommended a dose of 3.0 mg/m² given over 15 minutes every 21 days. Dose-limiting toxicities were diarrhea, neutropenia, malaise, and asthenia. Dose escalation of Tomudex up to 4.5 mg/m² has been reported [136], with a recommended phase II dose of 4 mg/m². These higher doses have produced increased myelosuppression and elevated hepatic transaminases.

Phase II trials of Tomudex using the 3-mg/m² dose have demonstrated significant activity in patients with advanced colorectal carcinoma (31/124 patients [25%], with 2 complete responses), breast cancer (11/45 patients [24%], with 2 complete responses), as well as in patients with pancreatic, non-small-cell lung cancer, and ovarian cancer [137]. Minimal toxicity was observed in these trials.
Phase III trials will randomize patients with colorectal cancer to either Tomudex or a standard 5-day regimen of fluorouracil/leucovorin. **AG-331**--Other folate antimetabolites undergoing clinical trials are AG-331 and LY231514. AG-331 lacks a glutamate moiety but is very lipophilic, which facilitates tissue penetration. The lack of polyglutamation contributes to its favorable toxicity profile. Phase I trials with both 1- and 24-hour continuous infusions, daily for 5 days, are currently being conducted. **LY231514** undergoes extensive intracellular polyglutamation, which results in a more sustained drug effect. Data from two phase I studies are available [138]. In the first study, the drug was administered weekly for 4 weeks every 42 days. Dose-limiting neutropenia was encountered at 40 mg/m². Two minor responses in patients with colorectal cancer were documented. In the second study, LY231514 was administered every 21 days. Reversible neutropenia was the dose-limiting toxicity, with dose escalation up to 600 mg/m². Minor responses in six patients with colorectal cancer and partial responses in two patients with pancreatic cancer were reported.

**New Approaches To Anticancer Therapy**

The chemotherapeutic compounds described above have direct cytotoxic effects on cancer cells through interaction with DNA, RNA, or protein synthesis. Another approach to cancer therapy is the use of agents that alter the cellular phenotype and thereby induce a less malignant state. Examples of such agents are angiogenesis inhibitors, differentiating agents, signal transduction inhibitors, and gene therapy. This approach to treating cancer is quite novel, and the clinical development of these compounds is evolving. Standard cytotoxic agents produce tumor shrinkage and objective responses, whereas these agents may produce only cytostasis, and therefore, stable disease. Standard phase I and II clinical trials are not designed to assess end points such as time to tumor progression or time to relapse. A successful development strategy for these compounds with unique mechanisms of action must include early randomized trials in which the novel agent is/is not given in combination with a standard agent or is/is not given after adjuvant therapy. Randomized trials are more expensive, but are equipped to evaluate whether these novel agents should become part of a standard therapeutic regimen.

The section below will focus on three angiogenesis inhibitors that are currently undergoing phase I/II testing. **Angiogenesis Inhibitors**

Abundant preclinical literature demonstrates that tumors are dependent on angiogenesis for tumor growth and metastasis [139]. In human breast cancer, angiogenesis is an independent negative prognostic factor in node-negative tumors [140]. These data support the significance of angiogenesis in tumor biology and suggest that it can be utilized as a target for novel therapeutic strategies. Angiogenesis inhibitors fall into two broad categories: protease inhibitors (which inhibit the proteases required for the penetration of the basement membrane by endothelial cells) and endothelial cell growth-factor inhibitors (which inhibit the growth factors required by endothelial cells). Tecogalan sodium, recombinant human platelet-factor 4, and TNP-470 are three angiogenesis inhibitors that are currently being tested in cancer patients. **Tecogalan sodium** is a sulfated polysaccharide polypeptidoglycan isolated from the cell walls of the bacterium *Arthrobacter* [141]. Its antiangiogenic effect is thought to be mediated by inhibition of the binding of basic fibroblast growth factor to endothelial cell receptors. Phase I clinical trials of tecogalan in solid tumors and in AIDS-related Kaposi's sarcoma (KS) are currently being conducted at several sites. The primary toxicities observed to date have been fever, rigors, and prolongation of the activated partial thromboplastin and prothrombin times [142]. The coagulation toxicities have been ameliorated by prolonging the infusion duration at a given dose. Several standard dosing schedules of this compound are being investigated, as well as prolonged administration by continuous intravenous infusion. **Recombinant human platelet factor 4** is an antiangiogenic protein undergoing phase I/II testing in metastatic colon carcinoma and AIDS-related KS. When used via an intralesional injection in AIDS-related KS, this compound produced a 57% response rate in injected lesions (two complete responses) [143]. The primary toxicity was pain at the injection site. A dose-finding study in metastatic colon cancer examined schedules utilizing 30-minute infusions given up to 5 times a week; no significant biochemical, hematologic, or coagulation toxicities were noted [144]. **TNP-470** is a fumigillin analog that has demonstrated potent antiangiogenic activity both in vitro
and in vivo [145]. Phase I/II studies are currently being conducted in AIDS-related KS and hormone-refractory prostate cancer. Although no measurable responses have been reported, in one AIDS-related KS trial two patients given the higher dose levels experienced significant reductions in painful extremity edema [146]. Toxicities have been mild, and consist primarily of fatigue without muscle weakness [147].

Summary

The treatment of patients with advanced malignancies has often been discouraging, owing to the poor response rates and significant toxicity of currently available antineoplastic agents. Recently, various new agents with novel mechanisms of action have been developed and are in clinical trials. For the first time in decades, the possibility of improvement in the treatment of patients with advanced and refractory malignancies exists.

Encouraging phase I and II activity of camptothecin and its analogs has stimulated further development of these agents alone and in combination with other cytotoxic agents. Similarly, gemcitabine is being studied alone in patients with advanced pancreatic cancer, and as a component of combination regimens. The promising results obtained with docetaxel in patients with metastatic breast cancer, as well as in patients with non-small-cell lung cancer, also warrant further study. Finally, an understanding of the metabolism and mechanisms of action of fluorouracil has created new possibilities to enhance its clinical activity. These new modulators extend the spectrum of activity of fluorouracil. Continued evaluation of these exciting compounds will further define their role in the management of cancer patients.

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