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ORIGINAL ARTICLE

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New promising anticancer agents in development: what comes next?

Abstract Anticancer drug development has recently shifted in part to development of more innovative anticancer agents. The increasing knowledge of the pathogenetic mechanisms involved in cancer cell growth has enabled the introduction of drug screening that is more mechanism-based. The realization that new targets should be preferentially evaluated as sites for anticancer drug treatment has led to the introduction of drugs such as the taxanes. Following this logic, several new drugs are being developed. Minor groove-binding agents such as carzelesin and oral platins lacking organ toxicity, such as JM216, have recently entered clinical studies. The activity of gemcitabine is a result of its being a cytidine analogue and being competitively incorporated by DNA; the drug has shown interesting activity in non-small-cell lung cancer and, although registration is imminent, issues regarding the optimal dose and administration schedule have yet to be resolved. Tomudex is a thymidylate synthase inhibitor with interesting activity in colorectal cancer. Activity in colorectal cancer is also of interest for irinotecan, the first clinically applied topoisomerase I inhibitor, an enzyme that is another example of a new target for anticancer drugs. Irinotecan has produced consistent response rates of 20–30% in six different studies in colorectal cancer. The other topoisomerase I inhibitor that is in the advanced stage of development is topotecan. This drug has shown activity in second-line chemotherapy for ovarian cancer and small-cell lung cancer. Another interesting feature of topotecan is the availability of an oral formulation with consistent bioavailability. Drugs interfering with cellular signal transduction, such as the protein kinase C inhibitors, are in the development spotlight. Finally, the use of old drugs in new ways, such as immunoconjugates of doxorubicin, holds promise for the near future.

Key words Cancer · Topoisomerase · Antimetabolite · Minor groove · Platin

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Introduction

In the late 1970s/early 1980s, new anticancer drug development focused largely on analogue development. With a few exceptions this approach has not been productive, and many investigators have even stated that this approach is "boring." In recent years we have witnessed a switch toward development of more innovative new anticancer agents either by the use of previously known targets in a more sophisticated way or on the basis of the realization that new targets should be preferentially evaluated as sites for anticancer drug treatment. The latter has led to the introduction of innovative drugs such as the taxanes.

Following this logic, several new drugs are being developed or are near registration. Reviewing all the drugs presently under development is an impossible task. In view of this limitation, this review is restricted to those drugs that have recently been registered or are close to registration and to a sample of the drugs presently under study in Europe.

Innovative use of well-known targets

Although, as stated above, some investigators consider analogue development to be boring, this approach has led to the introduction of some well-established drugs. Two of the drugs that are currently in the advanced stage of development (gemcitabine and tomudex) are antimetabo-

lites and, therefore, have some resemblance to very old drugs. However, for both drugs, increased knowledge of cell biology has produced refinements to their mechanism of action. In a similar way, drugs with different mechanisms of action are being developed.

Carzelesin

The DNA sequence-specific minor groove-binding alkylating agents have recently attracted much attention. One of these is carzelesin, presently under study in the European Organization for Research and Treatment of Cancer (EORTC) Early Clinical Studies Group (ECSG). Carzelesin was found to inhibit DNA synthesis by stabilizing the native B-form DNA helix through reversible binding to the N^3 position of adenine in the minor groove [66]. Carzelesin is a prodrug containing a nonreactive chloromethyl precursor to the cyclopropyl function. Activation requires hydrolysis of a phenylurethane substituent followed by ring closure to form the cyclopropyl-containing DNA-reactive intermediate. Carzelesin has activity against L1210 leukemias and a variety of rodent solid tumors as well as a panel of early-stage human xenografts, including colon CX-1, lung LX-1, ovarian 2780, and prostate DU-145 (unpublished results). Further studies have revealed that the drug induces regression in advanced-stage ovarian 2780 tumors [40] and in a variety of colon adenocarcinoma and rhabdomyosarcoma xenografts [31], showing no apparent cross-resistance to vincristine, melphalan, or topotecan [31].

The EORTC-ECSG has performed two phase I studies. With a daily × 5 schedule, dose-limiting toxicity was observed at a dose of 40 μg/m² per day, consisting of leukocytopenia and thrombocytopenia that were delayed and cumulative [67]. Bolus administration every 4 weeks appeared more practical, although it produced similar side effects [6]; this schedule at a dose of 150 μg/m² will be used in phase II studies.

JM 216

JM 216 [bis-acetoammine-dichlorocyclohexylamine-platinum(IV)] is a novel platinum complex that is active in cisplatin-resistant cell lines through the oral route. A split-dose schedule appeared most effective [42]. In a phase I study performed at the Royal Marsden Hospital, London, pharmacokinetics showed saturable absorption after single bolus administration [37]. With a daily × 5 schedule, 31 patients were treated at doses over the range of 30–140 mg/m² per day; toxicity consisted mainly of myelosuppression at dose levels at which pharmacokinetics did not show saturation. The maximum tolerated dose (MTD) appeared to be 120–140 mg/m² per day when the drug was given every 4 weeks. Evidence of antitumor activity was noted in patients with ovarian cancer, non-small-cell lung cancer (NSCLC), and mesothelioma. There was a linear relation between the area under the curve and the maximal concentration (C_{max}) for both free and total platin, and the terminal half-life of free platin was 7.45 ± 4 h. A dose of 100 mg/m² per day × 5 is recommended for pretreated patients and that of 120 mg/m² per day × 5, for non-pretreated patients [37]. Phase II studies have recently been initiated in small-cell lung cancer (SCLC), ovarian cancer, and NSCLC.

Table 1 Gemcitabine in NSCLC: phase II studies[a] (*CI* Confidence interval)

Dose (mg m^{-2} week^{-1})	Number of responses/ number of patients	Response rate (%)	95% CI	Reference
800–1000	16/ 79	20	12–31	[4]
1000	41/189	22	16–28	[46]
1000–2800	8/ 31	26	12–45	[25]
800	1/ 30	3	0–17	[62]
1000–1250	15/ 76	20	12–31	[2]
1250	6/ 29	21	8–40	[7]
1250	33/151	22	16–30	[26]
Total	119/585	20		

[a] The median response duration was approximately 8 months

Gemcitabine

Gemcitabine (2′,2′-diafluorodeoxycytidine) is an antimetabolite with close resemblance to the endogenous nucleoside cytidine. Therefore, it is a proper substrate for deoxycytidine kinase, the enzyme that phosphorylates nucleosides into nucleotides. The cytotoxic effect of gemcitabine relates to competitive incorporation of the nucleotide into the growing DNA strand, resulting in inhibition of DNA synthesis.

Different phase I studies using different schedules have produced various dose-limiting toxicities, but the side effects of gemcitabine are diverse. The drug induces leukocytopenia and thrombocytopenia, fatigue, hepatotoxicity, nausea, vomiting, and flu-like syndrome. A broad range of phase II studies have been performed, most using a schedule comprising 3 weekly administrations followed by a 1-week rest period. In most studies the starting dose was 800 mg/m² given over 30 min; however, it has become clear that higher doses can be used. In ovarian cancer, response rates of approximately 20% were observed in patients with disease refractory to platinum-based chemotherapy [41, 44]; however, as a third study did not yield responses, the role of gemcitabine remains unclear.

The most convincing evidence for the activity of gemcitabine has been obtained in NSCLC. A total of seven phase II studies have been conducted using doses of 800–2800 mg/m² given weekly for 3 weeks followed by a 1-week rest (Table 1) [2, 4, 7, 25, 26, 46, 62]. The results of only one study were negative; those of the other six showed a response rate of 20–26%. Given this narrow range and the overall 20% response rate obtained in the 585 patients studied, it is quite likely that this response rate is a true reflection of the actual activity. Overall, the median duration of response was 8 months in a patient population

Table 2 Gemcitabine + cisplatin in NSCLC: activity

Gemcitabine	Cisplatin	Q (weeks)	Number of patients	Response rate (%)	Reference
1000 mg/m², days 1, 8, 15	100 mg/m², day 15	4	60	38	[63]
1000 mg/m², days 1, 8, 15	100 mg/m², day 15	4	38	46	[3]
1000 mg/m², days 1, 8, 15	100 mg/m², day 2	4	46	58	[19]
1000 mg/m², days 1, 8, 15	100 mg/m², day 1	4	26	42	[58]

that usually has a life expectancy of 3–6 months. Comparative studies have not yet been performed. This response rate is on the same order of magnitude as that achieved with a wide variety of other drugs and therefore, gemcitabine should presumably not be used as monotherapy for NSCLC.

On the basis of this conclusion, the results obtained with gemcitabine in combination with cisplatin, presumably the most active single agent in NSCLC, are interesting. In view of their different toxicities, it seemed attractive to combine gemcitabine with cisplatin. The recommended dose from a phase I study was 1000 mg/m² gemcitabine given on days 1, 8, and 15 with cisplatin at 100 mg/m² given either on day 1 or 2 or day 15 of a 28-day cycle. After establishing the recommended dose in a phase I study, Steward et al. [63] performed a phase II study in 60 patients. The response rate was 38%, but the duration of response has not been reported in full detail; this is also true for the other three studies that confirm this level of activity (Table 2) [3, 19, 58]. Given the confidence limits of the response rates observed in these studies, we may assume that the actual response rate in large numbers of patients will be between 40% and 50%, which can also be achieved using other regimens. Therefore, one must ask whether the toxicity profile favors the use of this regimen. The major side effects seen in all three studies were myelosuppression and nausea and vomiting. Neutropenia of grades 3–4 occurred in 47–51% of courses; thrombocytopenia of grades 3–4 in 25–51%, and severe nausea/vomiting, in 50–53% despite the use of adequate antiemetics. Other side effects were mainly mild. However, it should be noted that comparative studies have not yet been reported. In view of these data, the conclusion should be that until comparative studies including large numbers of patients have been performed, the combination of cisplatin and gemcitabine cannot be recommended for standard use in NSCLC, although gemcitabine has recently been registered in several countries.

Tomudex

Thymidylate synthase catalyzes the reductive methylation of deoxyuridine monophospate to deoxythymidine monophosphate, the rate-limiting step in the de novo synthesis of deoxythymidine triphosphate (TTP). As TTP is the only nucleotide specific for DNA synthesis, thymidylate synthase has been postulated to be an attractive target for anticancer agents; tomudex is a water-soluble inhibitor of thymidylate synthase.

Two phase I studies using bolus administration every 3 weeks have been performed ([36]; unpublished results). The side effects observed as being dose-limiting were elevation of serum liver enzyme levels, malaise, nausea, and decreasing performance score. The recommended dose for phase II studies was taken from the European phase I study as 3.0 mg/m². The initial phase II program included studies in colorectal cancer, breast cancer, pancreatic cancer, NSCLC, and ovarian cancer. On the basis of previous experience with the parent compound and observations from the phase I studies, the expectations were high for ovarian cancer; however, the phase II study resulted in a response rate of only 7% [20]. Similarly, activity was only modest in NSCLC and pancreatic cancer [20]. However, a response rate of 25% was seen in 46 patients with pretreated breast cancer, and most exciting was the 29% response rate achieved in 177 patients with colorectal cancer [20]. Therefore, the latter disease was used as the initial target for phase III comparative studies.

In the first randomized study, 439 patients with previously untreated advanced colorectal cancer were randomized to receive either tomudex given at 3 mg/m² every 3 weeks (n = 222) or 5-fluorouracil (5-FU) at 425 mg/m² per day plus leucovorin at 20 mg/m² per day (n = 212) given on 5 consecutive days every 4–5 weeks [69]. The latter is worldwide the most frequently used regimen of 5-FU and leucovorin. Five of the patients registered never received treatment. Prognostic variables and patients' characteristics were well matched between the two groups. At a median follow-up of 5.3 months the response rate was higher (20%) in patients receiving tomudex than in those receiving 5-FU + leucovorin (13%; P = 0.059, odds ratio 1.7), indicating that patients were 1.7-fold more likely to respond to tomudex than to 5-FU + leucovorin. The time to progression and overall survival were similar in both arms. The important difference was seen in side effects and palliation. Most importantly, tomudex was associated with significantly less grade 3–4 leukocytopenia and mucositis ($P < 0.001$). However, tomudex was also associated with a higher incidence of elevated liver enzymes, although these elevations were reversible, self-limiting, and did not coincide with subjective changes in patients' well-being. In contrast, more patients in the tomudex group showed improvements in performance status and weight gain, stressing the relative lack of important toxicity. Moreover, as a result, patients treated with tomudex spent less time in hospital for treatment. Clearly, tomudex is as active as the present standard chemotherapy, 5-FU + leucovorin, in colorectal cancer, has fewer side effects, and is easier to give.

Drugs acting on new targets

Taxanes

Taxanes have been reviewed extensively elsewhere and are therefore not discussed in this review.

Topoisomerase I inhibitors

In the late 1960s/early 1970s, camptothecin, extracted from the tree *Camptothecan accuminata*, showed hints of antitumor activity in limited clinical studies [28, 45]. However, the drug also caused unpredictable severe toxicity, mainly consisting of myelosuppression, hemorrhagic cystitis, and diarrhea, leading to the discontinuation of its development [15, 43, 45]. Only in the mid-1980s was the nuclear enzyme topoisomerase I identified and reported as the sole target of camptothecin [32].

Topoisomerase I is a monomeric 100-kDa polypeptide encoded by a single copy gene located on chromosome 20q12-13.2 [21, 35, 60]. It relaxes torsionally strained (supercoiled) duplex DNA in such a way that replication and transcription can proceed. This is achieved by the formation of a covalent adduct between topoisomerase I and DNA, known as the cleavable complex. This intermediate induces a single-strand nick in the phosphodiester backbone of DNA, allowing the intact strand to pass through the nick. DNA relaxation results from swiveling at this nick and plays an important role in DNA replication and RNA transcription. Subsequently, the enzyme-bridged breaks are resealed by topoisomerase I (religation). All topoisomerase I inhibitors stabilize the cleavable complex between DNA and topoisomerase I reversibly. However, stabilization of the cleavable complex is not sufficient for the induction of cell death. The cytotoxicity of the drugs can be explained by the so-called fork-collision model. The interaction between an advancing DNA replication fork and cleavable complexes may result in irreversible arrest of DNA replication, formation of a double-strand break at the fork, and conversion of the cleavable complex into cleaved complexes. These events lead to arrest of the cell cycle in the S/G_2 phase and, ultimately, to cell death [16, 34]. It should be noted that data are available for all topoisomerase I inhibitors presently being studied in clinical trials showing that cytotoxicity increases with exposure duration. Short-term exposure to high concentrations is less effective than long-term exposure to low concentrations [10].

Most advanced in clinical development are irinotecan (CPT-11) and topotecan. Irinotecan is a semisynthetic analogue of camptothecin, has improved water solubility, and is a prodrug. In vivo it is enzymatically converted to its active metabolite (SN-38), which has antitumor activity $\geq$100-fold that of the parent compound [38, 39]; the half-life of SN-38 is long and varies from 10–30 h [16].

Irinotecan was clinically developed in Japan, Europe, and the United States. The Japanese studies have been reviewed elsewhere, and in Japan the drug was registered in 1991. The following review relates to the European and United States trials. The phase I studies [16] mainly involved weekly and 3-weekly regimens, with single doses being given over 30–90 min. The dose-limiting toxicities in all these studies were neutropenia and diarrhea. The neutropenia is dose-related, generally of brief duration, and noncumulative. The diarrhea can be divided into two specific types: an early-onset type that begins during or immediately after irinotecan infusion and a delayed type that occurs after several days as secretory diarrhea. Whereas the first type is fairly well controlled by the use of standard doses of anticholinergic drugs and, to some extent, by serotinin-receptor antagonists, the second type can be prevented only by high-dose loperamide administration. With this type of support the MTD can almost be doubled [1]. In addition, very recent and preliminary data suggest that the new antisecretory antidiarrheal agent acetorphan may reduce the duration of the diarrhea [24].

As stated above, data from in vitro studies are available that indicate that irinotecan may have increased therapeutic efficacy when given at a low dose for protracted periods [30]; however, few clinical studies have taken this potentially relevant information into account. Even if one considers the very long terminal half-life of the active metabolite SN-38 (10–30 h), the most frequently studied weekly schedule does not mimic continuous exposure for protracted periods. Catimel et al. [11] recently reported the results of their phase I study of irinotecan; the only other clinical phase I study exploring protracted exposure was performed by Ohe et al. [48] and involved a 5-day continuous infusion. In the study of Catimel et al. [11], irinotecan was infused intravenously over 30–90 min on 3 consecutive days. The main side effects related to this schedule, again, were diarrhea and leukocytopenia. High-dose loperamide administration was without clear efficacy in reducing the severity and/or duration of diarrhea. It is a matter of concern that the investigators suggest that this schedule of drug administration may result in leukocytopenia that is cumulative. This would hamper further development of prolonged-exposure schedules.

The previously reported study on a 5-day continuous-infusion schedule [48] concluded that dose-limiting toxicity was reached at 40 mg/m^2 per day. Two of six patients had grade 4 diarrhea; however, there is no mention in this report of any effort to decrease the severity and/or duration of the diarrhea using concomitant medication. Moreover, the coinciding leukocytopenia appears to be relatively mild. Therefore, with extended support the dose-limiting toxicity associated with this schedule could presumably have been higher. Bearing the latter in mind, it is also interesting that regardless of the administration schedule, all recommended doses for phase II studies have been centered on a total dose per course, with the dose intensity being roughly 100 mg/m^2 per week. Apparently the clinical data indicate that the dose intensity is independent of the administration schedule. This further stresses the need to explore protracted exposure on the basis of the available preclinical data [30].

In view of the focus of phase I studies on weekly or 3-weekly administration schedules, all phase II studies

Table 3 Phase II studies of irinotecan in colorectal cancer (*CT* Chemotherapy, *PD* progressive disease, *NG* data not given)

Number of evaluable patients	Prior CT?	Dose and schedule	Median response		
			Response rate (%)	Duration (months)	Reference
49	No	350 mg/m^2 q 3 weeks	29.5	8.5	[56]
19	No	125 mg/m^2 × 4 q 6 weeks	32	NG	[14]
13	No	125 mg m^{-2} week^{-1} × 4 q 6 weeks	15	NG	[51]
21	Yes	125 mg m^{-2} week^{-1} × 4 q 6 weeks	24	NG	[51]
44	Yes	125 mg m^{-2} week^{-1} × 4 q 6 weeks	25	NG	[55]
91	Yes	350 mg/m^2 q 3 weeks	20	9	[9]
62	Yes (PD)	350 mg/m^2 q 3 weeks	16	NG	[9]

performed with irinotecan have made use of one of these schedules. Focusing on the European and United States studies, the most interesting and, presumably, most convincing evidence of the antitumor activity of irinotecan has been obtained in colorectal cancer. Six phase II studies have been reported, one of them being stratified for pretreatment. Two studies used a 3-weekly schedule with a dose of 350 mg/m^2, and the other studies used a weekly schedule at a dose of 125 mg/m^2 with a 2-week rest period after 4 weeks. Response rates were quite similar and varied from 15% to 32% [9, 14, 51, 55, 56]. In all, 318 evaluable patients have been studied, and the overall response rate is 22% (Table 3). The efficacy of irinotecan as second-line therapy for colorectal cancer is particularly interesting because such patients do not usually respond to any type of treatment. Moreover, the only study that obtained response duration [55] was a large French study in 91 patients that indicated a mean response duration of 9 months for a pretreated patient group, which is relatively long.

Topotecan is a semisynthetic camptothecin analogue that also has improved water solubility. It undergoes pH-dependent reversible hydrolysis of the E-ring lactone, whereas some studies have suggested that only the closed lactone form is active [21, 33]. There have been numerous phase I clinical studies using topotecan, involving many drug administration schedules [16]. The dose-limiting toxicity is transient, noncumulative neutropenia, and the drug appears to have few other side effects. Topotecan has a half-life of 1–4 h [16]. The in vitro data on long-term exposure [30] and the objective responses observed in the phase I studies with a daily × 5 schedule mean that extensive clinical phase II studies of this schedule are currently being performed. It appears that the drug is active in a variety of tumor types, with the most interesting activity being noted in ovarian cancer [64] and SCLC [5]. A closer resemblance to the prolonged-exposure model has been achieved using a continuous-infusion schedule over 21 days [29]. In addition to leukocytopenia, this schedule induces thrombocytopenia. It should be noted that in the phase I study using 21-day continuous infusion, several responses were reported in tumor types that are usually considered chemotherapy-resistant. A 21-day infusion schedule is cumbersome for the patient, and recent data suggest that myelosuppression may be cumulative [18].

As the oral bioavailability of topotecan is approximately 30%, with limited interpatient variation [17], this route of administration may provide a more convenient approach to achieving prolonged clinical exposure. A phase I study of a 21-day exposure regimen using this oral formulation has been reported [59]. This study reported dose-limiting diarrhea at a dose of 0.6 mg/m^2 b.i.d.; myelosuppression was mild. Therefore, the recommended dose is 0.5 mg/m^2 b.i.d., but it was suggested that due to the saturable depletion of topoisomerase I, shorter exposure periods should be investigated.

The topoisomerase I inhibitors GI 147211, 9-aminocamptothecin, and its prodrug 9-*N*-camptothecin have also recently entered clinical studies. Topoisomerase I inhibitors show synergistic in vitro cytotoxicity with other anticancer agents such as cisplatin and etoposide. Early data from clinical studies appear to support this observation [34]. However, further preclinical studies should be performed to determine the mechanism of interaction and optimal scheduling of the different drugs.

Farther beyond the horizon, some new targets and brand-new concepts are emerging in the clinical setting. These include ways to interfere with the cell membrane and cell signals.

Signal-transduction interference

The cell membrane has proved to be the key site of many elements involved in the control of fundamental cell processes [12, 57]. Cells receive information at their exterior surface and, due to their size or hydrophilicity most of the information-delivering molecules cannot enter the cell. Therefore, the information must be transduced after binding to exterior membrane receptors to elicit the appropriate biological response in the cell interior (for further details, see the review by Workman [68]). Drugs that interfere with such processes are one of the new treatment concepts emerging in anticancer therapy, and several drugs that interfere with the signal-transduction pathway have entered the clinical development stage.

Membrane-interactive lipids exert a wide variety of cellular actions [8], and several have undergone limited clinical studies. The drug studied most extensively clinically is hexadecylphosphocholine (miltefosine), which was

inactive in phase II studies using oral application. However, this drug was found to function as a growth factor for both white blood cells and platelets [54]. Further preclinical studies have confirmed these clinical observations [47], and the drug is currently under consideration as a hematopoietic growth factor.

The other target that is presently being investigated in clinical studies is protein kinase C (PKC), an enzyme with many functions [27]. Bryostatins are activators of this enzyme [50], which causes cytotoxicity. Bryostatin I is currently in phase I studies. However, most interest is focused on PKC inhibition, producing cell death. PKC inhibitors such as CGP 41251 and others are currently nearing the stage of clinical trial.

Other new targets

The list of new targets for potential anticancer drug development can be extended considerably. However, reviewing each and every one of these is beyond the scope of this article. Most important is the conclusion that many investigators involved in this field have realized that progress in the systemic treatment of cancer could result from adequate use of these new targets rather than from efforts to develop drugs with reduced toxicity.

Teaching old drugs new tricks

The innovative use of older targets is discussed above. A better understanding of mechanisms of action can also revitalize interest in drugs that have undergone "pharmacoptosis" previously [65]. This revitalization of interest initiated by Von Hoff [65] has further stimulated polyamine research as a potential pathway for anticancer treatment, and the EORTC-ECSG has recently begun clinical trials with the polyamine inhibitor CGP 48664. However, old drugs can be used in many ways. Dose intensity has been in the spotlight for a number of years.

Increases in dose intensity can be achieved by increasing the dose per administration without changing the treatment schedule. This has become possible with the recent introduction of supportive drugs such as hematopoietic growth factors, serotinin-antagonist antiemetics, and techniques such as peripheral stem-cell transplantation. With a few exceptions, studies on dose-intensity increases achieved using these methods have not been rewarding. Therefore, interval shortening without changing the dose per administration has recently received increased attention. Early data indicate interesting results. For example, renewed investigation of the potential of frequent administration of high doses of cisplatin [52] with or without other drugs has produced interesting results in head and neck cancer [53] and ovarian cancer (unpublished results). These studies should be extended.

Since antitumor treatment using cytotoxic drugs is far from tumor-specific, several ways to make existing drugs more specific have been explored. One of these is the use of immunoconjugates, which involves coupling of a tumor-specific antibody to a cytotoxic drug [49]. Coupling of a polymer to a drug is another possibility [22].

A recently developed immunoconjugate is BR96-DOX [49]. BR96 is an antibody against the Le^y antigen that is overexpressed by most human cancer cells. One molecule of BR96 can bind eight molecules of doxorubicin, and the immunoconjugate is internalized by the tumor cell, making doxorubicin more readily available at its site of action. An example of a polymer conjugate in clinical trials is PK1 [23, 61], in which the polymer is attached to doxorubicin through a peptidyl moiety. The complex enters the cell through endocytosis, after which doxorubicin is enzymatically released, resulting in tumor-cell-specific availability. These strategies hold theoretical promise for clinical activity, but study results must be awaited.

Prodrug therapy can also be explored in a different way. Prodrugs used in cancer chemotherapy are nontoxic and pharmacodynamically inert, but in cancers with an appropriate activating enzyme they are transformed into highly toxic metabolites. In general, the prodrug approach to cancer chemotherapy has been disappointing because cancers have only rarely been found to have a unique activating enzyme. The antibody-directed enzyme prodrug therapy (ADEPT) approach overcomes this problem by directing enzymes to tumors through linked enzyme-antibody conjugates [13]. In a number of human tumor-xenograft systems, enzymes have been linked to different antibodies to direct them to various human tumor xenografts. When antibodies were linked to the enzyme carboxypeptidase G2 followed by administration of nitrogen mustard (prodrugs that are substrates for the enzyme), tumor regression was observed in every case, although the tumors were insensitive to conventional agents such as cisplatin, actinomycin D, methotrexate, and 5-FU [13]. Again, results of clinical trials will have to be studied before we can draw any conclusions on the beneficial effects of this approach.

Conclusions

Recent developments in anticancer drug research have yielded important results. Drugs making use of innovative effects on old targets have been developed and show activity in a variety of tumor types. In addition, drugs using new targets, such as the taxanes and topoisomerase I inhibitors, have produced important improvements in the therapeutic potential for cancer patients. By these methods it is likely that anticancer drug development will add new agents to the existing arsenal in the near future.

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