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The development of new chemotherapeutic agents

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There is a great need for new drugs to treat the increasing numbers of patients with disseminated cancers. Many of the known anticancer drugs, including the taxoids, docetaxel (Taxotere®) and paclitaxel (Taxol®), are derived from natural products and there will be many more active compounds to be discovered amongst the 300 000 plant species available for evaluation. Cytotoxic agents may kill cancer cells by a variety of means. Thymidilate synthase inhibitors such as LY231514 and raltitrexed (Tomudex®) have shown activity against a variety of solid tumours including colorectal cancer. The antifolate, trimetrexate, and the nucleoside analogue, gemcitabine, have also shown anticancer activity. Amongst the topoisomerase I inhibitors, CPT-11 is being developed for use against colorectal cancer. Non-cytotoxic agents which interfere with processes such as angiogenesis may also have a role in future treatments for disseminated cancers.

Keywords: LY231514, raltitrexed (Tomudex®), trimetrexate, gemcitabine, CPT-11.

Introduction

Within Europe there are an estimated 1.1 million cancer deaths every year, more than two-thirds of which are due to systemic disease which is refractory to current therapeutic options. Chemotherapy and hormonal therapy are undoubtedly the most successful approaches to systemic cancer therapy that are available to the clinical oncologist. The current portfolio of active compounds includes 31 chemotherapeutic agents and about 11 hormonal agents. Many of these compounds come from nature and there is a large pool of as yet undiscovered compounds in the estimated 300 000 plant species available. Less than 10% of these have been extracted and only 3% have been evaluated in even the most basic antitumour assays. Less than 500 agents have been evaluated clinically for antitumour activity. Taxoids are the latest addition to the antitumour armamentarium that is derived from nature.

Several new classes of antitumour agents have been developed over recent years, including agents that are not directly toxic to cancer cells, as well as cytotoxic compounds (Table 1). This review will concentrate on examples from several of these classes of new agents.

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Cytotoxic agents

LY231514

This new thymidilate synthase inhibitor is taken up into the cell using the reduced folate carrier system and is polyglutamated within the cell, leading to high intracellular concentrations. LY231514 has shown preclinical activity in models of colorectal, kidney, hepatocellular and non-small-cell lung cancers (NSCLC). Clinical phase I studies have shown that the dose-limiting toxicity is neutropenia, and the recommended dose and schedule is 600 mg/m^2 every 21 days [1]. Phase I clinical studies are being initiated in cancers of the breast, cervix, oesophagus, head and neck, kidney, pancreas and stomach, as well as NSCLC and colorectal cancer.

Raltitrexed (Tomudex®)

This potent thymidilate synthase inhibitor has been shown to be myelotoxic in phase I studies, and also to show hepatotoxicity, skin toxicity and to cause diarrhoea, nausea and vomiting [2]. The recommended dose and schedule for phase II studies is 3 mg/m^2 every 21 days [3]. Results of phase II studies are summarized in Table 2.

Raltitrexed and 5-fluorouracil (5-FU) with folinic acid have been compared in a phase III trial in patients with colorectal cancer without prior treatment. Raltitrexed was shown to be as active as 5-FU/folinic

Table 1. Classes of new antitumour agents with clinical promise

Chemotherapeutic agents
Antimetabolites:
Thymidilate synthase inhibitors
Antifolates
Nucleoside analogues
Taxoids
Topoisomerase I interacting agents
Non-chemotherapeutic agents
Hormonal agents
Differentiation-inducing agents
Antiangiogenesis agents

acid with regard to time to progression and time to death, and was reported to show fewer side-effects than the 5-FU/folinic acid combination [7].

Trimetrexate

This compound is a new antifolate and acts as an inhibitor of dihydrofolate reductase causing depletion of intracellular reserves of reduced folate, impaired nucleotide synthesis and consequently reduced synthesis of RNA and DNA [8]. In contrast with methotrexate, trimetrexate does not interfere with the transport of reduced folates and is not polyglutamated within the cell [9]. Both leucovorin and thymidine can act as antidotes to trimetrexate. In phase I trials, trimetrexate showed myelotoxicity, with additional instances of local phlebitis, rash and acute hypersensitivity reactions [10,11]. The recommended dose and schedule is either 6.8–8.0 mg/m^2 for 5 days every 3–4 weeks, or a single dose of 220 mg/m^2 every 3–4 weeks. Phase II studies have demonstrated moderate clinical activity against cancers of the breast, head and neck, bladder, prostate, and NSCLC [12–18]. Trimetrexate has also shown activity against childhood recurrent acute lymphoblastic leukaemia and childhood renal cell cancer.

Gemcitabine

Gemcitabine is an important nucleoside analogue for the treatment of solid tumours. Gemcitabine has activity against pancreatic cancer and a phase III trial has been conducted [19,20]. Patients were randomly assigned to receive gemcitabine or 5-FU. One of the important clinical endpoints of this study was clinical benefit to the patients, and significantly more patients experienced clinical benefit in the gemcitabine group, compared with the 5-FU group (Table 3). There was also a significant survival advantage in the gemcitabine group, particularly when the 9-month survivals were compared (Table 3).

CPT-11 (Campto®)

CPT-11 is one of a whole new class of compounds, the topoisomerase I inhibitors. CPT-11 is a water-soluble derivative of camptothecin and is hydrolysed in the blood, gastrointestinal tract and liver, to its active form, SN-38. This compound exists in both lactone and acid forms and there is differential activity between the two forms, with the lactone form having the higher antitumour activity and the acid form being more myelotoxic [21,22]. CPT-11 has extensive antitumour activity in preclinical model systems, including established tumour cell lines, freshly explanted human cancers, mdr-expressing cell lines, murine tumours and human tumour xenografts [23]. The dose-limiting toxicities established in phase I studies are neutropenia, diarrhoea, nausea and fatigue, and the recommended dose and schedule is 350 mg/m^2 every 3 weeks, or 220 mg/m^2 every 2–3 weeks [24]. The results of phase II studies are shown in Table 4. Colorectal cancer is the prime tumour target for CPT-11.

Table 2. Summary of phase II studies with raltitrexed

Tumour type	*n*	Response rate (%)	95% CI	Ref.
Colorectal	176	26	19–33	[4]
Breast	46	25	13–37	[5]
Pancreas	22	14	0–28	[6]

CI, confidence interval.

Table 3. Phase III study with gemcitabine in pancreatic cancer

Treatment	Clinical benefit (%)	Survival	
		Median (months)	At 9 months (% patients)
Gemcitabine	23.8*	5.7**	24
5-FU	4.8	4.4	6

*P< 0.002; **P< 0.003, compared with group given 5-FU. Data from Moore *et al.*, 1995 [19,20].

Non-cytotoxic agents

Antiangiogenesis and differentiation-inducing agents

There are a wide variety of agents under investigation for their ability to interfere with angiogenesis. These vary from old agents such as thalidomide, to very

Table 4. Summary of phase II results using CPT-11

Tumour type	Number of patients	Response rate (%) (95% CI)	References
Colorectal	178	18 (12–24)*	[25]
	160	26 (19–33)**	[26–29]
NSCLC: first-line	139	33 (25–41)**	[30–31]
Small-cell lung:			
First-line	8	50 (0–42)**	[31]
Second-line	64	41 (29–53)**	[31–33]
Cervix	117	23 (15–31)**	[34–37]
Ovary	55	23 (14–35)**	[34]
Pancreas	32	9 (0–19)**	[38]
Gastric	60	23 (12–34)**	[39]

CI, confidence interval; NSCLC, non-small-cell lung cancers; *Treatment schedule used, 350 mg/m^2 every 3 weeks. Remission duration 9.1 months; **Various schedules. Remission durations not reported.

recent agents such as interleukin-12. Some antiangiogenesis agents are in phase I and II trials, including platelet factor-4 and pentosan polysulphate. There is a wide variety of classes of compounds under investigation for their ability to cause cells to differentiate. These include tyrosine kinase inhibitors, vitamin A and vitamin D derivatives and carbohydrates.

Conclusion

Successful analogue research, combined with the definition of new molecular targets for anticancer drugs, is moving the concept of cancer treatment away from tumour cell kill towards cell differentiation and manipulation of the microenvironment of cancer cells. The clinical development and integration of these new drugs and new approaches into cancer treatment in the clinic will improve the outlook for patients with systemic disease.

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