Recent advances in cytotoxic therapy for gastrointestinal carcinoma: a review[1]

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Single-agent therapy

Until recently the use of cytotoxic drug therapy in gastrointestinal cancer has been confined to the administration of single drugs to patients with advanced, incurable, disease. The results of this approach are summarized in Table 1. The modest success of 5-fluorouracil, noted soon after its introduction 18 years ago, has tended to inhibit the evaluation of other agents, clinical resources being largely devoted to determining the optimum dose and route of administration for 5-fluorouracil. Mitomycin-C has been widely used in Japan, but there were fatalities with high doses when it was first used in the West. At lower doses it is a safe and valuable agent, but the stigma of the original toxicity has inhibited its acceptance.

By the early 1970s it became clear that intermittent intravenous administration was the optimum regimen for 5-fluorouracil and nothing more could be expected from variations in the route of administration and dose schedules (Moertel 1975). Clinicians began to explore other drugs and this shift of attention corresponded with the appearance of several new compounds that were immediately assessed. This move directly from 5-fluorouracil to new agents has meant that many of the established anti-cancer drugs have been inadequately assessed in gastrointestinal cancer. The first group of new drugs to be screened were the nitrosoureas, comprising BCNU, CCNU and methyl-CCNU (Me-CCNU). The initial assessment suggested that MeCCNU and BCNU were active in stomach and large-bowel cancer. Subsequent comparative studies in large-bowel cancer showed that MeCCNU was more effective than BCNU and that, with an overall response rate of 26%, it might have an activity comparable to

Table 1. Results of single-agent therapy in gastrointestinal carcinoma (Wasserman et al. *1975)*

	Agent	No. of patients	Response rate
Oesophagus	Bleomycin	42	17%
	5-fluorouracil	18	17%
Stomach	5-fluorouracil	448	23%
	Mitomycin-C	211	30%
Pancreas	5-fluorouracil	212	28%
	Mitomycin-C	44	27%
Large-bowel	5-fluorouracil	2107	21%
	Mitomycin-C	218	16%
	Cyclophosphamide	71	21%
	Methotrexate	111	17%

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Table 2. Preliminary assessments of new drugs

	Site	No. of patients	Response rate	Reference
Adriamycin	Stomach	8	50%	Frytack *et al.* 1975
	Large bowel	57	7%	
ICRF159	Large bowel	25	12%	Marciniak *et al.* 1975
Cytembena	Large bowel	26	0	Moertel *et al.* 1975*a*
Chromomycin-A	Large bowel	27	0	Moertel *et al.* 1975*b*

5-fluorouracil (Moertel 1975). Recent series reporting response rates of only 12% (Giles *et al.* 1974) and 9.5% (Cedermark *et al.* 1976) in colorectal cancer have been less encouraging and have shown that, in common with the other nitrosoureas, MeCCNU has the major side effect of delayed bone marrow toxicity. The nitrosoureas have rapidly become established in the management of gut cancer in America. In Britain the evaluation is proceeding more cautiously, and their place is far from certain. The results of initial assessments of other new drugs are shown in Table 2. These figures are generally disappointing, but adriamycin in stomach cancer and ICRF 159 in rectal cancer may prove of some value.

Combination chemotherapy

In gut cancer combination cytotoxic therapy is in its infancy, but there are a few results available. A randomized study in gastric carcinoma has shown the combination of BCNU and 5-fluorouracil to be superior to 5-fluorouracil alone (Moertel 1975) and an Eastern Cooperative Oncology Group study with MeCCNU and 5-fluorouracil claimed a 52% response rate (Moertel 1975). A similar study in the UK, using the same two agents, has produced only a 7% response (R Kingston 1976, personal communication). Results in large-bowel cancer are summarized in Table 3. The series reported by Falkson *et al.* (1974) and by Moertel, Schutt, Hahn, Marciniak & Reitemeier (1975) were both prospective studies which showed the combination to be more effective than 5-fluorouracil alone. In advanced bowel cancer one of two clinical problems is encountered: pelvic recurrence or blood-borne metastases. Cytotoxic drug therapy is of little benefit in pelvic recurrence, and radiotherapy is to be preferred; but for patients with liver or lung secondaries chemotherapy can be rewarding, as the series of 16 patients with predominant hepatic metastases demonstrates (Priestman 1973). In pancreatic cancer there has been a report of increased survival in patients with advanced disease treated by cytotoxics (Mallinson *et al.* 1976). The numbers were small, but this was a prospective study and survival was significantly prolonged compared with untreated controls.

Table 3. Results of combination cytotoxic therapy in large-bowel carcinoma

Regimen	No. of patients	Response rate	Reference
5-fluorouracil + MeCCNU	128	30%	Baker *et al.* 1975
5-fluorouracil + vincristine + MeCCNU	39	43%	Moertel, Schutt, Hahn & Reitemeier 1975
5-fluorouracil + BCNU + DTIC	28	43%	Falkson *et al.* 1974
5-fluorouracil + vincristine + methotrexate + cyclophosphamide	16	66%	Priestman 1973

Cytotoxic drugs and radiotherapy

Bleomycin and 5-fluorouracil are both said to have radiosensitizing effects in addition to their cytotoxic activity. Response rates of 62% (Kolaric *et al.* 1976) to 100% (Okamoto 1971) have been claimed, using the combination of bleomycin and radiotherapy in squamous cell carcinoma of the oesophagus. These were uncontrolled studies, however, and the preliminary results of a prospective trial from Cardiff have shown no benefit from adding bleomycin to radiation therapy (Priestman 1977*a*). The role of 5-fluorouracil is more promising. Moertel *et al.* (1969) demonstrated significantly prolonged survival in patients with advanced pancreatic and gastric cancer when 5-fluorouracil was added to radiotherapy. Furthermore, Arnott (1975) has shown that the duration and dose of radiation required for palliation in advanced rectal cancer may be significantly reduced by the addition of 5-fluorouracil.

Adjuvant chemotherapy

A number of studies have reported recently on the value of long-term 5-fluorouracil administration as an adjuvant after resection of rectal carcinoma in the hope of reducing the incidence of recurrence or metastasis. Three trials have suggested that 5-fluorouracil is of value (Li & Ross 1976, Mackman *et al.* 1974, Mavligit *et al.* 1976), but all have relied on historical controls. The two studies showing no benefit (Grage *et al.* 1975, Lawrence *et al.* 1975) were, however, prospective randomized series. The value of 5-fluorouracil as an adjuvant in rectal cancer is doubtful, and it has been argued that the next step, which is already being taken in America, should be trials using a combination of drugs. When there is no regimen of established value, to start such trials appears premature; moreover, by relying on cytotoxic treatment these patients may be missing the opportunity for adjuvant radiotherapy. There is increasing evidence that radiotherapy given at the time of resection helps to reduce the incidence of pelvic recurrence (Priestman 1977*b*). A number of multicentre trials are under way to establish whether such treatment is best given pre- or post-operatively, and what the optimum radiation dose is.

A number of studies in gastric cancer have employed single-agent short-term adjuvant chemotherapy after gastrectomy, but none have shown any real benefit. A controlled study reported by Rake *et al.* (1976) has suggested, however, that prolonged chemotherapy may improve results after gastrectomy. Although the numbers in this study were small, it has prompted the establishment of a multicentre trial of long-term cytotoxic therapy in operable gastric cancer; the results from this work will be eagerly awaited.

Conclusion

Interest in chemotherapy of gastrointestinal cancer is slowly increasing, but one of the major obstacles to progress is the great pessimism that is felt generally about these cancers. Certainly there have not been any major breakthroughs comparable to those seen in Hodgkin's disease or childhood cancer in recent years. But there have been a number of encouraging developments which, if incorporated into a systematic plan of sequential controlled clinical trials, may well demonstrate improvements in remission rates and survival figures which will help to relieve the gloom.

[For a comprehensive list of references, *see* Priestman (1976).]

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