Progress report

Cytotoxic therapy for gastrointestinal carcinoma

The purpose of this review is to outline what has been achieved in the drug treatment of alimentary carcinoma in recent years. It is suggested that the results demonstrate the increasing value of cytotoxic therapy in these diseases and indicate ways in which the development of such treatment may proceed. Cytotoxic drugs have been used alone and in combination with either surgery or radiotherapy in the management of gastrointestinal carcinoma.

Cytotoxic drugs alone

At present the use of cytotoxic therapy is almost invariably restricted to the advanced stages of the disease when surgery and radiotherapy have no more to offer. Carcinomas of the gut are relatively slow growing tumours with doubling times of about three months. In advanced disease the proportion of dividing cancer cells (the growth fraction) declines and avascular and necrotic areas of tumour appear, harbouring viable cancer cells in the resting (G₀) phase of the cell cycle. Cytotoxic drugs damage only dividing cells and are carried to those cells by the blood stream. So the diminished growth fraction and increasing avascularity in the late stages of solid tumour growth serve to inhibit cytotoxic action. Giving the drugs so late in the course of the disease is to give them at the least opportune time and the earlier cytotoxic therapy is started the greater the chance of success. This is true of all solid tumours but patients with gut cancer are at an additional disadvantage in that they are the group least likely to tolerate the gastrointestinal side effects so often associated with cytotoxic therapy.

This is especially true of squamous cell carcinoma of the oesophagus where the advanced stage of disease at presentation and the general debility of the patient by the time drug treatment is considered have meant that chemotherapy has been little used in this condition. As a result, it has the reputation of being one of the most cytotoxic-resistant of all cancers. There have been hopes that this situation might be changed by bleomycin. This antimitotic antibiotic was originally developed in Japan and was subsequently found to be selectively concentrated in squamous cells and therefore of particular value in squamous cell carcinoma. A number of series have reported promising results with this drug in oesophageal cancer with response rates as high as 60% and in 1973 a review of the world experience with bleomycin found an overall response rate of 33% in 42 patients. None of these papers, however, gives full clinical details. Encouraged by these apparent successes, a subsequent prospective study failed to show any subjective or objective improvement in 14 patients with squamous cell carcinoma of the oesophagus treated with Bleomycin and concluded that the drug was of no value, when used alone, in this disease. Although its value as a single agent is therefore in doubt, one promising feature of bleomycin is that it is not myelotoxic, in
contrast with the great majority of anticancer drugs, and may therefore be a useful agent in combination chemotherapy.

For many years the chemotherapy of gastrointestinal adenocarcinoma has been dominated by a single drug—the antimetabolite 5-fluorouracil. To try and exploit this agent to the full, a variety of dosage regimes and techniques of administration have been employed and in the past there has been considerable controversy over their relative merits.

Initially, an intravenous loading dose of 15 mg/kg daily for three to five days followed by once or twice weekly maintenance therapy was recommended. Subsequent studies showed that a single weekly intravenous injection, with no loading dose, gave comparable results with less toxicity. It was then suggested that prolonged intravenous infusion of the drug over 60 or 120 hours was superior to rapid intravenous injection. In some centres this idea still prevails, although prospective studies have in the past clearly shown the superiority of rapid intravenous injection.

For patients with hepatic metastases arterial infusion of 5-fluorouracil into the hepatic artery or aorta was a popular method of treatment in America in the 1960s. A number of workers reported favourable results using this technique with response rates up to 60% on 5-fluorouracil. A review of this technique has considered, however, that the discomfort to the patient, the morbidity and mortality associated with the procedure, and its expense could not be justified by the results obtained. Indeed, there has never been any convincing evidence that the results were better than those achieved with intravenous 5-fluorouracil.

A variation of this technique was reported in 1970 when promising results were obtained by combining infusion of 5-fluorouracil into the portal vein with hepatic artery ligation. A recent study has reiterated the value of combining hepatic artery ligation and cytotoxics, though in this case the 5-fluorouracil was given intravenously. There has, however, been no prospective study to confirm that hepatic artery ligation improves the results of 5-fluorouracil therapy.

The latest fashion in 5-fluorouracil therapy was initiated in 1971 when a report suggested the value of oral administration. A clinical trial at that time also showed an increased response rate when the drug was given by mouth.

Subsequent pharmacological studies have shown that the uptake of 5-fluorouracil from the gut is highly unreliable and a recent prospective trial has shown that, although it may be possible to obtain similar remission rates with oral therapy, the duration of these remissions is significantly shorter than those seen as a result of intravenous administration.

No method of 5-fluorouracil administration has been proven to be superior to once weekly intravenous therapy. If the treatment of gastrointestinal adenocarcinoma is to progress, it must be by the use of new drugs or drug combinations and not by further exploitation of single agent therapy with 5-fluorouracil. The results of 5-fluorouracil therapy are summarized in Table 1.

Another drug of value in advanced gut cancer is mitomycin-C. This antimitotic antibiotic was developed in Japan and is still associated, in many people's minds, with unacceptable toxicity. This is largely due to the initial studies on the drug in America which suggested that the response rate was only marginally greater than the mortality from treatment. Subsequent review
of these results, however, revealed that the dose used in these studies had been greatly in excess of that recommended by the Japanese\textsuperscript{30}. Once a suitable dose regime was established, mitomycin proved to be a useful drug\textsuperscript{31}. Results of Mitomycin therapy are summarized in Table 2.

A recent development in cancer chemotherapy has been the isolation of the nitrosoureas. These drugs are still under investigation and are not generally available in Britain. Initial reports from America on their use as single agents in gastrointestinal cancer have been encouraging and these results are summarized in Table 3.

Two other cytotoxic drugs have caused considerable interest in recent years. The first of these is streptozotocin which was initially shown to have a diabetogenic action due to the disruption of beta cells in the islets of Langerhans\textsuperscript{32}. In 1968 it was successfully used in the treatment of a malignant islet-cell tumour\textsuperscript{33} and subsequent reports have established its value in this condition\textsuperscript{34–36} and also indicated its value in malignant carcinoid tumour\textsuperscript{34}. It was hoped that it might prove of value in adenocarcinoma of the pancreas but apart from one marginally favourable report\textsuperscript{37} there has been no evidence of this.

The second agent is doxorubicin. This new drug has been of great value in adenocarcinoma of the breast and soft tissue sarcoma and is probably the most effective single agent in these conditions\textsuperscript{38}. The results of its use in gut cancer have therefore been awaited with great interest but, unfortunately, have proved relatively unimpressive\textsuperscript{38}. The results are summarized in Table 4

\begin{table}[h]
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\begin{tabular}{llll}
\hline
Site & Patients (no.) & Response (\%) & Reference \\
\hline
Stomach & 448 & 23 & Comis and Carter (1974)\textsuperscript{72} \\
Pancreas & 212 & 28 & Carter and Comis (1975)\textsuperscript{73} \\
Large bowel & 2107 & 21 & Carter and Friedman (1974)\textsuperscript{74} \\
\hline
\end{tabular}
\caption{Results of 5-fluorouracil therapy in gastrointestinal adenocarcinoma}
\end{table}

\begin{table}[h]
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\begin{tabular}{llll}
\hline
Site & Patients (no.) & Response (\%) & Reference \\
\hline
Stomach & 44 & 30 & Comis and Carter (1974)\textsuperscript{72} \\
Pancreas & 27 & 11 & Carter and Comis (1975)\textsuperscript{73} \\
Large bowel & 40 & 17.5 & Carter and Friedman (1974)\textsuperscript{74} \\
\hline
\end{tabular}
\caption{Results of mitomycin-C therapy in gastrointestinal adenocarcinoma}
\end{table}

\begin{table}[h]
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\begin{tabular}{llll}
\hline
Site & Drug & Patients (no.) & Response (\%) & Reference \\
\hline
Stomach & BCNU & 33 & 18 & Comis and Carter (1974)\textsuperscript{72} \\
& Methyl-CCNU & 27 & 11 & Moertel (1975)\textsuperscript{28} \\
Pancreas & BCNU & 18 & 0 & Moertel (1975)\textsuperscript{28} \\
Large bowel & BCNU & 64 & 12.5 & Carter and Friedman (1974)\textsuperscript{74} \\
& Methyl-CCNU & 40 & 17.5 & Moertel (1975)\textsuperscript{28} \\
\hline
\end{tabular}
\caption{Results of nitrosourea therapy in gastrointestinal adenocarcinoma}
\end{table}

\begin{table}[h]
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\begin{tabular}{llll}
\hline
Site & Patients (no.) & Response (\%) & Reference \\
\hline
Stomach & 8 & 50 & Frytak (1975)\textsuperscript{39} \\
Pancreas & 3 & 0 & \\
Large bowel & 57 & 7 & \\
\hline
\end{tabular}
\caption{Results of Doxorubicin in gastrointestinal adenocarcinoma}
\end{table}
and it was concluded that, if nothing else, the drug might prove of value in combination therapy in gastric cancer.

Many of the advances in cancer chemotherapy in recent years have been as a result of the use of intermittent combination drug treatment. While this technique has led to dramatic improvements in some diseases, evidence for its value in gastrointestinal cancer has accumulated more slowly. A number of regimes have been reported as being of value and these are summarized in Table 5.

It is important that these results are seen as a starting point and not a conclusion. Pessimism over the value of chemotherapy and the relative success and simplicity of single agent therapy with 5-fluorouracil have tended to inhibit the trial of new agents or combinations of drugs as they have become available. Indeed, in a recent review of the data available to the National Cancer Institute, it was found that in carcinoma of the oesophagus only one of the 30 common cytotoxic drugs had been adequately assessed and in carcinoma of the pancreas only three agents had been studied. The situation was little better in gastric cancer where only eight drugs had been evaluated\(^{40}\). There is still a great deal to be learnt about cytotoxic therapy for gastrointestinal cancer.

Chemotherapy and radiotherapy

With the possible exception of oesophageal cancer, the primary treatment for gastrointestinal carcinoma is surgery wherever possible and radiotherapy has been reserved for inoperable, residual, or recurrent growth.

Dysphagia is the most distressing symptom for patients with carcinoma of the oesophagus and this may be exacerbated in the early stages of radiation treatment as a result of the inflammatory reaction associated with radiotherapy. It has been reported that the injection of methotrexate or 5-fluorouracil before starting radiotherapy reduces the likelihood of this complication\(^{41}\). The principal interest in combining cytotoxic and radiation therapy, however, has been in their simultaneous use in the hope that the drugs would act as radiosensitisers making radiation more effective in these relatively radioresistant cancers.

Bleomycin has been shown to potentiate radiation in squamous cell carcinoma in animals\(^{42}\) and there have been a number of reports suggesting

<table>
<thead>
<tr>
<th>Site</th>
<th>Response (%)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 5FU + BCNU*</td>
<td>41</td>
<td>Kovach et al (1974)(^{15})</td>
</tr>
<tr>
<td>2 5FU + mitomycin + cytosine arabinoside</td>
<td>55</td>
<td>Ota et al (1972)(^{14})</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 5FU + BCNU*</td>
<td>33</td>
<td>Kovach et al (1974)(^{18})</td>
</tr>
<tr>
<td>2 5FU + BCNU</td>
<td>75</td>
<td>Lokich and Skarin (1972)(^{17})</td>
</tr>
<tr>
<td>Large bowel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 5FU + methyl-CCNU + vincristine*</td>
<td>43</td>
<td>Moertel et al (1975)(^{14})</td>
</tr>
<tr>
<td>2 5FU + vincristine + BCNU + imidazole carboxamide</td>
<td>43</td>
<td>Falkson et al (1974)(^{19})</td>
</tr>
<tr>
<td>3 5FU + vincristine + cyclophosphamide + methotrexate</td>
<td>66</td>
<td>Priestman and Hanham (1972); Priestman (1973)(^{46,81})</td>
</tr>
</tbody>
</table>

Table 5  Drug combinations of value in gastrointestinal adenocarcinoma

*Prospective studies in which combination therapy was superior to single agent therapy with 5FU.
the possible value of combined radiotherapy and Bleomycin in the treatment of oesophageal cancer\textsuperscript{43,44}. The clinical details available are too few and the numbers reported too small to form an opinion on the value of such therapy at present.

More information is available with 5-fluorouracil and radiotherapy in adenocarcinoma. A synergistic effect with radiation and 5-fluorouracil was noted in 1958\textsuperscript{46} and its action as a radiosensitiser was subsequently confirmed\textsuperscript{46}. After promising results from random series\textsuperscript{47,48}, a prospective trial of radiation versus radiation + 5-fluorouracil (given on the first three days of treatment only) in patients with inoperable adenocarcinoma was reported\textsuperscript{49}. These impressive results are summarized in Table 6. The figures for gastric and pancreatic carcinoma were at once supported by results from South Africa\textsuperscript{50} and the rectal series has been substantiated by another recent paper\textsuperscript{51}. Despite these results, the use of combined radiotherapy and chemotherapy has not been extensively pursued and is another area for further investigation.

**Chemotherapy and surgery**

The use of cytotoxic treatment in addition to surgery, with the object of trying to prevent recurrent or metastatic cancer, has been termed adjuvant chemotherapy. The concept is not new and its application has had a great impact on the survival figures in a number of childhood cancers\textsuperscript{52} and recent results have suggested its value in carcinoma of the breast\textsuperscript{53}.

Adjuvant chemotherapy has been used in gut cancer, thiotepa\textsuperscript{54,55}, mitomycin-C\textsuperscript{94}, and 5-fluorouracil\textsuperscript{57} have been used in stomach cancer, and nitrogen mustard\textsuperscript{58} and 5-fluorouracil (given intravenously\textsuperscript{59} and intraluminally\textsuperscript{60}) have been employed in carcinoma of the bowel. The results of these studies have been generally disappointing with, at best, only minimal evidence of improved survival.

These studies may, however, have been based on a false premise. For in these series, cytotoxic therapy was given only at operation or during the immediate postoperative period. The aim of treatment was to destroy cancer cells released into the circulation at operation, which, it was presumed, might form future metastases. Attitudes to the circulating cancer cell have changed in recent years and it is now felt that its importance in the formation of metastases has been overstated\textsuperscript{61} and there is good evidence that in rectal carcinoma this is the case\textsuperscript{62}.

In recent years, therefore, the emphasis in adjuvant therapy has changed from an attempt to destroy the circulating cancer cell to efforts to eradicate minute foci of residual disease or clinically undetectable micrometastases. In slow growing tumours such as the gastrointestinal adenocarcinomas such treatment must be prolonged for periods of up to two years if it is to succeed.

<table>
<thead>
<tr>
<th>Site</th>
<th>Mean survival time in months</th>
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<tbody>
<tr>
<td></td>
<td>Placebo + XRT</td>
</tr>
<tr>
<td>Stomach</td>
<td>5.8</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6.6</td>
</tr>
<tr>
<td>Large bowel</td>
<td>16.5</td>
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</table>

Table 6  *Results of radiotherapy and 5-fluorouracil in advanced gastrointestinal carcinoma* (Moertel, 1969)
Studies have recently been reported employing long-term adjuvant chemotherapy with cyclophosphamide in stomach cancer \(^{63}\) and 5-fluorouracil in colorectal carcinoma \(^{64,65}\). Unfortunately, the results have again been equivocal with no definite evidence of improved survival.

These studies have employed only single agent therapy and it is reasonable to suggest that the full potential of adjuvant cytotoxic therapy will not have been explored until a trial using intermittent combination therapy is undertaken. It is important, however, that great caution be used in the selection of patients for such treatment. In advanced disease all patients will ultimately die from their cancer but in early disease a number of patients will survive whether or not cytotoxic therapy is given. The long-term side effects of anticancer drugs are still relatively unknown. The fact that a number of patients receiving adjuvant therapy would already have been cured by their primary surgery, but will still be exposed to the immediate side-effects of cytotoxic agents and survive to experience any long-term complications of treatment, means that such adjuvant therapy should only be given to groups of patients where there is known to be a high risk of recurrence or metastases. Probably, the condition most suited to such a trial is rectal carcinoma where previous clinicopathological studies have allowed the definition of such an at risk group (those patients with Dukes stage B or C disease or those who have tumour in the lower two-thirds of the rectum) \(^{66,67}\).

**Chemotherapy and immunostimulation**

The importance of the immune system in cancer therapy is only just being explored but there have been results (using Corynebacterium parvum) indicating that non-specific immunostimulation may enhance the results of cytotoxic therapy in advanced cancer \(^{68}\). More recently, it has been shown that Corynebacterium parvum used alone may induce remission in advanced cancer including carcinoma of the gastrointestinal tract \(^{69}\). The possibility of future combined chemotherapy and immunostimulation is a further avenue for the development of cytotoxic therapy.

**Conclusions**

It is easy to be pessimistic about the results of cytotoxic therapy in gastrointestinal carcinoma. All too often this pessimism is based on personal experience comprising the treatment of a handful of near terminal patients with single agent 5-fluorouracil therapy. The object of this review is to show that there have been modest successes in this field in recent years and that these achievements justify the further exploration of the use of cytotoxic therapy in gastrointestinal carcinoma. Ways in which this exploration could proceed may be summarized as follows:

1. Controlled trials to evaluate new drugs, and more particularly drug combinations, in these carcinomas in order to establish optimum treatment schedules.

2. Further study of the combination of radiation and cytotoxics in inoperable disease.

3. Controlled trials to assess the value of non-specific immunostimulation as an adjuvant to cytotoxic therapy.

4. Consideration of the use of combination schedules of proven value in
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advanced disease being employed as adjuvant therapy after primary surgery in those patients considered to be ‘at risk’ of developing local recurrence or metastases.

Some work on these various aspects is already in progress but, before embarking on any new studies with cytotoxic drugs, it is important to bear in mind certain factors if this work is to contribute to the understanding of cytotoxic therapy in gut cancer as well as benefiting individual patients.

The search for the optimum drug regime should proceed in logical stages by a series of prospective clinical trials initially testing single agents to find those which are of most value in a given condition and subsequently by trials of different combinations and different dose schedules of those drugs. Such a process is time consuming and tedious but is the only way to extract the maximum benefit from the drugs available.

The criteria for assessing the response to treatment should be standardized. In solid tumour chemotherapy the criteria of response to treatment vary considerably and, as a result, some series appear to have vastly better results than others using similar regimes. To try and standardize criteria of response in given diseases is an important and difficult task. A start has been made in breast cancer by the recent suggestions put forward by the British Breast Group. In gut cancer, the problem is complicated by the frequent lack of clinically measurable disease and it would seem that the most important criteria in assessing response in this region is to compare survival times in similar groups of patients on different treatments. After all, prolonged survival is the ultimate objective of treatment and therefore the best measure of its success.

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