Perspectives and Prospects in the Chemotherapy of Gastrointestinal Cancer*

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The goal governing dosage schedules for the chemotherapy of gastrointestinal cancer has been, in general, to induce significant drug toxicity in order to insure maximum therapeutic effect. The pursuit of maximum therapeutic effect led logically to the development of "Life Islands" which permit the isolated, relatively germ-free care of patients treated with intensive chemotherapy. However, intensive chemotherapy may have deleterious effects on patients other than that of increased susceptibility to infection. It is, therefore, important to be aware of the alternative approaches implied in a recent analysis of data obtained from the Eastern Clinical Drug Evaluation Program (CDEP). In this cooperative study, Bross et al. (1966a, b, c) have shown that patients manifesting drug toxicity do not necessarily show a greater frequency of tumor regression than do patients without toxicity.

In the CDEP program a total of 956 patients were treated with 5-fluorouracil (5-FU), dimethylurethamine (AB-132), mitomycin C, chlorambucil, and 6-mercaptopurine (6-MP) in a 60-day study of objective response. There was no increase in tumor response with high toxicity scores. In fact, the patients with the greatest toxicity showed a somewhat lower tumor response. These data (Ausman, 1965; 1966; Bross, 1965; Bross et al., 1966a, b, c) suggest that overt toxicity may not always be necessary to obtain an oncolytic effect. This is further supported by a recent study of the Eastern Solid Tumor Group which compared 5-FU, fluorodeoxyuridine (FUDR), and methotrexate (MTX) at dose levels producing comparable toxicity in a group of patients with colon-rectal and breast cancer (Hall, in press; Schneiderman and Krant, 1966). With increased toxicity a plateau was reached beyond which no significant further regression of tumor could be obtained, and survival, despite tumor response, was shortened in comparison to those patients showing tumor response but minimal drug toxicity (fig. 1).

These observations as well as those of Ansfield (1964) and others (Cudmore and Groesbeck, 1964; Groesbeck and Cudmore, 1963) are supported by animal data (Louis, 1965) and suggest that it is not necessary to take patients to toxic drug levels to achieve a significant remission. Such data should reinforce our awareness of the possible deleterious effects of drug action on survival and remind us that the gain afforded by tumor regression can be lost in the morbidity and mortality induced by drugs.

The Eastern CDEP data suggest that 5-FU and mitomycin C can produce significant therapeutic effects without severe toxicity (Ausman, 1965; 1966; Bross, 1965; Bross et al., 1966a, b, c). Therefore, it is important to avoid severe

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diarrhea, stomatitis, and marrow depressions with white counts below 3,000/mm^3 or platelet counts below 75,000/mm^3. When used this way, 5-FU becomes of more general clinical usefulness in gastrointestinal cancer.

A renewed interest in alkylating agents has resulted from observations indicating objective tumor regression (>50% shrinkage) in colon-rectal cancer with AB-132 (8 of 33), gastric cancer with AB-132 and chlorambucil (6 of 26), and pancreatic cancer with AB-132 and chlorambucil (6 of 8) in a study by the Eastern CDEP (Ausman, 1965; 1966; Bross, 1965; Bross et al., 1966a, b, c).

Chlorambucil showed no activity in 15 patients with rectal cancer, while 5 of 12 responded to AB-132. Chlorambucil was given by mouth and appeared to be most effective in the upper gastrointestinal tract. Unfortunately, this study as performed by the Eastern CDEP was non-comparative and limited to only two months of observation in ambulatory patients. More critical studies of these agents need to be done. In the meantime, the ease with which chlorambucil can be given makes it worthy of serious consideration as a useful agent in gastric and pancreatic cancer, although its superiority to other alkylating agents has not been clearly shown. Similarly, AB-132 or another parenteral alkylating agent can be used in colon-rectal cancer.

Chemotherapy Combined with Surgical Treatment

Laboratory evidence has supported the usefulness of adjuvant prophylactic chemotherapy at the time of surgery in the absence of known disease. However, the clinical applications of this evidence have shown puzzling results. There is no improvement in recurrence rates in men with colon-rectal cancer who received high-dose thio-TEPA (0.8 mg/kg) at the time of surgery, although women show a significantly increased survival time (U.C.L.A. Statistical Unit, 1965). In this study a high dose, with its increased mortality and morbidity, was felt necessary. Fluorodeoxyuridine (FUDR) used as an adjuvant by the Veterans Administration study shows no significant difference in recurrence rate at 30 months (personal communication, M. W. Wolcott, 1965). These studies await simultaneous controls but evidence supports the possibility

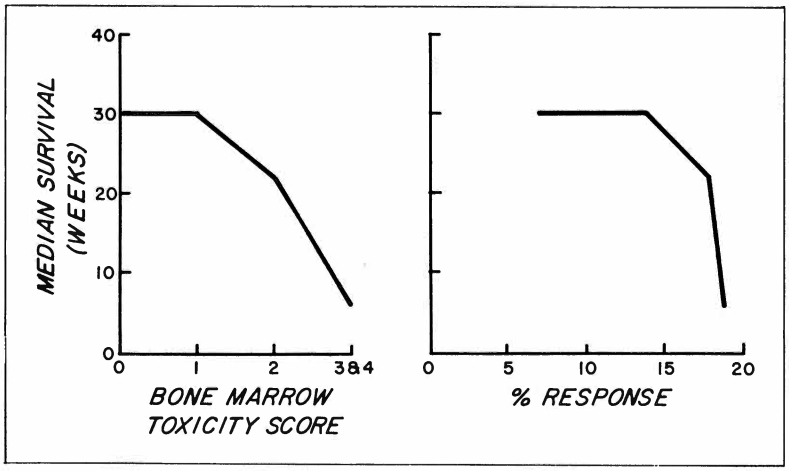

Fig. 1—Colon and rectum cancer. Eastern group double blind, 3 drug study (all drugs combined). Data and graph courtesy of M. A. Schneiderman, M. J. Krant, and T. C. Hall of the Eastern Solid Tumor Group. A major portion of this data was presented in *Cancer Chemotherapy Rept.* 50: 107–112, 1966.

that repeated 5-FU administration increases the survival of patients with occult tumor left behind.

Recently, Mackman and Curreri (1967) reported the results of a "second-look procedure" evaluating patients who had curative resections for colon cancer but who showed positive mesenteric node or serosal involvement at the time of "curative" resection. Post-operatively, these patients were given 5-fluorouracil for four or more courses prior to their "second-look," one year post operatively. Twenty patients were examined, 17 of which had no tumor at the end of this one-year period. An additional 11 patients who had direct extension to adjacent organs or structures, who were treated with only palliative resection, were examined following four to 10 courses of 5-fluorouracil. Seven of these patients were free of tumor, and three had tumor which was removed for possible "cure."

This experience has recently been supported by a report by Rousselot et al. (1967, in press) who have reported on the survival of patients over a five-year period following the effectiveness of both intraluminal 5-fluorouracil administration and systemic intravenous 5-fluorouracil in the post-operative period. This was a comparative study between nitrogen mustard and 5-fluorouracil. Adjuvant nitrogen mustard had no effect on statistics regarding recurrence rate. However, for 5-fluorouracil in those patients who had nodes (stage 3) significant improvement appeared. At five years the survival rates were 65% for the 5-fluorouracil treated versus 32% in a nationwide control series and 26% in the St. Vincent's Hospital control series. There was no apparent improvement in survival rates in stage 1 and 2 colon cancer cases (negative nodes) as compared to those seen on the basis of the nationwide averages and this reflects the over all effectiveness of surgery in early colon cancer.

These studies despite the lack of concomitant controls point out the possible usefulness of an adjuvant drug in the treatment of colon carcinoma particularly when known tumor is left behind.

The value of massive intermittent chemotherapy in the absence of clinical disease as applied to acute leukemia is a proven one (Hananian, Holland, and Sheehe, 1965), but proof of an analogous situation in colon-rectal cancer is only suggestive and requires further data. A study of this kind for gastric and bowel cancer using repeated courses of cytoxan or mitomycin C is being conducted in Europe (Karrer, 1964a and b), and the results should be of great interest when they become available.

Wood et al. (1961) and others (Cliffton and Agostino, 1963; Koike, 1964) found a decrease in the viability of circulating tumor cells following the administration of fibrinolysins or anticoagulants. The adjuvant anti-tumor action of anticoagulants has not been explored at the clinical level, but there are controversial retrospective epidemiological data that suggest that cancer patients who received anticoagulants for post-surgical phlebitis or coronary disease may have shown an increase in tumor-free survival time (Michaels, 1964). Based on this evidence, a study using heparin or fibrinolysin in the postoperative period deserves serious consideration.

Regional perfusion has limited value except in very special cases (e.g., primary or metastatic disease to liver) and may not offer more palliation than is produced by systemic drug administration. However, the aggressive approach of repeated intra-arterial administration of cytoxan and 5-FU by Bierman's group (Mesler, Winer, and Bierman, 1965) deserves closer attention as does the work of Sullivan et al. (1965) on prolonged intra-arterial infusions.

The frequency of cancer cell seeding in abdominal wounds has led to the development of animal screening methods to develop effective agents for wound irrigation that would kill tumor cells. The clinical use of monoxychlorosene (Chlorpactin XCB) and mechlorethamine (HN_2) and Thiotepa (TSPA) followed on these observations. Despite the demonstrated optimal activity of Na Hypochlorite and HN_2 as tumorcidal agents in an animal tumor implantation screen, long-term follow-up of head and neck cancer patients receiving post-operative wound irrigation with these agents has shown accelerated tumor take in the irrigated area when compared to wound washing with normal saline (Mukhtar et al., 1963). More recent five-year survival data fully supports these observations. These studies indicate that so called "topical chemotherapy" or "cytocidal wound irrigation" and should be absolutely contraindicated in the treatment of gastrointestinal cancer until long term follow-up indicates the efficacy of newer agents.

Radiotherapy Adjuvant Chemotherapy

Radiotherapy in combination with chemotherapy for synergistic or additive effect has a valid rationale, based on data of responsive animal tumors, when combined with AB-132 (Regelson and Pierucci, 1964), 5-FU (Heidelberger and Ansfield, 1963; Baclesse, Duplan, and Romer, 1964), or mitomycin C (Baclesse et al., 1964). Results from past clinical studies of this type are difficult to analyze owing to the absence of concomitant controls. In addition, such large doses of both drugs and radiation were used that the therapeutic gain possible through a more judicious selection of dosage levels may have been lost. One cannot expect patients with advanced cancer to show increased survival time when treated with combinations of radiation or drugs that would result in severe debilitation from either agent alone. Despite these difficulties there are reports of increased survival for patients with cancer of

the pancreas or stomach treated with 5-FU in conjunction with radiation (Moertel et al., 1965). The current Veterans Administration long-term continued study which uses combinations of FUDR with radiation may give a more definitive answer, but systemic or local effects on host resistance could nullify the anti-tumor effect.

New Approaches to Chemotherapy

Of particular interest are drug combinations which may act synergistically or additively by interfering with alternative metabolic pathways to eliminate the resistant tumor population. Most of the studies reported so far are preliminary and have not unequivocally demonstrated the virtues of combination chemotherapy in gastrointestinal cancer over the action of single agents. A report of regression in a pancreatic and epidermoid cancer with the combination of 6-thioguanine with duazomycin A is encouraging and is based on sound rationale (Lefkowitz et al., 1965).

Animal data in the area of collateral sensitivity has not been systematically applied to human tumors. The results of one collateral sensitivity study that could be applied immediately demonstrated that a 5-FU resistant tumor in rodents showed increased response to alkylating agents (Rutman, 1964). To my knowledge this observation, which calls for the use of an alkylating agent after failure to respond to 5-FU, has not been tested clinically. Similarly, there are laboratory observations that uracil mustard makes transplanted Sarcoma-180 tumor cells in mice more sensitive to the anti-tumor action of 6-thioguanine (Booth, Creasey, and Sartorelli, 1964). Reports of synergistic inhibition of S-180 by mitomycin C and 6-thioguanine or 5-FU (Sartorelli and Booth, 1964) are also clinically interesting, since the clinical pharmacology of these agents is well known.

A study is warranted on the use of methotrexate in 5-FU resistant patients based on the hypothesis that the resistant tumor may be dependent on a de novo pathway of thymidylate synthesis (Welch, 1963). However, Weiss and Jackson (1961) gave patients with gastrointestinal tract cancer MTX (5 mg orally per day) following 5-FU and found no evident therapeutic gain. More recently evidence has accrued that MTX can increase the level of thymidylate synthetase in human leukemia (Roberts, 1966). Thus pretreatment with MTX may deleteriously effect the response of tumor cells to 5-FU.

Suitable for more immediate study is the verification of suggested evidence in man that glucose enhances 5-FU therapeutic effect (Gotto, Belkhode, and Touster, 1964; Kessel, 1966; Lemon et al., 1963). Inosine (Gotto et al., 1964) or adenosine (Kessel, 1966) also results in increased tumor-cell uptake of 5-FU. These observations may have clinical bearing and should be tested in comparative studies.

The importance of varied dosage regimens is seen in the observations that the prolonged intravenous administration of 5-FU is less toxic than rapid drug administration. However, any therapeutic gains from prolonged infusion may be offset by the convenience of rapid intravenous injection and greater control of dosage. Moertel et al. (1964) have found no improvement in therapeutic results with 5-FU in prolonged intravenous administration as opposed to the single rapid daily loading program. Similar anti-tumor results, but with considerable decrease in toxicity, have now been observed clinically by Ansfield (1964) using 12 mg/kg/day for four days as compared to the earlier program of 15 mg/kg/day for four days, and the lower dose should clearly be the one of choice. Furthermore, the selection of patients for treatment with 5-FU should exclude severely debilitated patients, since such patients show a

decreased drug tolerance. This is supported by data in the nutritionally deprived rat (Wolberg and Curreri, 1960). In using 5-FU, it is well to remember that reports of a high order of regression such as that of Vaitkevicius et al. (1961), objective regression in 20 of 55 patients with adenocarcinoma of the large bowel, are tempered by the observation that regression was clinically worthwhile in a small proportion and even that occurred at the expense of severe toxicity in many patients. However, as discussed earlier, the evidence that responses can be seen in the absence of discomforting clinical toxicity or serious hematopoietic depression indicates that 5-FU might be given to advanced cancer patients for shorter periods and at lower dosage to avoid toxicity. In such a study Young et al. (1960) obtained responses in 10% to 15% of patients with bowel cancer with total dosage ranging from 30 to 150 mg/kg. Similar results have been obtained by Ansfield (1964) and others (Cudmore and Groesbeck, 1964).

The topical administration of 5-FU in a 10% ointment base has resulted in the disappearance of metastatic cutaneous adenocarcinoma of the bowel without damage to normal skin (Klein et al. 1965). This observation, while limited in its application, is pertinent to a consideration of using local 5-FU for palliation of recurrent or residual tumor. Up to 10% of 5-FU is adsorbed by the gastrointestinal lining of the tumor segment (Cole, 1963). Patients have tolerated up to 8 mg/kg/day P.O. for up to six weeks with gastrointestinal side effects occurring, on an average, in 18 days and hematologic toxicity in 21 days (Ellison, 1962). Although anti-tumor effects have been seen (Cole, 1963; Ellison, 1962; Kennedy and Theologides, 1961; Khung, 1965), the virtues of local intraluminal instillation of 5-FU into tumor-involved segments of bowel in prophylactic or adjuvant studies have not been adequately explored.

There are other agents becoming available, and reports of new drugs are awaited with interest. For example, antibiotics which behave similarly to actinomycin D, such as chromomycin A_3, olivomycin, and mithramycin, which combine with DNA to impede RNA synthesis (Ward, Reich, and Goldberg, 1965) may show promise (Mayevsky, 1964; Akopliants, 1962). Studies of ethidium and daunomycin which have effects in common on purine metabolism (Ward et al., 1965) may prove useful. 6-Azauridine has been reported to produce objective improvement in one of three gastric and pancreatic carcinoma patients for periods of four to five months (Welch et al., 1960).

There is fairly extensive Japanese literature regarding the clinical efficacy of a variety of porphyrin derivatives (Fukuyama, Tsuji, and Nakagawara, 1963; Matsubara et al., 1963; Tazaki, 1962; Tazaki and Furue, 1961). Hematoporphyrin mercury was reported to inhibit nucleic acid metabolism in stomach and intestine with an increased uptake of the drug in tumor as compared with normal tissue. This compound was said to produce objective and subjective improvement in several patients with gastrointestinal cancer (Fukuyama et al., 1963; Tazake, 1962; Tazaki and Furue, 1961). Similar effectiveness was reported for a cobalt protoporphyrin preparation (Fukuyama et al., 1963; Matsubara et al., 1963). It is hoped that an evaluation of these reports will not take as long as those studies involving mitomycin C.

In early clinical trials the toxicity which eventually blunts the initial enthusiasm of extended trial is frequently minimized. It was this type of experience with mitomycin C that delayed its entry into clinical practice. Much of the Japanese work with mitomycin C has been associated with its administration as an adjuvant at the time of surgery (Frank and Osterberg, 1960; Osada, 1963; Shiba, 1963). A three-year survival rate of 66% in comparison with a control of 30% was found by Osada et al. (1963) in patients with gastric cancer who had undergone palliative surgical resection. Skepticism is in order, since one can also find reports indicating increased survival time in patients treated after gastrectomy with mechlorethamine, nitromin, sarkomycin, or carzinophilin (Ishiyama, 1965), P_{32} and TSPA (Osada, 1963). Hoerr (1965) has found an 11% five-year survival rate in palliative surgical resection for gastric cancer even in the absence of chemotherapy. Similar results have been obtained in untreated bile duct tumors (Lippman, McDonald, and Longmire, 1959). Therefore, isolated case reports of long term responses must be analyzed carefully, as they may be related to the selection of a group of long-term survivors that are present in any given gastrointestinal tumor population.

Varied approaches to dosage and timing of drug administration are important in any program of drug evaluation. This was dramatically demonstrated when the "old" drug, methotrexate, was used in a new way which led to the cure of choriocarcinoma (Li, Hertz, and Spencer, 1956). Modified methotrexate regimens increased survival of children with acute leukemia (Selawry and James, 1965; Acute Leukemia Group B, 1965) and are producing responses in bronchogenic carcinoma (Ross and Selawry, 1965) and bowel cancer (Condit, Shnider, and Owens, 1962). The twice-a-week administration of methotrexate (0.25 mg/kg or 0.6 mg/kg) for gastrointestinal cancer is under study by the Eastern Solid Tumor Group, and the results are awaited with interest.

As suggested by this review, much remains to be done in the chemotherapeutic approach to gastrointestinal cancer. The conservative use of 5-FU and alkylating agents have a place provided that severe toxicity is avoided. The sur-

gical adjuvant use of 5-FU has a rational basis and its application to patients with nodal involvement or disease left behind is warranted. It is hoped that studies will continue that can lead to comparative information pertinent to evidence of objective regression of disease and the practical reality of increased survival.

Summary

5-Fluorouracil (5-FU) is the best agent for the treatment of all gastrointestinal cancers but should be used with restraint, since severe toxicity does not guarantee increased response or survival time. Experimental work suggests that glucose enhances cellular uptake of 5-FU. Alkylating agents are definitely useful and occasionally produce long-term responses. Mitomycin C shows activity but is not available. There are reports of responses to methotrexate, vinca alkaloids, and mithramycin, but their place in the management of gastrointestinal cancer is not established. The usefulness of alkylating agents or 5-FU as adjuvants to surgery is not clear, but evidence is accumulating which supports the adjuvant use of 5-FU when disease is left behind. There is laboratory evidence that anticoagulation can prevent tumor recurrence, and this should be studied further. The best combination chemotherapy has not been determined. Regional chemotherapy offers a logical approach, but comparative data with systemic treatment are lacking, although techniques for protracted infusion, particularly of primary and secondary hepatic tumors, may justify its increased use. Wound washing with available contact tumoricidal agents is contraindicated, as it may increase local recurrence.

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CORRECTION: Vol. 3, No. 1 (Spring), 1967, p. 36. In table 1, a number of stage I patients included in the period from 1955 to 1960 were treated surgically (with or without additional irradiation); most, however, were irradiated only. Stage II through IV patients received irradiation only.