Recent Advances in Gastrointestinal Cancer

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INTRODUCTION

Colorectal carcinoma accounts for the majority of all gastrointestinal cancers and is the second leading site of cancer, excluding skin cancers, in overall incidence in the United States.[1] Cancer of the stomach, although decreasing in frequency, is still an important cause of morbidity and mortality. Unfortunately, data from large numbers of patients such as can be found in Cancer Patient Survival Report No. 5 show only very modest increases in survival for patients with these diseases in recent years.[2]

Gastric Carcinoma

Most patients who develop gastric cancer have regional or distant disease at diagnosis. The presence of regional nodal involvement is almost synonymous with incurability since virtually all these patients are either non-resectable at the time of operation or rapidly develop systemic recurrences. Any improvement in treatment results would be expected to be produced by chemotherapy or immunotherapy rather than from localized forms of treatment.

Fortunately, gastric carcinoma is relatively responsive to chemotherapeutic treatment, and at least four drugs have now been identified as active in treatment of this condition, namely 5-fluorouracil (5-FU), Adriamycin, mitomycin-C, and semustine (methyl-CCNU). Although semustine is the nitrosourea that has been most extensively used in the chemotherapy of gastrointestinal neoplasms, it is still an investigational drug and therefore is not always conveniently available. Other nitrosoureas that are on the market are probably similar in activity.

Percentage of response and increase in survival with single-drug therapy have been modest, and for this reason the drugs have been combined into a variety of multiple-drug regimens. Most of the possible two and three-drug combinations of the four active drugs have been tried.

Table 1 shows response rates and survival figures for some of the most extensively tested combinations. The combination of 5-FU and semustine was one of the first advocated as being superior to 5-FU alone in the treatment of gastric carcinoma. More recently 5-FU plus Adriamycin plus mitomycin-C (FAM) combinations have become more popular. The FAM regimen was initially reported to have a 50% response rate in gastric carcinoma. The most recent update of over 60 patients indicates that the response rate is holding at approximately 43%.[3]

The FAM regimen (Table 2) is a well-tolerated treatment which gives partial or complete responses in about one half of the patients and benefits other patients by stabilizing the disease, resulting in prolonged survival for the population of treated patients. Quality of survival for many is good, and it is not uncommon to see responses lasting for over one year.

One problem with the treatment is cumulative marrow toxicity which is attributed to the mitomycin-C in the regimen. This tends to limit the treatment that can be given after the first few cycles. The cycles of treatment are similar to other day-1, day-8 treatments given every eight weeks.

Other combinations of these drugs which utilize different doses and regimens have also been tried. Two of these used at the Sloan Kettering Institute known as MIFA I and MIFA II confirm that these drugs in combination are effec-

TABLE 1
Combinations Used in Treatment of Gastric Carcinoma

	Response Rate	Med. Survival Weeks
5-FLUOROURACIL + Semustine	9–45%	17–25
5-FLUOROURACIL + ADRIAMYCIN + MITOMYCIN-C	21–43%	24–34
5-FLUOROURACIL + ADRIAMYCIN + Semustine	36%	22–30
5-FLUOROURACIL + MITOMYCIN-C	—	17
ADRIAMYCIN + MITOMYCIN-C	—	—

tive in the treatment of gastric cancer.[4] Table 1 indicates treatment results of these and other combination treatments for gastric cancer. The median survival of patients with untreated advanced gastric carcinoma is four months or about 17 weeks from diagnosis. Since the figures in Table 1 show the survival in weeks from the time of treatment rather than diagnosis for the entire population of treated patients, not just the responders, one can see that a doubling of the survival time for the better combination is achievable.

Dr Charles Moertel from the Mayo Clinic has recently analyzed data combined from several cooperative groups. Using a statistical model, he concluded that 5-FU and Adriamycin contribute most to the treatment of gastric cancer.[5] This is a combination that has not received extensive use, and the projected value of the treatment needs confirmation in a large clinical trial.

Colorectal Carcinoma

Although there have been a number of attempts to improve results in treatment of colorectal cancer, most of these have been futile or have achieved only very modest success. The surgical treatment of colorectal cancer has been standard for several decades, and although some recent studies indicate that preoperative and postoperative radiation therapy given adjuvantly in high-risk patients would be beneficial, particularly in patients with carcinoma of the rectum, these suggestions have not met with widespread acceptance.

Five-fluorouracil has been a standard treatment for colorectal cancer for 20 years, and one might summarize the clinical experience of a number of investigators' attempts to improve results by manipulating the 5-FU dose, schedule, or route of administration by simply stating that no schedule of treatment has been definitely shown to be superior to any other.[6] The most common schedules used have been daily intravenous treatments for five days repeated at five-week intervals or one intravenous treatment administered weekly.

Administered orally, 5-FU gives response rates similar to the intravenous treatments of the drug. However, Moertel[7] has reported that the duration of response is shorter with the oral form of treatment. Absorption is erratic, averaging about 50%. Because of these facts and because no oral form of treatment has been marketed, use of this drug by this route of administration has not gained wide acceptance.

Response rates with 5-FU in colorectal carcinoma average approximately 20%. Two forms of therapy which have a response rate above 10% are the nitrosoureas and mitomycin-C. Other drugs have either had limited use in colorectal cancer or have given response rates of 10% or less, leaving only a few drugs that have a significant response rate in this disease.

A number of combinations have been devised for the treatment of colorectal carcinoma, the more extensively tested combinations being: 5-FU with semustine, mitomycin-C or hydroxyurea; 5-FU plus semustine plus vincristine; and 5-FU plus semustine plus dacarbazine. Response rates for the combinations were initially

TABLE 2
FAM Regimen

Day 1	Day 8	Day 29	Day 36
F	F	F	F
A		A	
M			

F = 5-Fluorouracil	600 mg/M^2
A = Adriamycin	30 mg/M^2
M = Mitomycin-C	10 mg/M^2

Cycles of treatment are repeated every eight weeks.

reported to exceed the results of 5-FU alone. The combination of 5-FU, semustine and vincristine has been said to have response rates in the range of 35 to 40% by at least three different groups.[8,9,10] However, as additional studies and survival data are reported, the superiority of this combination over 5-FU alone has not been confirmed.[6]

Median survival for patients after proof of incurability is approximately 30 to 32 weeks with 5-FU alone, and for the combinations the survival has been in the same range. Consequently, the current consensus is that no combination of drugs for the treatment of colorectal carcinoma has proved to be superior to 5-FU alone. At this time other combinations are being tried which, it is hoped, will yield results surpassing those with only 5-FU.

There is controversy regarding whether or not 5-FU alone increases survival in patients with colorectal carcinoma. To my knowledge, no prospective randomized trials have been done comparing 5-FU with no treatment in patients with advanced disease. Used many years ago for the treatment of advanced colorectal cancer, 5-FU was shown to yield responses and was felt to be beneficial, not only in achieving these responses but also in extending the life of the patient. No one has since been willing to compare it to no treatment.

One can easily demonstrate that 5-FU responders live longer than non-responders. Additionally, retrospective analysis indicates that 5-FU produces a modest increase in median survival in a population of treated patients. Moertel's own data[11] demonstrated that 5-FU treated patients live longer throughout the entire survival curve than matched historical controls. This difference was discounted by Moertel who stated that there is no evidence showing that 5-FU prolongs survival, attributing the difference to patient selection. This is only an opinion, and different interpretations are possible.

A number of surgical adjuvant trials have been conducted in patients with colon and rectal carcinomas. One of the earliest studies utilized thiotepa or fluorodeoxyuridine (FUdR) after surgery. This particular study showed no effect. However, it is of interest that these patients, followed over a decade, had no increase in carcinogenicity or other late toxicity which could be ascribed to those treatments.[12] More recently a number of studies have been done utilizing 5-FU in adjuvant treatment. In the non-randomized studies using historical controls, 5-FU was reported to produce a beneficial effect[13,14]; in the randomized studies the 5-FU, in all cases, produced a slight prolongation of disease-free interval and survival in the treated group.[15–19] Initially, the difference was judged not to be statistically significant; however, a recent statistical analysis using cumulative results involving larger patient numbers resulted in the conclusion that there is a statistically significant improvement, at least for some subsets of 5-FU-treated patients in the adjuvant setting. Results of these studies are still pending.

In an article in the *Annals of Internal Medicine,*[20] Drs Weiss and Devita stated that at the present time whether or not a patient receives adjuvant chemotherapy for colorectal carcinoma is a decision that needs to be individualized for each patient. This is primarily because the results of 5-FU have been marginal at best, and the potential benefits of therapy may be overridden by a variety of other factors: disease stage (patients with Duke's B2 or C stage lesions, *eg,* extension through the muscular layer and/or involved nodes are customarily treated); age of the patient; histologic grade of the tumor; economic factors; and convenience of travel to the treatment center for the patient. Following a trial of adjuvant treatment, the decision to continue treatment should be based on the patient's tolerance tempered by the knowledge of limited survival benefit.

Other Gastrointestinal Tumors

There are three uncommon types of gastrointestinal malignancies, all of which show significant response rates to treatment with chemotherapy.

Leiomyosarcomas are found in the stomach and in the bowel. Recurrent or metastatic tumors respond to treatment with Adriamycin in approximately 30% of cases, and if combined with dacarbazine, the response rate may be 10% higher. The treatment for metastatic leiomyosarcomas of the bowel is the same as for other metastatic sarcomas.

Lymphomas also occur in the gastrointestinal tract, and although their natural history may be somewhat different from those originating elsewhere, the chemotherapeutic treatment is basically similar. Where the histology predicts a favorable outcome, treatment would probably

consist of cyclophosphamide plus vincristine plus prednisone (COP) therapy and the unfavorable ones treated in addition with Adriamycin and possibly with Bleomycin.

Carcinoid tumors are also responsive to chemotherapeutic treatment. About one third of these patients with advanced disease show objective responses to treatments with 5-FU and streptozotocin in combination. More recently Adriamycin has been used as a single agent. Treatment for this condition is still very much in a stage of evolution.

Other Advances

The biologic marker known as carcinoembryonic antigen (CEA) which has been developed for clinical use in the last decade, has contributed materially to our ability to stage and follow patients with colorectal carcinoma. The initial hope was that the test would be useful as a diagnostic and screening tool. It has not proved to be very useful for this purpose. However, it has been found to be beneficial as a prognostic indicator. Patients with high levels of CEA prior to surgery will not do as well as patients with normal levels. It can also be utilized to assess adequacy of treatment or to evaluate disease recurrence and treatment response. It has been suggested that CEA-producing tumors are inherently more likely to metastasize and are less controllable by the body's immune processes. This biological difference, if confirmed, will undoubtedly influence future treatment strategies.

Table 3 presents data taken from a study where 2,372 patients of an unselected population were screened for malignancy using CEA values.[21] Seventy-three of these patients were found to have elevated CEA levels above 5 ng/ml. Workup of these 73 patients resulted in the finding of malignancy in only 11 patients. Nine had a CEA-related malignancy and two had an incidental malignancy. The false-positive rate, therefore, was calculated at 87%.

TABLE 3
Use of CEA in Screening an Unselected Population[21]
2372 people followed 5 years
87% False Positive 64% False Negative

	CEA LEVEL <5 ng/ml	CEA LEVEL ≥5 ng/ml	
Developed a CEA related Cancer	16	11*	25
Never developed Cancer	2000+	62	
		73	

(3% of total population)

* two others were found to have incidental cancers not related to CEA evaluation.

More disturbing than even the high false-positive rate was the fact that 16 patients who were CEA-negative developed a CEA-associated cancer during the follow-up period for a false-negative rate of 64%. Only 3% of the 2,372 patients had elevated CEA levels which is consistent with the fact that 95% of a normal population are known to have CEA below 2.5 ng/ml. (In this population, 97% had the CEA level below 5 ng/ml.) The low incidence of cancer in this population of 2,372 resulted in the high false-negative percentage. CEA testing may play a role in screening certain high-risk populations, but it is not suitable as a screening mechanism for carcinoma of the colon in unselected populations.

It was originally thought that CEA would be specific for colon carcinoma since the antigen was obtained from fetal colonic tissue. However, it was soon found that it is non-specific for colon carcinoma, being elevated in a variety of other malignancies including breast, lung, pancreas, stomach and bladder carcinomas, and in other malignancies. CEA is also elevated in patients with liver disease, pancreatic cysts, gastrointestinal polyps and other benign conditions. The CEA is not specific for a particular primary site and is not even as specific as one would like for malignancy.

With the understanding of certain characteristics of biologic markers shown in Table 4, CEA tests can be used quite advantageously for a number of purposes. In general, biologic markers are non-specific for histologic types of neoplasms and often are not even specific for malignancy. The specificity and sensitivity tend to be inversely related. By developing a more sensitive assay, more positive results will be obtained in patients with non-malignant conditions or with tumor types other than those anticipated. In contrast, if normal levels are drawn at a higher concentration, the test is more specific. For example, most patients with CEA over 10 ng/ml will have a malignancy.[22] The percentage of patients with positive markers increases with the stage of the disease. Reports of CEA elevation in the 90% range are applicable only

TABLE 4
Some Characteristics of Biologic Markers

1. In general biologic markers are non-specific for a histologic type of neoplasm and often are not even specific for malignancy.
2. Sensitivity and specificity tend to be inversely related.
3. The percentage of patients with positive markers increases with stage of disease.
4. Not all patients develop positive markers.
5. Marker status is not a dependent variable in relatipn to staging.

to patients with advanced colorectal carcinoma. The figure is much lower for patients with localized or regional disease only.

Not all patients develop positive markers. Only those patients with certain phenotypic cancer cell expressions will show marker elevation. Other patients having histologically-similar tumors will never be marker positive. Therefore, it is futile to attempt to manipulate a test to give results 100% of the time or to look for new markers that will do this.

The percentage of CEA positivity in patients with colonic cancer was initially reported in excess of 90%. Later the percentage fell, the reason being that initially patients with advanced disease were tested, and in the later series more patients with earlier stages of disease were tested.[23] The percentage of CEA elevation directly correlates with the stage of disease; however, it is not a dependent variable, meaning that the distribution of CEA positives in patients of various stages has a tendency toward randomness. In general, CEA and other biologic markers are not dependent variables in relation to the stage of disease or any other known prognostic factor. This means that prognostication is improved by considering marker values along with stage, grade of tumor and other standard prognostic indicators.

CEA is also useful in following colorectal patients for recurrence. The majority of patients who are found to have recurrences will have shown at least one CEA elevation greater than 2.5 ng/ml more than three months before documentation of recurrence. One study[24] showed 54% of the patients having this marker positive (>2.5 ng/ml) more than three months prior to the documentation of recurrence. If a higher positive value (5 ng/ml) is used, 41% will have an elevation three months before clinical tumor recurrence. An additional number of patients will have markers positive for three months or less prior to recurrence. The percentage of patients who show elevated CEA prior to recurrence of colon cancer is higher than in rectal cancer. (Table 5).

In colon cancer only 14% are never elevated prior to documentation of recurrence compared to 32% for rectal cancer. While this looks quite good as a tool for predicting recurrences, it has to be tempered by the fact that matched controls also have a high percentage of at least one elevated CEA value. The matched controls were patients with the same age, the same disease, and treatment, who had not had a recurrence during periods of equal follow-up. Some of these patients will eventually turn out to have a recurrence because it is known that the CEA can be elevated for as long as several years prior to recurrence. Some of these patients have random increases in CEA value; others have benign causes of the elevation.

It is known that patients who receive blood products at the time of their surgery sometimes develop CEA elevations that plateau and later decrease[25] secondary to hepatitis or undetermined factors in the absence of acute or chronic liver disease. The problem in following these patients is to separate those who have random elevations or benign conditions from those who have a recurrence of malignancy. In order to distinguish those with random elevations, a CEA nomogram has been developed to indicate when values are statistically increased. Nomograms are published in the literature,[26,27] but to be valid, each laboratory should construct its own based on the precision of its test. While the nomogram is useful in differentiating patients who have a random increase from those with a true increase in CEA levels, repeating the value several times helps in making this differentiation.

It is important to make a diagnosis of recurrence earlier using CEA elevations. Some of these patients may be candidates for second surgery; others will be candidates for radiation therapy or chemotherapy. In considering possible patients for second surgery, it is necessary to separate those patients who are going to have an operable malignancy from those who have random fluctuation of the CEA, benign conditions, and inoperable lesions. Using the nomogram, one can distinguish most random fluctuations. Benign conditions tend to be

TABLE 5
Percentage of Patients With Established Tumor Recurrence Who Exhibit CEA Elevations [24]

Primary Tumor Site	>2.5 ng/ml >3 mos before recurrence	>5 ng/ml >3 mos before recurrence	>2.5 ng/ml <3 mos before recurrence	>5 ng/ml <3 mos before recurrence	Never elevated
COLON	58	45	28	26	14
RECTUM	42	31	26	32	32
COMBINED	54	41	29	28	17

nomogram positive as are both operable and inoperable malignancies. The operable malignancies and random fluctuations would not be expected to have elevated liver enzymes. The degree of CEA elevation helps to discern the operable and inoperable malignancies. High elevations correlate with metastatic disease and more specifically with liver metastases.

To determine operable cases one looks for patients with minimal elevations of CEA. In one series the mean elevation in the operable patients was 6.5 ng/ml compared to 15.5 ng/ml in those who had inoperable malignancy.[28] Additional information can be gained by looking at the character of the rise. If a benign condition exists, the CEA tends to plateau at levels usually less than 10 ng/ml. For any type of malignant condition, an exponential rise occurs; the slope of the rise for those who are operable is less than that for the inoperable ones. The value is probably in the range of 0.5 ng/ml/mo or less for operable cancers and >1 ng/ml/mo for inoperable patients.[29]

A factor to be considered in the decision for reoperability is the interval between surgery and observed CEA elevation. The benign causes of the CEA elevations occur earlier after surgery than the operable malignancies.[27] Any CEA elevations that occur early are more likely to be associated with inoperability. If they are caused by tumor, they probably are rising at a more rapid rate than those that occur later. Patients whose CEA elevations occur more than five months after surgery are more likely to be eligible for reexploration. These factors are summarized in Table 6.

It is important to stress that the decision regarding reoperation is not based on just the CEA level. A careful determination must be made that the patient does not have clinical metastatic disease by obtaining a chest x-ray, liver scan, serum chemistries, and other appropriate tests such as sonography, abdominal CT scan, and liver biopsy if other tests are negative. Careful monitoring and testing will exclude five sixths of the patients for consideration for

TABLE 6
Differential Diagnosis of CEA Elevation

Cause of CEA Elevation	Nomogram	Liver Enzymes	Degree of Elevation	Character of Rise	Time of Occurrence Post-Resection
Random Fluctuation	− or ±	−	Depends on Baseline Value	Not Verifiable	Random
Benign Condition	+	Often +	Usually <10ng/ml	Non Exponential (Plateau)	Median Time < 5 mo.
Operable Malignancy	+	−	Mean 6.5 ng/ml	Exponential Slope <1ng/ml/mo	Median Time > 5 mo.
Inoperable Malignancy	++	Often +	mean 15.5ng/ml	Exponential Slope > 1ng/ml/mo	

"second-look" surgery. Of the remaining one sixth, the resectability rate may be as high as 30%.[30] Increasing the percentage of patients operated on will decrease the resectability percentage. The cure rate for the patients who are resected a second time is not known.

A practical strategy for following patients with colorectal cancer with CEA assays is presented. Preoperative levels should be obtained for establishing a base line and serve as a prognostic indicator. The test should be repeated postoperatively. Two weeks after surgery is both convenient and appropriate; however, if the CEA level has not returned to normal, the test should be repeated.

Apparently not all CEA values return to normal promptly. If they remain elevated, it is important to establish a base line for nomogram analysis. Subsequently, values are obtained every two months for the early detection of recurrence. After one year the test could be run less frequently. If a significant elevation is encountered outside the normal nomogram range, the test is repeated serially, two or three times, to verify elevation and determine, if possible, the character of the rise. Concurrently, the patient is evaluated carefully for metastatic disease. Selected patients may be candidates for surgery.

In patients who have developed metastatic disease, CEA can be used for evaluation of chemotherapeutic or radiotherapeutic response. The CEA appears to be more correlated with tumor burden if its value is below 100 ng/ml. While this correlation is sometimes erratic, it is the most valuable tool available in patients who do not have measurable disease.

CONCLUSION

Chemotherapy has produced significant improvement in treatment results for gastric carcinoma, but to date only minimal improvement has been achieved for colorectal carcinoma. Earlier application of radiation therapy, specifically preoperative and postoperative radiation therapy, particularly for patients with carcinoma of the rectum, is sufficiently attractive for further study.

The primary area of improvement for patients with colorectal carcinoma has been in our ability to assess the status of the disease and in our beginning understanding of the biologic differences in patients with the disease. Ultrasonography and CT scanning are relatively new procedures whose effect on the overall problem remains to be assessed. Carcinoembryonic antigen testing is clearly an important advance, and there is every indication that other useful markers will be developed.

The net effect of all these developments is the increased ability to select patients accurately for given treatments and to follow treatment results more precisely. It is known from previous experience that in those diseases in which the assessment of results is difficult, progress has been slow. Therefore, it is anticipated that more rapid improvements in treatments in the coming years will ultimately be reflected in the overall survival statistics of these diseases.

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