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Distribution of 5-Fluorouracil-^{14}C in Body Tissues after Systemic and Regional Administration in Gastric Cancer

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This study was to determine which of two routes of administration of 5-fluorouracil (5-FU) is more effective, by measuring the radioactivity in the body tissues of gastric cancer patients after the administration of 5-FU-^{14}C via the systemic intravenous and the regional intra-arterial routes.

After the drug was administered intravenously in one group of patients, and intra-arterially in another, samples of portal venous blood, the liver, the lymph nodes, and the normal and the cancerous tissues of the stomach were obtained. The radioactivities of the samples were measured, and it was found that those of the regional lymph nodes, the liver, and the normal and the cancerous tissues of the stomach were much higher in the latter group. The regional intra-arterial route is the more effective way to administer 5-FU in patients with stomach cancer.

Key Words: 5-FU, administration, gastric cancer, systemic, regional.

Although wide resection of cancer may be the only means to achieve a complete cure, chemotherapy and radiotherapy are used in inoperable cases with vital organ involvement or distant metastases and recurrent cases for which further surgery is not feasible. With the development of various new agents, chemotherapy is now conducted in various forms and research is done regarding the mode of administration, combination therapy and the duration of treatment.

Since 5-FU was introduced, it has been used for the treatment of gastrointestinal adenocarcinoma and other malignancies. It is the main component of combination chemotherapy for gastrointestinal adenocarcinoma. The route of administration selected invariably affects the anticancerous effect of some agents due to the fact that the blood and tissue concentration of the agents, which the route achieve, differ. Although most anticancer agents has been given intravenously, regional arterial administration has come into use since Klopp (1950) demonstrated that superior therapeutic effects could be obtained by selective arterial administration in animal experiments and clinical applications.

The rationale for regional arterial injection is based upon the assumption that the tissue concentration within the tumor mass can be increased by direct injection into the feeding vessels, thus leading to a better anticancer effect and a reduction in the complications. The superior anticancer effects of using this method has been actually observed (Cromer *et al.* 1952; Sullivan *et al.* 1959; Fortner *et al.* 1973; Cady and Oberfield 1974; Ramming 1983; Ensminger and Gyves 1983; Huberman 1983; Lokich 1983). However, no studies have been done comparing the actual concentration of the agent in the blood, in the cancerous and normal adjacent tissues resulting from the use of the two different routes of administration.

The purpose of this study is to find more effective means of administering chemotherapeutic agents by measuring the concentration of ^{14}C labeled 5-FU in the blood, the tumor, and the adjacent tissues after injecting into patients with stomach cancer.

MATERIALS AND METHODS

Five hundred mg of 5-FU labeled with 100 uCi of ^{14}C was given to each of 6 patients with stomach

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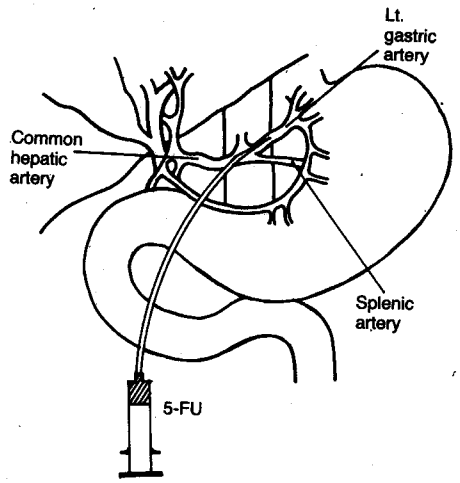

Fig. 1. Left gastric arterial infusion.

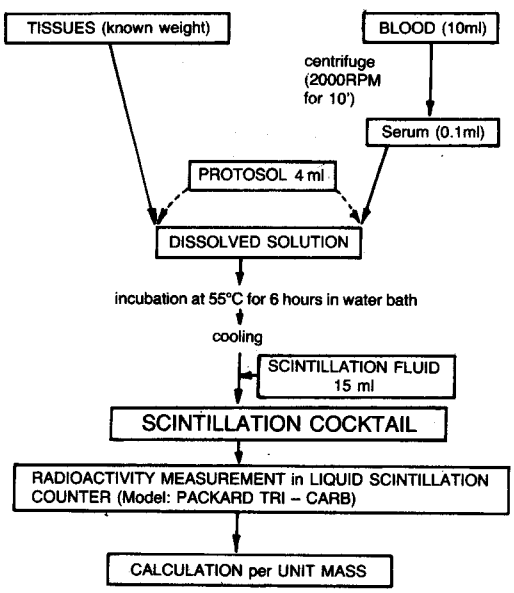

Fig. 2. Illustrates procedure used to determine degree of concentration of 5-FU by measuring radioactivity.

cancer who were found to have completely resectable tumors on exploratory laparotomy. In order to create a constant setting for systemically and regionally administered groups, the blood and the tissue samples were collected after an equal period of time had elapsed following the injection. Three of the patients received 5-FU-^{14}C through a "scalp" needle inserted into the left gastric artery, which mainly supplied the tumor mass. Ligation of the left gastric artery was left undone, to maintain the blood flow (Fig. 1). The other three patients received 5-FU-^{14}C via the antecubital vein immediately after laparotomy.

In both groups, 10 ml of portal venous blood was collected 30 minutes after the administration of the 5-FU-^{14}C. Samples from the right and left lobes of the liver, and celiac lymph node and adjacent lymph nodes were obtained for biopsy at 45 and 60 minutes after the injection, respectively. Following the resection of the stomach, both normal and cancerous tissues were obtained for biopsy 90 minutes after the injection.

After weighing the samples, approximately 0.5 to 1.0 gm of the tissues were placed in each container. The portal venous blood was spun at 2000 rpm for 10 minutes and the serum was isolated. Then 0.1 ml of the serum was placed in a container. The tissues were completely liquified by the addition of 4 ml of Protosol and incubated at 55°C for 6 hours. The resulting solutions were well mixed and cooled. The addition of 15 ml of scintillation fluid turned them into scintillation cocktails whose radioactivity was measured by the Liquid Scintillation Counter (PACKARD TRI-CARB, U.S.A.). The measured radioactivities were standarized for weight of tissue and compared between 2 groups (Fig. 2).

RESULTS

The mean radioactivity in the serum of the portal venous blood was 1477 DPM when the regional artery injected and 2103 DPM when the injection was given intravenously. Although the mean radioactivity was lower for the regional injection, patients in both groups showed similar levels of radioactivity with the exception of one patient in the systemic intravenous group (case 3), who had a markedly increased level of 2818 DPM and raised the mean considerably (Table 1). Therefore, there seems to be essentially no difference in the distribution of 5-FU between the two groups.

In the liver tissue, the mean radioactivity in the right lobe with the regional arterial injection was 23126 DPM, which was markedly higher than the 7355 DPM obtained with the systemic injection. The same was true for the left lobe where the mean levels of 84943 DPM and 5966 DPM were obtained following the regional and systemic injections, respectively (Table 2). Therefore, the concentration of 5-FU in the liver

Table 1. Radioactivity of portal venous serum

Arterial Injection		Venous Injection	
Case	DPM*	Case	DPM*
1	1,529	1	1,530
2	1,048	2	1,962
3	1,854	3	2,818

*DPM indicates disintegration per minute.

Table 2. Radioactivity of liver tissue

	Arterial Injection		Venous Injection	
	Case	DPM	Case	DPM
Right lobe	1	26,280	1	8,281
	2	19,253	2	6,182
	3	23,845	3	7,603
Left lobe	1	116,203	1	8,099
	2	75,545	2	4,682
	3	63,082	3	5,118

Table 3. Radioactivity of the excised lymph nodes

	Arterial Injection		Venous Injection	
	Case	DPM	Case	DPM
Celiac LN*	1	8,154	1	5,778
	2	7,695	2	6,073
	3	8,248	3	6,195
LN adjacent to cancer	1	9,669	1	2,588
	2	8,547	2	1,727
	3	10,420	3	3,234

*LN indicates lymph nodes

Table 4. Radioactivity of stomach tissue

	Arterial Injection		Venous Injection	
	Case	DPM	Case	DPM
Cancer tissue	1	7,541	1	2,780
	2	4,999	2	2,495
	3	4,970	3	3,215
Normal tissue	1	3,977	1	2,093
	2	3,468	2	1,874
	3	3,768	3	2,358

was significantly higher with the regional arterial injection than with the systemic intravenous injection. Also, a much higher level of radioisotope in the liver compared with other tissues may be due to the fact that breakdown and excretion of 5-FU occured in the liver. However, the greater radioactivity observed in the left lobe over the right lobe can not be easily explained.

The mean radioactivity measured in the celiac lymph node was 8032 DPM with the regional injection and 6015 DPM with systemic injection. In the lymph node adjacent to the tumor, it was 9545 DPM with the regional injection, which was significantly greater than the 2516 DPM obtained with the systemic injection (Table 3). Consequently, the regional arterial injection also results in a higher level of 5-FU in the lymph nodes than the systemic injection does.

The analysis of the cancerous tissue itself in the stomach revealed a mean radioactivity of 5837 DPM following the regional injection, which markedly exceeded the value of 2830 DPM obtained following the systemic injection. In the normal tissue of the stomach, it was 3737 DPM following the regional injection and 2108 DPM following the systemic injection (Table 4). Therefore, in both cancerous and normal tissues of the stomach, the regional arterial injection results in a greater concentration of 5-FU than the systemic intravenous injection.

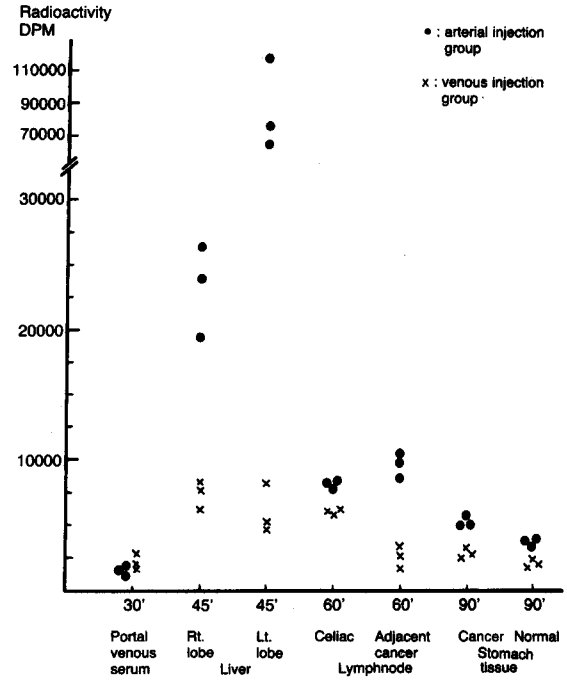

Fig. 3. Tissue distribution of 5-FU-^{14}C.

When these results are considered together (Fig. 3), the regional injection of 5-FU via the left gastric artery leads to a greater concentration of the agent than the systemic injection via the antecubital vein, in the right and left lobes of the liver, the celiac and adjacent lymph nodes, and the normal and cancerous tissues of the stomach.

DISCUSSION

Along with radiotherapy, chemotherapy remains to be used when regional spread of the cancer makes resection unsuitable. With the development of a greater variety of chemotherapeutic agents, the ways of administering agents have multiplied, e.g., they are used in various combination as well as singly, and they are scheduled in various specific ways for specific reasons.

Early in the development of antitumor agents it seemed reasonable to believe that by directly administering antitumor agents to the local feeding vessels, the concentration of these agents would be increased in the tumor tissue, while the undesirable side effects would be reduced (Cromer *et al.* 1952; Sullivan *et al.* 1959; Clarkson *et al.* 1962; Fortner *et al.* 1973; Cady and Oberfield 1974, Ramming 1983; Ensminger and Gyves 1983; Huberman 1983; Lokich 1983). Klopp *et al.* (1950) administered nitrogen mustard into the artery supplying the tumor in patients with unresectable tumor. With this method, he observed regressive changes taking place in the tumor such as liquification of the cancer, softening and flattening of the boundary and reduction in the size of the ulcerative squamous cancerous masses. Cromer *et al.* (1952) reported that administration of nitrogen mustard into the local artery was much more effective than the systemic route for treating patients with unresectable cervical and vaginal cancers. Also, Sullivan *et al.* (1959) administered methotrexate locally, which had a significantly greater effect than administering it systemically by the intravenous route; in fact the tumor tissue involuted.

The localized arterial administration of antineoplastic agents has been especially useful for patients with unresectable hepatoma. Clarkson *et al.* (1962) were able to obtain worthwhile results in treating primary hepatoma by this method. Hepatoma almost always receives its blood supply from the hepatic artery, while the normal hepatic parenchyma is supplied, in the most part, by the portal vein. Therefore, hepatic artery ligation will destroy the tumor tissue without injuring the normal tissues. Nilsson *et al.* (1966) were able to observe necrosis of core tissue and shrinkage in the size of a tumor which had metastasized to the liver when the patients were treated by ligating the hepatic aretry. Fortner *et al.* (1973), in describing the findings of others regarding hepatic tumor, reported that when antitumor agents were locally infused via the hepatic artery, it was much more effective than when they were infused intravenously and, therefore, systemically. Antitumor agents infused through the hepatic artery increased the concentration of anticancer agents in the tumor tissue 5 to 20 times higher than in the surrounding normal tissue. The findings of the Fortner group were recently reemphasized by Ramming (1983). Their findings for metastatic tumor were similar to those for hepatoma: the local infusion method was a much more effective form of treatment, which increased the length of survival of their patients (Ariel and Pack 1967; Burrows *et al.* 1967; Wirtanen *et al.* 1968; Rapaport and Burleson 1979; Cady and Oberfield 1974; Lee and Lewin 1978; Grage *et al.* 1979; Hubeman 1983; Ramming 1983). Fujimoto *et al.* (1969, 1976) applied these findings to the treatment of stomach cancer. They studied the effects of infusing antitumor agents into the right gastroepiploic artery. Gastrectomy was done one week after the infusion and histologic examination of the resected tissue revealed necrosis or degenerating tumor tissue, cessation of DNA synthesis, and irreversible change in the tumor cell chromosomes. As found elsewhere, side effects were also reduced. Furthermore, survival rates were longer in the patients receiving these preoperative intra-arterial infusions of antitumor agents compared with those of the control group.

Yamada *et al.* (1976) compared systemic intravenous injection of 5-FU and direct submucosal injection of the drug into the colon of dogs by measuring 5-FU levels in the intra-abdominal lymph nodes. The injection of the agents directly into the submucosal tissue of the colon produced a higher local concentration of 5-FU than administration of the agent by the systemic route. Thomas (1978) also reported that injection of 5-FU through the submucosa of the stomach resulted in a higher concentration of the agent in the thoracic duct, the portal vein, and the peripheral arterial blood. Shukla *et al.* (1977) administered 5-FU-^{14}C or 5-FU-^{3}H in three ways: (1) systemically, and (2) locally into the gastrointestinal walls and (3) the lumen of the gastrointestinal tract. In the case of each of the patients, who were patients with gastrointestinal cancer, the level of 5-FU was determined indirectly from the measurement of radioisotopes in the portal venous blood, the liver, the systemic venous blood, the draining lymph nodes,

the cancerous tissue, and the normal gastrointestinal tissues, and it was found that the concentration of the drug was highest when the drug was administered locally, directly into the gastrointestinal wall, and lowest when it was injected into the lumen of the tract, however, locally.

In this study, among patients who were judged to have resectable stomach cancer, the group in which 5-FU-^{14}C was administered via the left gastric artery showed higher drug concentration than the systemically injected group in the liver parenchyma, draining lymph nodes, cancer and normal tissues of the stomach. It was particularly higher in the cancer tissues and the draining lymph nodes. However, it was similar to that in the portal venous blood. It is not clear in this study why the radioactivity in the liver parenchyma was higher in the arterially injected group, in spite of similar radioactivities of the portal venous blood. Further studies should be carried out to explain the above findings.

Our study suggests that regional intra-arterial injection of 5-FU at the time of surgery may be an effective way to control the dissemination of cancer cells during the operation.

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