Scholars Academic Journal of Biosciences (SAJB) **ISSN 2321-6883 (Online)**
Sch. Acad. J. Biosci., 2015; 3(5):464-467 **ISSN 2347-9515 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

8 Hours Infusional 5-Fluorouracil (5-FU) Concurrent with Neo-Adjuvant Radiotherapy in Locally Advanced Rectal Cancer

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Abstract: In order to selecting optimal treatment regimen in patients suffered advanced rectal cancer, combined adjuvant radiochemotherapy has been found to be more effective than radiotherapy or surgery alone. 5-fluorouracil (5-FU) given concomitantly within the first week of radiotherapy has been shown to be potentially effective, especially before surgical resection of tumor. In the present study, we planned a regimen including preoperative 5-FU infusion within 8 hours concurrently with radiotherapy to assess the efficacy of this protocol without needing hospitalization and with minimizing therapeutic regimen side effects in patients with locally advanced rectal cancer. Sixteen consecutive patients locally advanced rectal cancer (clinical stage T3–T4 or any T stage with positive nodal involvement) received 5FU delivered by continuous infusion within 8 hours, concomitantly with radiotherapy. 5FU dosage was planned at 1000 mg/m^2 (ranged 1500 to 1800 mg). Patients were clinically examined and laboratory parameters were assessed every week for six weeks and then were operated. At the 5FU dose of 1000 mg/m^2, 8 patients presenting with cytopenia that only 3 of them needed to subcutaneous injection of Neupogen. Gastrointestinal events including diarrhea was revealed in 6 patients that was improved by appropriate nutritional regimen and using Loperamide, but radiotherapy was stopped in other 2 patients. Five patients needed to blood transfusion because of the appearance of serum hemoglobin less than 8.5 g/dl. Two patients were administered to be rest at home for one week. All patients completed their treatment and underwent surgery 6 weeks later. The preoperative radiochemotherapy regimen used in the present study incurs a low rate of complications with an acceptable controlled morbidity. Routine use of preoperative adjuvant chemoradiotherapy including 5-FU 1000 mg/m^2 within 8 hours concurrently with radiotherapy can be warranted as standard treatment in locally advanced rectal cancer.
Keywords: adjuvant chemoradiotherapy, 5-fluorouracil, rectal cancer

INTRODUCTION

Colorectal cancer remains a major worldwide health problem. In the United States alone, it is estimated that there will be 148,610 patients diagnosed with colon cancer and 55,170 deaths this year [1]. Worldwide, approximately 1 million new cases per year are diagnosed, with 529,000 deaths [2]. The median age is in the seventh decade; however, colorectal adenocarcinomas can occur any time in adulthood.

Radiotherapy in combination with chemotherapy regimen has been extensively scheduled in locally advanced cancers and in this regard, efficacy of the combination of external radiotherapy especially combined with 5-fluorouracil (5-FU) has been widely evaluated in controlled trials [3]. In some studies, 5-FU given concomitantly within the first week of radiotherapy has been shown to be potentially effective, especially before surgical resection of tumor [4, 5]. Rectal Cancer treatment Algorithm showed in figure 1.

In order to selecting optimal treatment regimen in patients suffered advanced rectal cancer, combined adjuvant radiochemotherapy has been also found to be more effective than surgery alone [7,8], and has been suggested as the standard approach for patients with mid-low rectal cancer [9]. It has been also demonstrated that preoperative radiochemotherapy using 5-FU result in lower recurrence rate (25% to 30% versus 10%), and lower toxicity in comparison with postoperative radiochemotherapy regimen [10]. Furthermore, overall survival rate can be interestingly improved following former regimen [11].

However, recurrence and toxicity rate following preoperative infusion of 5-FU concurrently with radiotherapy directly depends on the dosage as well as on duration of drug infusion. In standard regimen, 1000 mg/m^2 5-FU is infused that needed to patient's hospitalization. This drug can be administered

by the two bolus and infusion methods that the appearance of cytopenia is more frequent in first and gastrointestinal complications is more prevalent in second method. In our country, because of high patient's load and also no possibility of hospitalization for all patients, 5-FU is routinely administered bolus and through reducing drug dosage lower than 750 mg. However, by decreasing its dose, the efficacy of radiochemotherapy using 5-FU may be considerably decreased. In the present study, we planned a regimen including preoperative 5-FU concurrently with radiotherapy within 8 hours to assess the efficacy of this protocol without needing hospitalization and with minimizing therapeutic regimen side effects in patients with locally advanced rectal cancer.

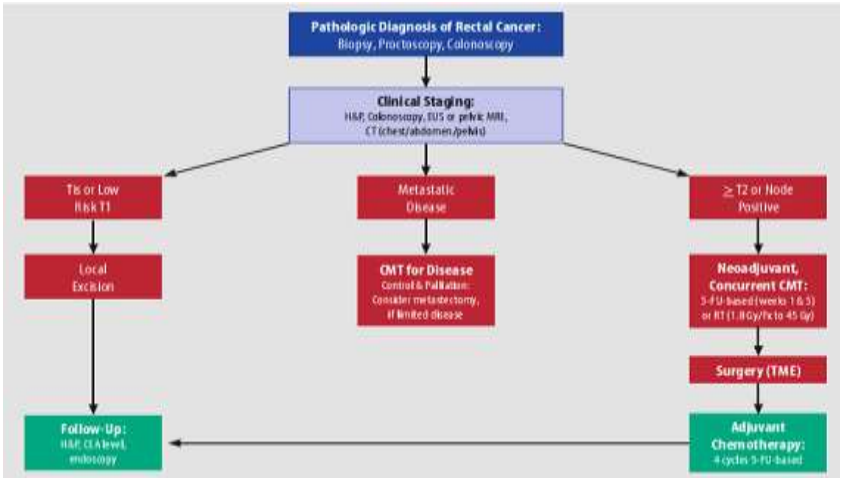

Fig-1: Invasive Rectal Cancer treatment Algorithm [6]

METHOD AND MATERIALS

The main objective of this study was to determine efficacy of 8-hour infusion of 5FU with routine dosage (1000 mg/m^2) concomitantly with radiotherapy and assess its-related side effects. Sixteen consecutive patients included in the study presented with locally advanced rectal Cancer that had been histologically documented. The tumors were locally advanced (clinical stage T3–T4 or any T stage with positive nodal involvement) according to the AJCC staging system. Other inclusion criteria were age > 18 years, and appropriate hematological parameters and liver and renal function. Pregnant women, those presenting with rectovesical fistula, inflammatory disease of the bowel, and a contra-indication to 5FU (uncontrolled ischemic heart disease or cardiac toxicities experienced while on 5FU therapy) could not be included in the study. All the patients signed an informed consent form prior to inclusion. The study protocol was approved by the institutional review board at the hospital and the principles of the Declaration of Helsinki. On admission, the patients were assessed by face to face interviewing and full physical and rectal examinations. A baseline laboratory workup was run on all patients and consisted in complete blood count, serum electrolytes, creatinine, total protein and liver function tests.

Chemotherapy consisted of 5FU delivered by continuous infusion within 8 hours, concomitantly with radiotherapy. 5FU dosage was planned at 1000 mg/m^2 (ranged 1500 to 1800 mg). Irradiation was delivered 5 days per week at a dose of 1.8 Gy/d to a total of 45 Gy. Patients were clinically examined and laboratory parameters were assessed every week for six weeks (at the end of chemoradiation) and then were operated. Within this time, all adverse events including cytopenia, gastrointestinal complications, or need to transfusion were evaluated and recorded.

RESULTS

Sixteen patients were enrolled in the study with the median age of 52 years (range: 42–66 years) and there were 10 men and 6 women. The tumors were accessible to digital rectal examination in all of them. At the 5FU dose of 1000 mg/m^2, 8 patients presenting with cytopenia that only 3 of them needed to subcutaneous injection of Neupogen. Gastrointestinal events including diarrhea was revealed in 6 patients that was improved by appropriate nutritional regimen and using Loperamide, but radiotherapy was stopped in other 2 patients. Five patients needed to blood transfusion because of the appearance of serum hemoglobin less than 8.5 g/dl. Two patients were administered to be rest at home for one week. Regarding treatment efficacy, all patients completed their treatment and underwent surgery 6 weeks later.

DISCUSSION

Approach of surgery alone in treatment of locally advanced rectal cancer has been reported to be accompanied with high recurrence rate, especially in tumors located lower in the rectum. Data from surgical studies showed local recurrence rates of 25-50% in tumors with staging T3-T4 or N positive after surgery alone [12-15].

Table-1: Five-year Actuarial Local Control and Relapse-free Survival after Surgery plus Postoperative Radiotherapy vs. Surgery Alone, According to Stage â€" Massachusetts General Hospital [16]

TNM Stage	Surgery Alone			Surgery plus Postoperative Radiation		
	No. of Patients	LC (%)	RFS (%)	No. of Patients	LC (%)	RFS (%)
T3N0	163	90	78	23	91	72[a]
T4N0	83	69	63	54	93	79[a]
T3N+	100	64	48	55	70	47[a]
T4N+	49	47	38	39	72	53[a]

LC, local control; RFS, relapse-free survival; TNM, tumor, node, metastasis [a]<0.05.

Table-2: Five-year Actuarial Local Control and Relapse-free Survival of Adjuvantly Irradiated Patients Based on 5-Fluorouracil (5FU) Administration â€" Massachusetts General Hospital [16]

TNM Stage	Without 5FU			With 5FU		
	No. of Patients	LC (%)	RFS (%)	No. of Patients	LC (%)	RFS (%)%)
T3N0	16	87	69	7	100	80
T4N0	37	94	78	16	100	83
T3N+	41	69	48	14	70	43
T4N+	24	67	53	15	79	52

LC, local control; RFS, relapse-free survival; TNM, tumor, node, metastasis

Dutch TME trial also reported 15% local failure two years after surgery alone in N positive cancer patients [17]. In this context, developing preoperative neo-adjuvant radiotherapy led to considerably reduce recurrence rate in comparison with surgery alone. A meta-analysis on 22 studies comparing surgery alone and neo-adjuvant radiotherapy showed significant lower recurrence and death rate in latter group [18]. Recently, controlled trials have supported replacing radiotherapy with radio-chemotherapy using 5-FU as a gold treatment for locally advanced rectal cancer. In the large EORTC 22921 trial comparing outcome of radiotherapy and radio-chemotherapy methods in rectal cancer patients, the first group received bolus 5-FU 350 mg/m²/d IV for 5days during the 1st and 5th weeks of radiotherapy and surgery was done 3 to 10 weeks later. The trial showed significant more reduction in tumor size, disease stage, and incidence of local recurrence in radio-chemotherapy group, however no significant discrepant was observed across the groups in overall survival [19]. Totally, it seems that although radio-chemotherapy with bolus 5-FU may not to achieve improvement in survival rate or distance metastasis, but significantly result in down-staging tumor and reducing local recurrence.

In our trial, we tried to show treatment tolerance of 8-hour bolus infusion 5FU 1000 mg/m^2 concomitantly with radiotherapy preoperatively. Our trial showed low complication rate and high efficacy of this treatment so that all 16 patients completed their treatment schedule, rare side effects including cytopenia, gastrointestinal complications, and need to transfusion were controlled well, and all could undergo surgical procedure successfully. The recent approach can be very important for our patients' population because of its certain effects on scrounging time and expenditures. It can also effectively reduce need to hospitalization and its-related complications in rectal cancer patients.

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