[Frontiers in Bioscience 11, 1275-1279, May 1, 2006]

Phase II study of neoadjuvant concurrent chemioradiotherapy with oxaliplatin-containig regimen in locally advanced rectal cancer

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1.ABSTRACT

The purpose of this phase II trial was to assess tolerance and efficacy of the combination of radiation, fluorouracil and oxaliplatin as neoadjuvant treatment in locally advanced rectal cancer. Between March 2001 and August 2004 , 28 patients M/18 F/10with locally advanced rectal cancer were entered in our study. All the patients underwent to the Radiotherapy with a total dose was 45 Gy and concurrent chemotherapy with Oxaliplatin 80 mg/mq G1 on weeks 1,3,5 followed by five day continous infusion of 5-Fluorouracile 300 mg/mq on five consecutive weeks. Surgery was planned 5 weeks later. Surgery was performed in all patients after a mean interval time of 5 weeks. Side effects and toxicity included grade II sec WHO diarrhea and grade II mucositis , grade I-II dysuria and skin reaction Downstaging to T0-2N0 was archieved in 18 patients (65%) with 4 (15%) achieving a pathologically complete response. Conclusions: Such a combined preoperative chemioradiotherapy and oxaliplatin-containig regimen is well tolerated with non increase in surgical toxicity.The good response rate observed warrants its use in further clinical trials.

2.INTRODUCTION

Despite continous advances in the diagnosis and treatment, rectal cancer continues to be a challenge for current oncology owing to its high mortality and increasing incidence. The treatment of stage II/III rectal cancer has historically been associated with a high risk of local recurrence and poor survival , wich led to the developed of adjuvant treatments in the hope of improving outcomes. In recent years there have been significant advances in the managment of rectal cancer. Two decades ago ,therapy for locally advanced rectal cancer included surgery followed by additional radiation therapy or based 5-fluorouracil chemotherapy. In contrast ,the last decade has brought hughes advances.In patients with resectable T3-T4 and /or node positive disease , radiation therapy (RT) combined with radical surgery has led to a decrease in the rate of local recurrences while preoperative irradiation has been associated with a possible increase in sphincter preserving procedures (1-2). The addition of systemic chemotherapy (CT) has further enhanced the local control,as well as improving the likelihood of sphincter preservation and survival. In fact preoperative chemotherapy is sometimes

performed with the hope of downstaging before undertaking surgical intervention into the vasculature or lymph ducts, to reduce the likelihood of tumor recurrence by decreasing the viability of the tumor cells or to act against hypothesized metastatic micro-lesions (3). Preoperative chemotherapy is thus being applied in a variety of treatment modalities to various forms of solid tumors. However in colorectal cancer patients scheduled for curative resection,preoperative therapy is controindicated if the toxicity associated with this treatment will lead to increased surgical time and/or a higher rate of postoperative complications. But during the last decade preoperative combined modality therapy with RT and 5FU based CT in the treatment of stage II-III rectal cancer has received increasing interest.

5-Fluorouracil (5-FU)- based CT has yielded better results than preoperative RT alone, but showed no survival advantage(3). On the basis of the favourable results of postoperative RT-CT combination, patients with clinical T3 and /or positive lymphnodes are commonly treated with combined modality therapy consisting of 45-50.4 Gy of RT plus either concurrent 5FU/leucovorin or continuous infusion 5-FU followed by surgery and four cycles of postoperative CT. Moreover, 5 Fluorouracil given by infusion is generally better tolerated than the bolus schedule: myelosuppression is less frequent and the main dose-limiting toxicities (DLTs) are stomatitis, diarrhoea and palmar-plantar erythro-dysesthaesia (hand- foot syndrome) (4-5). In these years oxaliplatin, irinotecan and raltitrexed have been developed and extensively studied in the first-line treatment of advanced colorectal cancer (6-7-8). The results of several studies have demonstrated that combination treatment may be more active than 5-Fluorouracil-folinic alone (9). Ongoing strategic studies are in progress to evaluate whether a combined regimen of 5-Fluorouracil – folinic acid-irinotecan or 5-Fluorouracil-folinic acid-oxaliplatin is superior to 5-Fluorouracil –folinic acid in preoperative radiochemotherapy of treatment locally advanced rectal cancer. Oxaliplatin is a newly developed platinum analog with significant activity in 5-Fluorouracil-refractory colorectal cancer. Clinical data indicate that oxaliplatin can at least partly reverse 5-Fluorouracil resistance. Oxaliplatin exhibits synergistic antitumor activity when combined with a protracted application of 5-Fluorouracil, whereas the combination of oxaliplatin with bolus 5-Fluorouracil is only additive. Experimental data in mice (10) have evidenced that the association of oxaliplatin (5mg/kg) plus radiotherapy (5Gy) arrests tumour growth with respect oxaliplatin or radiotherapy alone, indicating a radio-sensitization effect of the association.

In this study, we investigated and analyzed the effectiveness and toxicity of preoperative pelvic radiotherapy in combination with 5-fluorouracil and oxaliplatin in locally advanced rectal cancer.

3. PATIENTS AND METHODS

3.1. Patient selection

To be eligible for this study , a patient preoperatively had to meet the following criteria : a histologically proven colorectal cancer; a suitable candidate for surgery; no evidence of distant metastasis ; age < 75 years, no prior cancer, no double or multiple cancer present ; laboratory test values generally within the range of WBC count > 4000 /µl , Hb > 11.0 g/dl, Plt > 100.000/µl , AST and ALT < 40 U , BUN < 25mg/dl and negative urinary protein ; Performance Status 0-1 sec ECOG; no serious complications such as heart disease, hepatopathy, nepropathy, myelo-suppression ; patient not pregnant or potentially pregnant. Informed consent was obtained from the patient. Before study admission all patients underwent a complete history, physical examination, biopsy, digital rectal examination, rectoscopy, transrectal ultrasonografy, pelvic and abdominal computed tomographic scans, colonoscopy, and chest X-rays. A CBC with differential and serum chemistry (including electrolytes, creatinine, blood urea nitrogen, uric acid liver aminotrasferases, total bilirubin,alkaline phosphatase,and lactate dehydrogenase) was obtained within 1days before the start of treatment. Weekly blood counts were obtained and serum chemistry was repeated every third week or whenever clinically indicated.

3.2. Treatment plan

External beam radiotherapy was delivered with a Linear accelerator using 15 Mv photons in a box technique (3 or 4 fields). Treatment was performed using a Vac-Lock couches and personalized shielded fields, after a TC simulation and a 2D-3D treatment planning. Dose fraction was 1.8 Gy, total dose was 45 Gy (according to ICRU 50). The chemotherapy schedule were given with Oxaliplatin 80 mg/mq G1 on weeks 1, 3, 5 followed by five day continuous infusion of 5-Fluorouracile 300 mg/mq on five consecutive weeks. Surgery was planned 5 weeks later.

4. RESULTS

4.1. Patient characteristics

Between March 2001 and August 2004, 28 patients with locally advanced rectal cancer were entered in our study. 18 male and 10 female cases; median age 65 years, all with biopsy-proven rectal adenocarcinoma. The clinical stage (TNM) was T3N0M0 in 9 patients, T3N1M0 in 6 pts, T3N2M0 in 4 pts, T4N0M0 5 pts, and T4N1M0 4 pts (Table 1).

4.2. Toxicity

All patients completed treatment without modifications. Surgery was performed in all patients after a mean interval time of 5 weeks. Side effects and toxicity included grade II sec WHO diarrhoea in 6 patients (22%) and grade II sec WHO mucositis in 4 patients (15%). Grade I-II dysuria in 4 patients (15%). Grade I-II skin reaction was noticed in 2 patients (8%). Grade II piastrinopenia in 2 patients (8%).

4.3. Tumor response

Pathologic examination revealed that negative margins were obtained in 25 patients (90%). Downstaging to T0-2N0 was achieved in 18 patients (65%) with 4 (15%) achieving a pathologically complete response. Pathologic node positive was found in 0 of 4 pT0 patients, in 18 of

Table 1. Characteristics pretreatment

Characteristics	Number
Age years	
Median	65
Range	31-75
Male-Female ratio	18:10
Performance Status	
0	23
1	5
2	0
Adenocarcinoma	
Well differentiated	14
Moderately	8
Poorly	6
Distance from anal verge, cm	
Median	4
Range	1-6
Stage TNM (all M0)	
[1]u T3 N0	9
u T3 N1	6
u T3 N2	4
u T4 N0	5
u T4 N1	4
u T4 N2	0

[1] T stage assessed by endorectal ultrasound, T: tumor, N: Lympho Node, M: Metastasis, u: ultrasound

Table 2. Pathological Response

T Stage	Number
PT0	4
pT1	7
pT2	11
pT3	6
N Stage	
pN0	20
pN1	8
pN2-3	0

p: Pathology

pT1 or pT2 pts and in 6 of pT3. Pathological responses are shown in Table 2.

5. DISCUSSION

The treatment of rectal cancer has rapidly evolved during the last years, with an increasing use of preoperative radiochemotherapy. Surgery remains the common upfront treatment for patients who present clinically resectable rectal cancer at diagnosis (11). Postoperative radiotherapy and / or chemotherapy are usual for resected rectal cancer in the United States, but in European countries the current enthusiasm is for preoperative neoadjuvant therapy (12). Preoperative RT alone or combined with CT increase the chances of tumour downstaging and down-sizing and facilitates sphincter-sparing surgical procedures, thereby improving survival and quality of life (13-14). There is a greater emphasis on better patient selection using preoperative imaging (15).The aim is to maximize the potential for a histologically confirmed complete resection and sphincter-sparing procedures. Enormous advances have been achieved through improvements in surgical technique, pathologic staging and tumour downstaging. In the last decade, total mesorectal excision (16) has significantly contributed to decrease the incidence of local recurrence for extraperitoneal rectal cancer as well demonstred by Heald et al. (6% for all stage). Sphincter preservation is one of the major objectives of preoperative therapy. Although there are many published trials on preoperative CT-RT, only few of these reported results in patients with clinically resectable, invasive, low rectal cancer who, up on the initial clinical presentation, required an abdominal - perineal resection (APR) prior to treatment. Total mesorectal excision is now accepted as the optimal surgical approach, although the availability of this technique differs from country to country and hospital to hospital. Randomize trials have provided evidence that preoperative radiotherapy is more dose-effective and achies more effective local control than postoperative radiotherapy (17-18-19). However, whether preoperative combined modality therapy is more effective than preoperative RT alone has not yet been established. Overall preoperative CT-RT allowed sphincter preservation in approximately 75% of patients who required an APR. In almost all the reported series combined modality treatment included conventional RT (45-50.4 Gy) and either concurrent bolus 5-FU/leucovorin or continuous infusion 5-FU with or without postoperative CT. To confirm the suggestion of an increased rate of sphincter preserving procedures, randomized trials are in progress which should determine the effectiveness of preoperative versus postoperative combined modality treatment.

Currently chemoradiotherapy using 5-Fluorouracil as a radiosensitizer is considered the common approach for rectal cancer in the neoadjuvant setting. There are a number of mechanisms by which 5-Fluorouracil could increase radiation sensitivity at the cellular level. First is through the killing of S-phase cells, which are relatively radioresistant. Probably, radiosensitization occurs only when cells take up 5-Fluorouracil prior to radiation. Increased radiation sensitivity appears in cells which have inappropriate progression through S-phase in the presence of drug, i.e. from a disordered S-phase check-point.5 Fluorouracil alone has DNA –directed (through the inhibition of thymidylate synthase) and RNA –directed (through incorporation in RNA) effects (4-5). Phase I-II studies in selected patients suggested an improvement in local tumour control and in tumour down-sizing and downstaging, favouring sphincter preserving procedures. In addition fewer acute and chronic side effects were reported with preoperative than with postoperative combined modality treatment. In general the incidence of grade 3-4 acute toxicity reported with combined modality treatment ranged from 15% to 25% , the pathological complete response rates from 9% to 29% and the incidence of local recurrence from 3% to 17%.

Oxaliplatin a novel antineoplastic platinum derivative , has shown a stronger cytotoxic effect than cisplatin and carboplatin (20) In randomized trials for metastatic colorectal cancer its combination with 5-FU and leucovorin resulted in higher response rates and

progression-free survival rates than 5 FU/leucovorin alone (21-22). Based on these data and on the radiosensitizing, properties reported in some preclinical studies (23), a number of combination regimens of oxaliplatin plus 5FU and preoperative RT in locally advanced rectal cancer. The weekly administration of oxaliplatin (60 mg/mq) for six cycles and continuous infusion 5FU (225 mg/mq/day) combined with 50.4 Gy of RT appeared to be more effective than the intermittent four week schedule of Oxaliplatin (130 mg/mq) and five day infusional 5-FU (350 mg/mq/day for 5 days combined with 45 Gy of RT. The pathological complete response rate was 29% with the weekly regimen and 15 % with the four week schedule (24-25). Tolerance to treatment was generally good with both combination regimens. The data presented in this study confirm the preliminary reports in this neoadjuvant treatment. Such a combined preoperative chemoradiotherapy and oxaliplatin containing regimen is well tolerated with no increase in surgical toxicity. The good response rate observed warrants its use in further clinical trials. Local response to preoperative CT/RT was highly satisfactory and allowed conservative surgery in 90% of patients. The encouraging results of this study suggest that in combination with radiotherapy, oxaliplatin has the potential to place continuous infusion 5-FU as the standard treatment for rectal cancer.

6. REFERENCES

1. Kapiteijn E. , C.A. Marijnen , I. D. Nagtegaal , H. Putter, W. H. Steup, T. Wiggers, H. J. Rutten , L. Pahlmam , B. Glimelius, J. H. van Krieken, J. W. Leer, C. J. van de Velde, Dutch Colorectal Cancer Group: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*, 345:638-646, (2001)

2. Boulis-Wassif S. , A. Gerard, J. Loygue. Final results of a randomised trial on the treatment of rectal cancer with properative radiotherapy alone or in combination with 5-Fluorouracil, followed by radical surgery. *Cancer*; 53: 1781-1818 (1984)

3. Frei E. III. What's in a name – neoadjuvant. *J Natl Cancer Inst*,80:1088-9 (Editorial) (1988)

4. Lawrence T.S. , J. E. Tepper, A. W. Blacstock. Fluoropyrimi-dine-radiation interactions in cells and tumors. *Semin Radiat Oncol*,7:267-273 (1997)

5. Rich T. A. Irradiation plus 5-Fluorouracil : cellular mechanism of action and treatment schedules. *Semin Radia. Oncol*,7: 260-266 (1997)

6. Raymond E. , S. G. Chaney , A. Taamma , E. Cvitkovic. Oxaliplatin : a riview of preclinical and clinical studies. *Ann.Oncol*., 9:1053-1071 (1998)

7. Sargent D. J. , D. Niedzwiecki , M. J. O'Connel , R. L. Schilsky. Recommendation for caution with irinotecan, fluorouracil and leucovorin for colorectal cancer. *N Engl J Med* ,345:144-145 (2001)

8. Cocconi G. , D. Cunningham , E. Van Cutsem , E. Francois , B. Gustavsson, G. van Hazel , D. Kerr, K. Possinger, S. M. Hietschold. Open randomized, multicenter trial of raltitrexed versus fluorouracil plus high- dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. *J Clin Oncol* 16: 2943-2952 (1988)

9. Van Cutsem E. , C. Verslype. Integration of new cytotoxic agents in the managment of advanced colorectal cancer: where are we now and where do we go? *Educational Book ASCO*,240-247 (2002)

10. Mc Mullen K. P. , A. W. Blackstock. Chemoradiation with novel agents for rectal cancer. *Cl Colorectal Cancer* , 2:24-30 (2002)

11. Nelson H. , D. J. Sargent. Refining multimodal therapy for rectal cancer. *N Engl J Med* 345: 690-692 (2001)

12. Wils J. , P. O' Dwyer , R Labianca. Adjuvant treatment of colorectal cancer at the turn of the century: European and US perspective. *Ann Oncol*, 12:13-22 (2001)

13. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable cancer. *N Engl J Med* ; 336:980-987 (1997)

14. Glynne - Jones R. , J. Debus. Improving chemioradio-therapy in rectal cancer. *Oncologist* 6 (Suppl.4): 29-34 (2001)

15. Wagman R. , B. D. Minsky , A. M. Cohen , J.G. Guillem, P. P. Paty. Sphincter preservation in rectal cancer with preoperative radiation therapy and coloanal anastomosis : long term follow- up. Int *J Radiat Oncol Biol Phys* , 42:51-57 (1998)

16. Heald R. J., R. D. H. Ryall. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet*; i:1479-1482 (1986)

17. Glimelius B. , L. Phalman. Perioperative radiotherapy in rectal cancer. *Acta Oncol* 38: 23-32 , (1999)

18. Pahlman L. , B. Glimelius. Pre- or postoperative radio-therapy in rectal and rectosigmoid carcinoma.report from a randomized multicenter trial. *Ann Surg* 211:187-195, (1990)

19. Glimelius B. , U. Isacsson, B. Jung. Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose-response effect favoring preoperative treatment. *Int J Radiot Oncol Biol Phys* 37: 281-287 (1997)

20. Rixe O. , W. Ortuzar , M. Alvarez , R. Parker , E. Reed , K. Paull , T. Fojo. Oxaliplatin , tetraplatin, cisplatin, and carboplatin : spectrum of activity in drug-resistance cell-lines and in the cell line of the National Cancer Institute's Anticancer Drug Screen panel. *Biochem Pharmacol* 52:1855-1865 (1996)

21. de Gramont A. , A. Figer , M. Seymour , M. Homerin , A. Hmissi , J. Cassidy , C. Boni, H. Cortes-Funes, A. Cervantes, G. Freyer, D. Papamichael, N. Le Bail, C. Louvet, D. Hendler, F. de Braud, C. Wilson, F. Morvan, A. Bonetti. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 18:2938-2947 (2000)

22. Giacchetti S. , B. Perpoint , R. Zidani , N. Le Bail , R. Faggiuolo, C. Focan, P. Chollet, J.F. llory, Y. Letourneau, B. Coudert, F. Bertheaut-Cvitkovic, D. Larregain - Fournier, A. Le Roi , S. Walter , R. Adam, J. L. Misset, F. Levi. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil - leucovorin as first - line treatment of metastatic colorectal cancer. *J Clin Oncol* 18:136-147 (2000)

23. Blackstock A. , S. Hess. Oxaliplatin in vitro and in vivo evidence of its radiationsensitizing activity-preclinical observations relevant to ongoing clinical trials. *Proc Am Assoc Cancer Res* , 41: 53 (2000)

24. Aschele C. , M. L. Friso , S. Pucciarelli , L. Sartor , S. Lonardi , G. De Salvo , G. Fabris . A phase II study of weekly oxaliplatin (OXA), 5-Fluorouracil continous infusion (CI) and preoperative radiotherapy (RT) in locally advanced rectal cancer (LARC) *Proc ASCO*,21:132A (2002)

25. Gerard J. P. , O. Chapet , C. Nemoz , P. Romestaing , F. Mornex . Preoperative concurrent chemoradiotherapy in locally advanced rectal cancer with high-dose radiation and oxaliplatin-containing regimen:the Lyon R0-04 phase II trial. *J Clin.Oncol.* 21:1119-11124 (2003)

Key Words: Oxaliplatin, Neoadjuvant, radiochemotherapy, Adenocarcinoma, Cancer, Neoplasm, Tumor, Rectum, Treatment, Therapeutics

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