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INFUSIONAL 5-FLUOROURACIL AND ZD1839 (GEFITINIB–IRESSA) IN COMBINATION WITH PREOPERATIVE RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER: A PHASE I AND II TRIAL (1839IL/0092)

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Purpose: To report the final data of a Phase I and II study (1839IL/0092) on the combination of an anti–epidermal growth factor receptor drug (gefitinib), infusional 5-fluorouracil, and preoperative radiotherapy in locally advanced, resectable rectal cancer.

Methods and Materials: Patients received 45 Gy in the posterior pelvis plus a boost of 5.4 Gy on the tumor and corresponding mesorectum. Infusional 5-fluorouracil (5-FU) and gefitinib (250 and 500 mg/day) were delivered during all radiotherapy course. An IORT boost of 10 Gy was allowed. The main endpoints of the study were to establish dose-limiting toxicity (DLT) and to evaluate the rate of pathologic response according to the tumor regression grade (TRG) Mandard score.

Results: A total of 41 patients were enrolled. The DLT was not reached in the 6 patients enrolled in the dose-escalation part of the study. Of the 33 patients in the Phase II, TRG 1 was recorded in 10 patients (30.3%) and TRG 2 in 7 patients (21.2 %); overall 17 of 33 patients (51.5%) had a favorable endpoint. Overall, Grade 3+ toxicity was recorded in 16 patients (41%); these included Grade 3+ gastrointestinal toxicity in 8 patients (20.5%), Grade 3+ skin toxicity in 6 (15.3%), and Grade 3+ genitourinary toxicity in 4 (10.2%). A dose reduction of gefitinib was necessary in 24 patients (61.5%).

Conclusions: Gefitinib can be associated with 5-FU–based preoperative chemoradiation at the dose of 500 mg without any life-threatening toxicity and with a high pCR (30.3%). The relevant rate of Grade 3 gastrointestinal toxicity suggests that 250 mg would be more tolerable dose in a neaoadjuvant approach with radiotherapy and infusional 5-FU. © 2008 Elsevier Inc.

Gefitinib, Preoperative, Chemoradiation, Rectal cancer, TRG, Dose-limiting toxicity.

INTRODUCTION

As established in Phase III randomized trials, neoadjuvant chemoradiation improves local control in patients with locally advanced rectal carcinoma; however distant metastasis remains the most common failure, and overall survival and disease-free survival (DFS) are not ameliorated by the addition of postoperative 5-FU chemotherapy (1–3). The introduction in clinical practice of biologic factors as markers of prognosis permitted identification of patients at higher risk and allowed use of these as targets for new therapeutic strategies.

Epidermal growth factor receptor (EGFR) plays a central role in tumor progression, being associated with shorter survival in primary colorectal cancer and radioresistance (4–9). Anti-EGFR drugs emerged as a promising therapeutic strategy in combination with radiotherapy; broad clinical experience has been achieved with head-neck cancer, in which the addition of cetuximab to radiotherapy resulted in superior

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local control and survival compared with radiotherapy alone (10, 11).

Gefitinib is a recently developed oral drug directed toward the intracellular tyrosine kinase domain of EGFR; when combined with different cytotoxic drugs, it showed an increase in growth inhibition in cancer cells (12) and also an enhanced ability of radiation to directly kill cancer stem cells, resulting in cellular radiosensitization through modified signal transduction, inhibition of repair of DNA damage, reduced repopulation, and improved reoxygenation during fractionated radiotherapy (13).

The objective of our study was to quantify the efficacy of the addition of gefitinib to preoperative chemoradiation in patients with locally advanced resectable rectal cancer.

METHODS AND MATERIALS

Study design

This was an open-label, noncomparative, two-part, Phase I and Phase II trial in patients with clinical Stage III rectal carcinoma. The trial was divided into two parts: a dose-escalating part (Part A), to determine the maximum tolerated dose (MTD) of gefitinib associated with chemoradiation; and a Phase II trial (Part B), to assess the response rate of the same treatment. In Part A, the primary objective was to characterize the safety profile of gefitinib at 250-mg and 500-mg daily doses, and to evaluate the safety and tolerability of the combination gefitinib, 5-FU and radiotherapy. In Part B the primary objective was to estimate the pathologic response according to TRG Mandard score in terms of percentage of TRG1 and TRG2; the secondary objective was to evaluate the response on imaging in terms of overall objective response rate (*i.e.,* complete response [CR] and partial response [PR]) and the disease control rate (*i.e.,* CR, PR, and stable disease). The quality of life–related objective of the trial was to assess the sphincter preservation rate.

Patient selection

Eligibility criteria included the following: histologically proven, resectable rectal carcinoma; clinical stages cT2N1-2M0 cT3N0-2M0 as assessed by digital examination, pelvic computed tomographic scan or magnetic resonance imaging (MRI), liver ultrasonography, chest X-rays, and barium enema; absence of positive lymph nodes outside the mesorectum and distant metastases; age $\geq$18 years; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Exclusion criteria were other malignancies either coexisting or diagnosed within the last 5 years, and contraindications to chemoradiation. All patients provided written informed consent.

Treatment

Radiotherapy was delivered in patients positioned prone on the up–down table (14), planned with three-dimensional treatment planning, using a standard three-field box technique.

A total dose of 50.4 Gy (1.8 Gy per day, five times per week) was delivered in 28 fractions, corresponding to 38 days of treatment. The clinical target volume 2 (CTV2) including the tumor, the entire mesorectum, the internal iliac, and the obturator nodes received a dose of 45 Gy. The CTV1 including the tumor, the corresponding mesorectum, plus 2 cm superiorly and inferiorly received a boost of 5.4 Gy. An IORT of 10 Gy was delivered on the tumor bed plus a minimum 1-cm margin.

5-Fluorouracil concurrent chemotherapy was administered by continuous intravenous infusion during the whole radiotherapy treatment period (225 mg/m^2 per day, 7 days per week).

In the case of Grade 3+ toxicity (excluding stomatitis), all treatments were stopped. If after 1 week toxicity resolved, chemoradiation was resumed. The 5-FU dose was reduced according to blood parameters as follows: to 80% with a white blood cell count of 2,000 to 1,000/mm^3 or platelet count of 50,000 to 25,000/mm^3, and to 70% with a white blood cell count of <1,000/mm^3, platelet count of <25,000/mm^3, and Grade 3 to 4 stomatitis. In any case, radiotherapy and chemotherapy were similarly delayed.

Gefitinib was administered during radiotherapy, once daily each day. The dose was 250 mg and 500 mg in Part A of the study and 500 mg in Part B. Dose escalation proceeded with the standard 3+3 design. First, 3 patients at each dose level were enrolled to allow close observation for toxicity. If one serious acute adverse event was observed at each dose level, the dose level would be rejected.

Toxicity was evaluated according to Common Terminology Criteria for Adverse Events v3.0 scoring systems (15). Dose-limiting events (DLT) were considered as any serious, acute, life-threatening adverse effects (*e.g.,* angioedema not requiring intubation but intravenous hydrocortisone treatment, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias requiring blood transfusion or convulsions that did not result in hospitalization).

Drug delivery interruptions were used as the first approach to manage toxicity. Repeated drug interruptions were allowed as required, for a maximum of 14 days on each occasion. If further interruptions were considered insufficient to manage the toxicity, dose reduction was considered. Only one dose reduction per patient was allowed. For patients receiving 500 mg of gefitinib, the dose was reduced to 250 mg. Patients continued to take the reduced dose of one tablet per day. For patients receiving 250 mg of gefitinib, no dose reduction was allowed.

After radiologic re-evaluation, surgery was performed 7 to 8 weeks from the end of chemoradiation. The choice of surgical procedure and the performance of a temporary colonostomy were at the surgeon's discretion. TME with a distal rectal margin of at least 2 cm for sphincter preservation was strongly recommended. Specimens were inked for radial margin determination. Biopsies were performed in any gross residual area where there was suspicion of residual tumor or in any tumor bed considered to be at risk.

Patients with pathologically positive nodes received six cycles of adjuvant chemotherapy with a bolus infusion of 400 mg/m^2 of 5-FU and leucovorin 200 mg/m^2, as well as 22 h of continuous infusion with 600 mg/m^2 of 5-FU, repeated for 2 days according to the De Gramont regimen (16).

Response criteria

Tumor response on imaging was assessed according to the World Health Organization (WHO) criteria (17). Response evaluation was assessed comparing the value of reference index before (IND1) and 6 to 7 weeks after the end of chemoradiation (IND2); IND was defined as the product of rectal wall quarter invaded by the tumor and tumor length (18). The reference index pre- and postchemoradiotherapy was calculated by the radiologist and discussed in a weekly meeting with the surgeons and the radiation oncologists in each Center. The length of the tumor was measured on the sagittal scan of MRI or on the lateral view of barium enema. The quarters of rectal wall involved by the tumor were assessed on axial scan of TC or MRI considering the rectum divided into four quarters (anterior, posterior, left lateral, and right lateral). All the examinations were performed with the rectum distended by air.