

A PHASE I STUDY OF ZD1839 (IRESSA) AND CONCOMITANT PREOPERATIVE RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER

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Purpose

Preoperative RT decrease the rate of locoregional failure in locally advanced rectal adenocarcinomas (LARA)

Hyperfractionated RT (HFRT) allows similar or higher doses to be delivered over a shorter time while possibly reducing late complications

Purpose

Growth inhibition induced by EGFR-targeting agents have been observed in several solid cancers.

ZD1839 (selective inhibitor of the EGFR tyrosine kinase activity) significantly enhanced the radiosensitivity in a human colon cancer xenograft model (Williams et al, 2001)

Aim

Primary objective:

To determine the recommended dose of ZD1839 when combined with concomitant HFRT in a preoperative setting in patients with LARA

Secondary objectives:

To estimate non-DLT toxicities, objective response rate, and early oncologic results

Patients and Methods

General design

RT 2 x 1.25 Gy / day

50 Gy / 40F / 4 weeks

ZD1839 dose escalation

250 mg / day

Surgery

6 weeks later

Adjuvant chemotherapy

In case of T4 or N+

Patients and Methods

Eligibility criteria

Proven adenocarcinoma

T3-4 and/or N1-2, M0

Age \leq 75 years

WHO performance: 0-2

Feasibility of 2 sessions / day

Pts suitable for surgery

Written consent

Patients and Methods

Patients characteristics (# 19)

From 09/2003 to 03/2006

Age (mean): 58.5 years (range: 35-72)

Gender: 14 M / 5 F

WHO performance 0 = 18, 1 = 1

Patients and Methods

Clinical TNM classification

T stage: T2 = 3, T3 = 15 (79%), T4 = 1

N stage: N0 = 7, N1-2 = 11, Nx = 1

M stage: M0 = 19

Results

Radiotherapy

All pts received the planned 50 Gy dose
(45 Gy to posterior pelvis + 5 Gy boost to the Tm)

All pts treated with 3 fields technique using X15-18 MV

Median RT duration: 28 days (range: 26-30)

Results

ZD1839 (Iressa)

All patients received a daily dose of 250 mg of Iressa

A second dose level was planned at 500 mg

The occurrence of a DLT (Grade 3 diarrhea / Dehydration / hospitalization) in the **first** treated patient prompted us to reconsider the dose escalation

Results

ZD1839 (Iressa)

Iressa was stopped in **two** patients due to acute toxicities (diarrhea -/+ abdominal pain, 2^{sd} and 4th week)

Results

Acute toxicities

	<u>Gr1</u>	<u>Gr2</u>	<u>Gr3</u>
Skin	31%	21%	21%
Diarrhea	26%	47%	15%
Nausea	10%	5%	5%
Rectum	21%	36%	10%
Urinary	6%	-	-

Results

Acute toxicities (2)

	<u>Gr1</u>	<u>Gr2</u>	<u>Gr3</u>
Infection	6%	-	-
Fatigue	42%	10%	-

Others

Acne	31.5%
Pharyngitis	10%
Abdominal pain	15%

Results

Surgery

Mean interval : 40 days

Abdominoperineal resection: 10 pts

Low anterior resection: 9 pts

All pts operated on with R0 margin except 1 (R1)

Anastomotic leakage: 1 pt

Perineal abscess: 2 pts

Results

Pathologic Tm response

Complete: 4 pts (21%)

Microscopic residue (≤ 1 cm): 6 pts (32%)

Macroscopic residue: 9 pts (47%)

Results

Clinical TNM stage /

Pathologic TNM

T0	0 (0%)	4 (21%)
T1	0 (0%)	2 (10%)
T2	3 (15%)	7 (36%)
T3	15 (79%)	6 (31%)
T4	1 (5%)	0 (0%)
N0	7 (36%)	15 (79%)
N1	7 (36%)	2 (10%)
N2	4 (21%)	2 (10%)
M1	0 (0%)	1 (5%)

Results

Early oncologic results

Mean F-U: 13 months (range: 6-28 months)

17 pts alive and 2 deceased from cancer

One locoregional failure observed (R1 patient)

2 patients presented with distant metastasis

Conclusions

- ✓ Iressa can be administered daily concomitantly with 50 Gy HFRT with manageable toxicity
- ✓ The maximum tolerated dose is 250 mg daily
- ✓ The major pathologic response rate observed (53% of patients) is encouraging

This study has been supported by the AstraZeneca group of companies