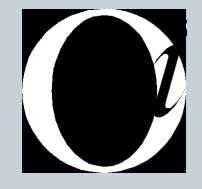


PHASE II STUDY WITH ORAL CAPECITABINE (XELODA®) AS RADIOSENSITISING AGENT IN NEOADJUVANT TREATMENT OF LOCALLY ADVANCED RESECTABLE RECTAL CANCER

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INTRODUCTION

• Preoperative chemoradiation became a standard part of treatment protocols in rectal cancer of stage II and III. Compared to postoperative chemoradiation, the advantage of preoperative application of chemotherapeutics and irradiation includes improved compliance, reduced toxicity and down-staging of the tumor in substantial proportion of patients. The latter may enhance the rate of curative surgery, permit sphincter preservation in patients with low-sited tumors and has positive impact on the quality of life of these patients.

• Orally administered capecitabine mimics the pharmacokinetics of continuous 5-FU infusion. The unique mechanism of capecitabine activation, preferably in tumor cells, may further enhance its efficacy and tolerability, offering the potential for enhanced therapeutic ratio.

METHODOLOGY

- Study design and entry criteria:
 - prospective phase II study
 - histologically verified adenocarcinoma of the rectum in clinical stage II or III
 - WHO PS ≤ 1, no prior radio- or chemotherapy
 - **enrolment: from 6/2004 to 1/2005, 57 patients**

- Evaluation of patients: weekly evaluation during radiotehrapy
- Surgery: 4-6 weeks after chemoradiation
- Treatment assignment and drug administration:

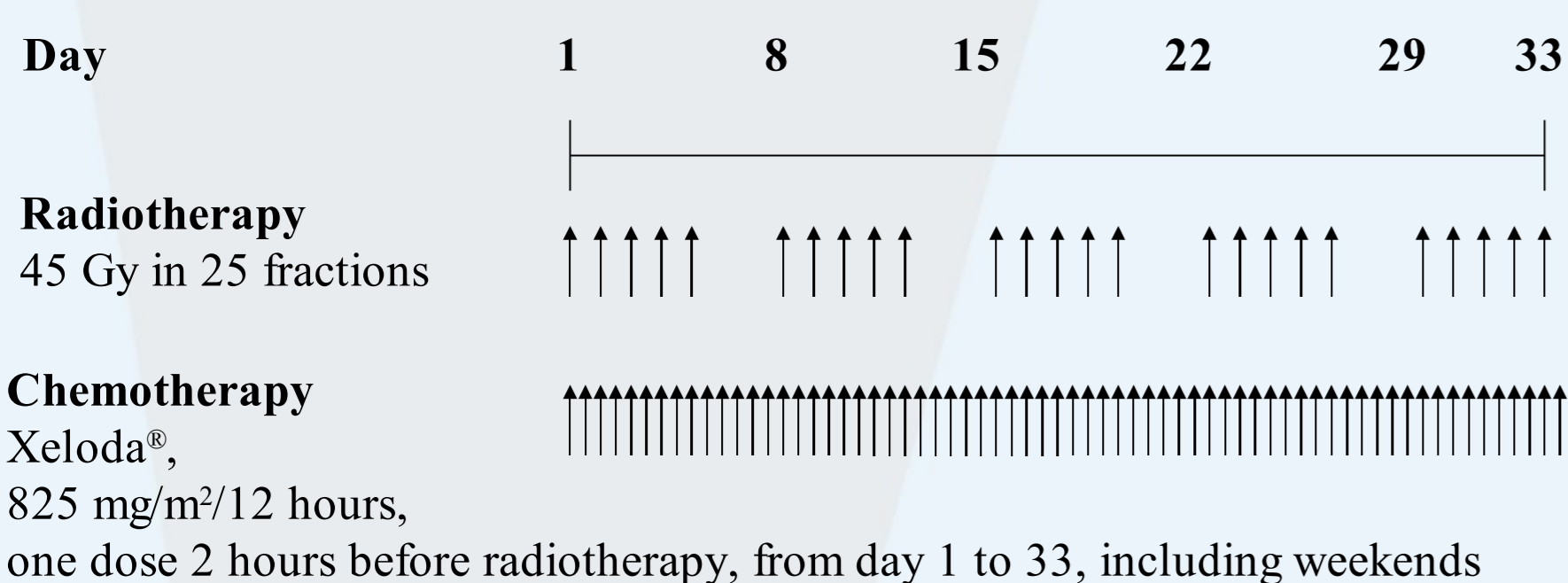


Table 6. Distribution of clinical and pathological stages.

Before surgery - cTN (57 patients)	After surgery – pTNM (55 patients)													% (N)		
	T0N0	T0N1	T1N0	T2N0	T2N1	T3N0	T3N1	T3N2	T4N0	T4N1	T4N2	T3N2M1				
T1N1			1													
T2N1				1		1										
T3N0	1		1	7		7	3					1				
T3N1	4	1	1	4	1	4	4	5					1			
T3N2							2	1								1
T4N0				1												
T4N1									1							1

	% (N)
pCR	9.1 (5/55)
Downstaging	
T	40 (22/55)
N	52.9 (18/34)
Overall	49.1 (27/55)
Upstaging	
T	5.5 (3/55)
N	20 (11/55)
Overall	10.9 (6/55)

+ cT3cN1 – died during chemoradiation
 cT4cN1 – explorative laparotomy only

OBJECTIVES

• **Primary objective:** the rate of pathologically determined complete remission rate (pCR) of the disease locally and regionally.

• **Secondary objectives:** the rate of sphincter preservation in locally advanced low-sited tumors, overall downstaging rate and toxicity.

RESULTS

Table 1. Patients' characteristics.

Patients' characteristics	% (N)
Age (years)	67 (34-81)*
Gender	
Male	75.4 (43/57)
Female	24.6 (14/57)
WHO performance status	
Stage 0	91.2 (52/57)
Stage 1	8.8 (7/57)
Tumor differentiation (grade)	
Well (G1)	7.1 (4/57)
Moderate (G2)	36.8 (21/57)
Poor (G3)	5.4 (3/57)
Not stated or unknown (GX)	50.9 (29/57)
Tumor distance from the anal verge (cm)	5.5 (1-12)*

* Mean (range)

Chemoradiation

Table 2. Side effects of preoperative chemoradiation (57 patients).

Side effect	Toxicity grade* - N (%)		
	1	2	3
Hemathological			
Anemia	3 (5.4%)	2 (3.6%)	
Leucocytopenia	5 (9.1%)	2 (3.6%)	1 (1.8%)
Non-hemathological			
Fatigue	14 (25.5%)	1 (1.8%)	
Nausea	11 (20%)		
Vomitus	6 (10.9%)		
Hand-foot syndrom	4 (7.3%)		
Diarrhoea	11 (20%)	5 (9.1%)	2 (3.6%)
Infection	4 (7.3%)	1 (1.8%)	1 (1.8%)
Impaired renal function			1 (1.8%)
Radiodermatitis	15 (27.3%)	1 (1.8%)	19 (34.5%)
Cystitis	5 (9.1%)		
Proctitis	12 (21.8%)	1 (1.8%)	1 (1.8%)

1 female patient died due to massive pulmonary embolism during chemoradiation (after receiving 27 Gy).

* According to NCI CTC (version 2.0)

Surgery

CONCLUSIONS

• Preoperative chemoradiotherapy with oral capecitabine as a radiosensitiser is safe, well tolerated and convenient for the patients.

• This treatment has a considerable downstaging potential and can increase significantly the possibility for sphincter preservation in a low-sited rectal primary tumors.

• Oral capecitabine represents a good alternative to protracted intravenous 5-FU in preoperative radiochemotherapy protocols from the standpoint of toxicity and downstaging potential.

Table 3. Efficacy parameters.

Parameter	% (N)
Died during chemoradiation (massive pulmonary embolism)	1.7 (1/57)
Explorative laparotomy only	1.7 (1/57)
Resected patients	96.5 (55/57)
Complete resection (R0)	96.4 (53/55)
Microscopic residual disease (R1)	3.6 (2/55)
Total sphincter preservation rate	65.5 (36/55)
Sphincter preservation in patients with tumors located ≤ 5 cm from anal verge	37 (10/27)

Table 4. Perioperative complications (56 patients).

Complication	% (N)
Delayed healing of the wound	21.4 (12/56)
Ileus	5.4 (3/56)
Febrile episode	8.9 (5/56)
Anastomotic leakage	1.8 (1/56)
Chronic diarrhoea	5.4 (3/56)
Death (due to sepsis)	1.8 (1/56)
None	55.4 (31/56)

Table 5. Types of surgery (57 patients).

Before chemoradiation (intended procedure)	% (N)
Anterior resection	7 (4/57)
Low anterior resection	43.8 (25/57)
Abdominoperineal resection	43.8 (25/57)
Coloanal reconstruction	5.3 (3/57)

Chemoradiation

After chemoradiation	% (N)
Anterior resection	7 (4/57)
Low anterior resection	56.1 (32/57)
Abdominoperineal resection	29.8 (17/57)
Hartmann's resection	1.7 (1/57)
Small pelvis exenteration	1.7 (1/57)
Explorative laparotomy only	1.7 (1/57)
Not operated on (died during chemoradiation)	1.7 (1/57)