Cetuximab plus Cisplatin, Irinotecan, & Thoracic Radiotherapy as Definitive Treatment for Locally Advanced, Unresectable Esophageal Cancer: a Phase II trial, SWOG-0414

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Purpose

RTOG-8501 established definitive concomitant chemoradiotherapy as a standard of care for pts with locally advanced EC. Median overall survival (OS) for pts has changed little over the past 2 decades. Based on phase I-II data of CDDP, CPT11, & TRT and separate phase I-III data of cetuximab, the SWOG GI Committee designed a phase II trial (S0414) to test this novel combined-modality approach.

Specific aims

1) 2-yr OS,
2) toxicity profile,
3) objective response rate (RR),
4) progression-free survival (PFS), and
5) association between gene expression levels & germline polymorphisms involved in DNA repair, drug metabolism, & the EGFR pathway, and clinical outcome.

Methods and Materials

Eligibility: cT4M0 disease or medically unresectable, biopsy-proven, primary EC (squamous cell or adenocarcinoma), thoracic-GE junction location, with adequate major organ function.

Cetuximab 400 mg/m^2 day 1 (cycle 1)
Cetuximab 250 mg/m^2 day 8, 15 (cycle 1), then day 1, 8, & 15 for subsequent cycles

CDDP 30 mg/m^2 day 1 & 8 (all cycles)

Irinotecan 65 mg/m^2/days 1 & 8 (all cycles)

TRT 50.5 Gy @ 1.8 Gy/fx (28 fxs), beginning day 1 of cycle 3

Each cycle was 21 days in length

Statistical Methods

Primary endpoint was set to be driven by accrual to the adenocarcinoma stratum; while SCCA pts are to be included in overall descriptive statistics for the trial.

If 2-yr OS ≤ 35%, this regimen was deemed to be worthy of further interest, and of considerable interest if ≥ 50%

Planned accrual was 75 adeno pts & 25 squamous cell pts over 18 months, with the regimen considered of further interest if 2-yr OS ≥ 43% in the adenocarcinoma stratum.

Power of a 1-sided 0.05 level test of 35% vs 50% 2-yr OS is 91%.

Results

22 pts enrolled & 21 evaluable
-1 ineligible (tumor < 20 cm from incisors)
21 pts are considered in this analysis
-15 men (93%)
-ECOG PStatus 0-1/2=20/1
-Adeno/SCCA=10/11
-Caucasian/Non-Caucasian=15/6
-Median age: 61 yrs
17 pts evaluable by RECIST criteria
-1 cCR (6%), 2 cPR (12%), 3 Stable Dx (18%)

2 deaths were due to protocol treatment (sudden death & GI necrosis)
6 pts had Gr 4 toxicities.
48% & 29% of pts had Gr 3 & 4 toxicity, respectively, including:
52% hematologic
24% fatigue
24% diarrhea
19% nausea/emesis
19% dehydration
19% anorexia.

Figure 1 shows Progression-free Survival

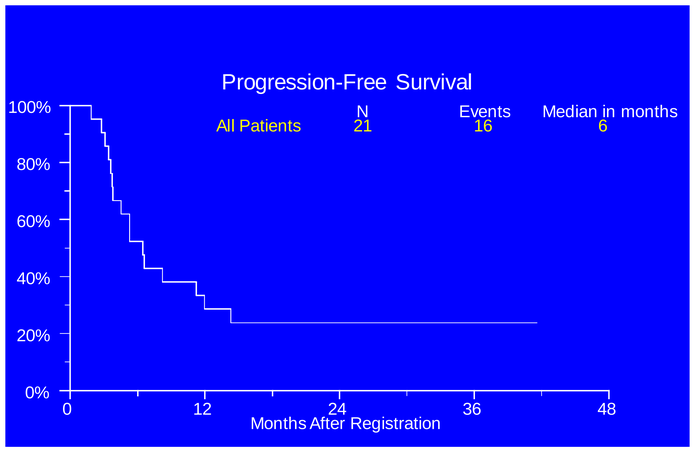

Fig. 1 Median progression-free survival is 6 months & 2-yr PFS is 24% (95% C.I., 8% to 47%)

Figure 2 Overall Survival

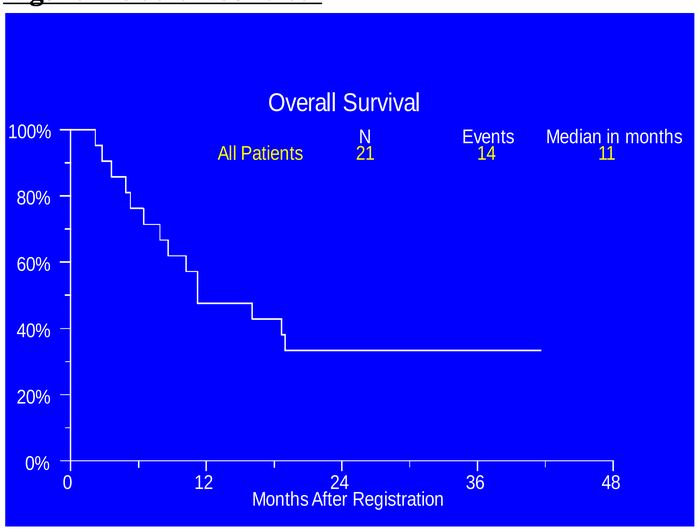

Fig. 2 Median overall survival is 11 months& 2-yr survival is 33% (95% C.I., 15% TO 57%)

Results

Table 1 lists the number of patients with a given type & grade of adverse event

ADVERSE EVENT	Grade 0	1	2	3	4	5
ALT	19	2	0	0	0	0
AST	19	2	0	0	0	0
Acne	8	5	7	1	0	0
Alkaline phosphatase	17	4	0	0	0	0
Alopecia	19	1	1	0	0	0
Anorexia	13	1	3	4	0	0
Bilirubin	20	1	0	0	0	0
CNS ischemia	20	0	0	0	1	0
Cardiac Arrhythmia-other	20	1	0	0	0	0
Constipation	12	8	1	0	0	0
Cough	19	2	0	0	0	0
Creatinine	20	0	0	0	1	0
Dehydration	17	0	0	4	0	0
Dermatology-other	20	0	0	1	0	0
Diarrhea	6	7	3	5	0	0
Dry skin	14	4	3	0	0	0
Dysphagia	13	2	3	3	0	0
Dyspnea	20	1	0	0	0	0
Esophagitis	17	1	1	2	0	0
Fatigue	5	7	4	5	0	0
Febrile neutropenia	20	0	0	1	0	0
Fever	20	1	0	0	0	0
GI Necrosis: col/cecm/append.	20	0	0	0	0	1
GI Pain: abdomen	19	0	1	1	0	0
GI Pain: esophagus	17	1	2	1	0	0
GI Perforation: colon	20	0	0	1	0	0
GI-other	20	1	0	0	0	0
GU Hemorrhage: bladder	20	1	0	0	0	0
Heartburn	19	2	0	0	0	0
Hemoglobin	11	3	4	3	0	0
Hemorrhage-other	20	1	0	0	0	0
Hyperglycemia	15	2	3	1	0	0
Hypermagnesemia	20	1	0	0	0	0
Hypertension	20	1	0	0	0	0
Hypoalbuminemia	16	1	3	1	0	0
Hypocalcemia	15	2	3	1	0	0
Hypokalemia	16	3	0	2	0	0
Hypomagnesemia	13	5	2	1	0	0

ADVERSE EVENT	Grade 0	1	2	3	4	5
Hyponatremia	15	5	0	1	0	0
Hypophosphatemia	20	0	1	0	0	0
Hypotension	19	1	1	0	0	0
Insomnia	20	1	0	0	0	0
Leukocytes	7	0	5	7	2	0
Lung Pain: chest/thorax	20	1	0	0	0	0
Lymphopenia	17	0	0	2	2	0
Mucositis, clin: oral cavity	17	3	1	0	0	0
Mucositis, funct: oral cav.	18	2	1	0	0	0
Musculo. Pain: back	20	1	0	0	0	0
Musculo. Pain: limb	20	1	0	0	0	0
Musculo. Pain: muscle	19	1	1	0	0	0
Nail changes	20	1	0	0	0	0
Nausea	2	10	5	4	0	0
Neurop: smell	20	1	0	0	0	0
Neuropathy-sensory	19	1	0	1	0	0
Neutrophils	7	1	7	3	3	0
Pain-other	20	1	0	0	0	0
Palpitations	20	1	0	0	0	0
Platelets	13	7	1	0	0	0
Pruritus	20	1	0	0	0	0
RT Dermatitis: ChemoRT derm.	19	1	1	0	0	0
Rash	19	2	0	0	0	0
Renal failure	20	0	0	0	1	0
Rigors/chills	20	1	0	0	0	0
Sudden death	20	0	0	0	0	1
Supra Arrhyth: Atrial Tachy.	20	1	0	0	0	0
Sweating	20	1	0	0	0	0
Taste alteration	17	3	1	0	0	0
Thrombosis/embolism	20	0	0	0	1	0
Typhlitis	20	0	0	0	1	0
Urinary retention	20	1	0	0	0	0
Vomiting	11	4	3	3	0	0
Weight Loss	11	2	7	1	0	0
MAXIMUM GRADE ANY ADVERSE EVENT						
Number	0	1	2	10	6	2

Discussions

SWOG-0414 is the first prospective multi-institutional, cooperative group trial to test the addition cetuximab, a novel chimeric monoclonal antibody that is directed against the external domain of the EGFR with platinum-based doublet chemoradiotherapy. One possible explanation for the unfavorable results is that the SWOG GI Committee had a trial for patients with clinically resectable esophageal adenocarcinoma open simultaneously, SWOG-0356. Hence centers with both trials open may have been more likely to offer patients with more favorable tumors the opportunity to enroll onto a more thoroughly tested oxaliplatin-based triple-modality regimen. It appears that induction therapy followed by definitive concomitant systemic therapy and radiotherapy, as designed in this trial, is not worthy of further development.

Conclusions

Concomitant cetuximab, CDDP, CPT11, & TRT was poorly tolerated in the first cooperative group trial with this regimen

Mortality approached 10%.

Single-institution phase II cetuximab-based CRT has yielded encouraging results in preliminary analyses in this disease.

Hence, the SWOG GI Comm. endorses enrollment on RTOG-0436 to further define the therapeutic ratio of cetuximab-based combined-modality Rx.

References

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