ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Successes and Failures of Combined Modalities in Upper Gastrointestinal Malignancies: New Directions

Daniel S. Jamorabo, MD,[*] Steven H. Lin, MD, PhD,[†] and Salma K. Jabbour, MD[‡]

Upper gastrointestinal malignancies generally have moderate to poor cure rates, even in the earliest stages, thereby implying that both local and systemic treatments have room for improvement. Therapeutic options are broadening, however, with the development of new immunotherapies and targeted agents, which can have synergistic effects with radiotherapy. Here we discuss the current state of combined modality therapy for upper gastrointestinal malignancies, specifically recent successes and setbacks in trials of radiation therapy with targeted therapies, vaccines, immunotherapies, and chemotherapies.
Semin Radiat Oncol 26:307-319

Introduction

Recent data estimate that out of 1,665,540 new cancers diagnosed in the United States in 2014, upper gastrointestinal (UGI) malignancies comprised 130,650 (7.8%), with approximately 36% pancreatic, 33% hepatobiliary, 17% gastric, and 14% esophageal.[1] The estimated mortality thereof was 92,660, of which approximately 43% were pancreatic, 29% were hepatobiliary, 16% esophageal, and 12% gastric. Pancreatic cancer in particular is the fourth-leading cause of death among all malignancies for both men and women in the United States. Overall, UGI cancers are often advanced, if not metastatic, at time of diagnosis,[2-4] which in turn increases morbidity and mortality.

The aggressiveness of UGI cancers has led researchers to evaluate multimodal approaches to treatment involving combinations of surgery, radiotherapy, and systemic agents. Other authors have discussed the synergy between radiation and systemic therapies, for instance the radiosensitizing properties of systemic therapies[5] as well as the potential "abscopal effect" of immunotherapy wherein local radiation facilitates distal control.[6] We present findings from recent studies on combined modality regimens for UGI malignancies and the ramifications thereof on treatment.

*Department of Internal Medicine, Rutgers Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ.
†Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX.
‡Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Rutgers University, New Brunswick, NJ.
Conflicts of Interest: None.
Address reprint requests to Salma K. Jabbour, MD, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, 195 Little Albany St, New Brunswick, NJ 08901-1914. E-mail: jabbousk@cinj.rutgers.edu

Targeted Therapies

Monoclonal Antibodies

Targeted therapies have been a mainstay in treating certain cancers because of their ability to selectively target tumor cells while sparing normal cells. Monoclonal antibodies (MABs) are a category of targeted drugs that generally target specific proteins in growth factor and angiogenic pathways, which are often overactive or otherwise dysfunctional in tumor cells. MABs have been evaluated in combination with chemotherapy or with radiation therapy[7] because of evidence that MABs can enhance radiation-induced apoptosis[8] and promote cell cycle arrest,[9] thereby preventing tumor repopulation. Recent studies aimed at using MABs with radiation therapy have shown promising results in treating UGI malignancies (Table 1).

Cetuximab

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor that has been used in colorectal cancer,[10] as well as in squamous cell carcinomas of the head and neck.[11] Recently, researchers have investigated its applicability in esophageal cancers, particularly since EGFR is widely expressed therein[12]

http://dx.doi.org/10.1016/j.semradonc.2016.05.001
1053-4296/

Table 1 Trials Combining Radiotherapy With Monoclonal Antibodies (MAB)

Primary Investigators	Site (#Accrued)	Regimen	Agent and Target	Key Findings	Tolerability and Toxicity
Meng et al[14]	Locally advanced esophageal SCC (55)	Paclitaxel, cisplatin, and 59.4 Gy (33 fractions) with cetuximab	Cetuximab, anti-EGFR MAB	80% partial or complete response and 1 year OS 93%.	Grade 3 neutropenia and mucositis in 18/55 (33%) and 7/55 (13%), respectively. No Grade 4 toxicities observed.
Becerra et al[16]	Esophageal ACA and GEJ (39)	Neoadjuvant cetuxiumab and 50.4 Gy (28 fractions)	Cetuximab, anti-EGFR MAB	48% complete response rate 3 months after surgical resection.	Grade 5 aspiration seen in 1/39 (2%). Grade 3 dysphagia in 7/39 (17%). Grade 4 toxicities did not occur in 5% or more of patients.
Lee et al[18]	Locally advanced esophageal ACA (19)	Neoadjuvant irinotecan, cisplatin, and cetuximab with 50.4 Gy (28 fractions)	Cetuximab, anti-EGFR MAB	Median OS 31 months and median PFS 10 months with 16% CR following surgery.	Grade 3-4 neutrophilia and dysphagia in 9/19 (47%) and 6/19 (31%), respectively. Grade 3 diarrhea also in 9/19 (47%).
Tomblyn et[19]	Esophageal ACA (21)	Neoadjuvant irinotecan, cisplatin, and cetuximab with 50.4 Gy (28 fractions)	Cetuximba, anti-EGFR MAB	2-years OS 33% and PFS 24% with overall response rate 18%.	Grade 3-4 toxicity in 76% (16/21), including 11/21 (52%) from hematologic derangements. GI necrosis and sudden death each occurred in 1/21 (5%).
Crosby et al[21]	Esophageal ACA and SCC (258)	Cisplatin, capecitabine, and 50.4 Gy (28 fractions) with and without cetuximab	Cetuximab, anti-EGFR MAB	Cetuximab group had higher rate of treatment failure at 6 months (77%) and lower median OS (22 months).	Cetuximab group had more (102/129; 79%) nonhematological Grade 3-4 toxicities (eg, dysphagia, rash) vs control group (81/129; 63%). Control group had more (36/129; 28%) Grade 3-4 hematological toxicity vs cetuximab group (27/129; 21%).
Ilson et al[22]	Esophageal ACA and SCC (328)	Capecitabine, paclitaxel, and 50.4 Gy (28 fractions) with and without cetuximab	Cetuximab, anti-EGFR MAB	No difference between cetuximab and control groups in terms of efficacy or safety.	Nearly equivalent rates of Grade 3 (45%-49%), 4 (17%-22%), and 5 (1%-4%) toxicities between groups.
Esnaola et al[23]	Unresectable pancreatic ACA (37)	Gemcitabine, oxaliplatin, cetuximab, capecitabine, and 54 Gy (30 fractions)	Cetuximab, anti-EGFR MAB	Median OS and PFS of 12 months and 10 months, respectively. PFS after 6 months of 62%. No survival benefit seen.	Grade 3-4 leukopenia in 5/37 (13%). Overall, well-tolerated regimen.
Zhao et al[25]	Esophageal SCC (11)	Cisplatin, 5-FU, and 60.2 Gy (34 fractions) with nimotuzumab	Nimotuzumab, anti-EGFR MAB	6-month OS 78%. 1-year OS and PFS of 67% and 100%, respectively.	No dose-limiting toxicity observed. Grade 3-4 esophagitis and leukopenia each seen in 2/11 (18%).
Ramos-Suzarte et al[26]	Esophageal ACA and SCC (63)	Cisplatin, 5-FU, and 45-50 Gy (25-28 fractions) with and without nimotuzumab	Nimotuzumab, anti-EGFR MAB	Nimotuzumab group had better median OS and response rates.	Grade 3-4 diarrhea more common in nimotuzumab group (6/33; 18%) than in control (2/30; 7%). Well-tolerated regimen.
Lockhart et al[96]	Locally advanced esophageal ACA (70)	Neoadjuvant docetaxel, cisplatin, panitumumab, and 50.4 Gy (28 fractions)	Panitumumab, anti-EGFR MAB	pCR rate 33% and near-pCR rate (ie, 10% or fewere viable cancer cells) another 20%.	Grade 3-4 esophagitis and lymphopenia seen in 13/70 (18%) and 30/70 (43%), respectively. Overall, Grade 4 toxicity in 48% (34/70) of patients.
Kordes et al[97]	Locally advanced esophageal SCC and ACA (90)	Neoadjuvant carboplatin, paclitaxel, panitumumab, and 41.4 Gy (23 fractions)	Panitumumab, anti-EGFR MAB	Low CR rate of 22% overall with 14% in ACA and 47% with SCC.	Grade 3-4 rash and neutropenia in 10/90 (11%) and 9/90 (10%), respectively.