ASTRO
TARGETING CANCER CARE

News Release

Embargoed until 11:00 a.m. Pacific time, Monday, September 25, 2017

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Aggressively reduced radiation therapy for HPV-related throat cancer achieves similar control rates with fewer side effects

Phase II trial indicates viability of half the standard dose for appropriately selected patients with oropharynx cancer following surgery

SAN DIEGO, September 25, 2017 – For certain patients with oropharyngeal cancer caused by the human papilloma virus (HPV), an aggressive reduction of radiation therapy after surgery may provide excellent cancer control while simultaneously reducing post-treatment side effects, improving quality of life and lowering treatment costs, according to research presented today at the 59th Annual Meeting of the American Society for Radiation Oncology (ASTRO). Patients in the phase II clinical trial received half the standard radiation dose but achieved equally high cure rates at two years following treatment.

Standard treatment for oropharyngeal squamous cell carcinoma (OPSCC) can include surgery to remove the cancer followed by radiation therapy with or without chemotherapy. While cure rates are excellent following therapy, treating the sensitive throat and neck regions often causes serious and potentially life-altering side effects.

Quality of life considerations have become even more salient in the past several decades, as today's average OPSCC patient is younger and will live a longer time with any side effects of treatment. Between 1988 and 2004, the rates of HPV-associated OPSCC more than doubled, while the rates of HPV-negative disease—which is typically caused by smoking and alcohol consumption—dropped by half. HPV-related disease also is biologically more responsive to radiation and chemotherapy, leading to high cure rates for these patients.

"The profile of the typical oropharynx cancer patient has changed, which means that our approach to

treating this disease needs to change, as well," said Daniel Ma, MD, lead author of the study and an assistant professor of radiation oncology at the Mayo Clinic in Rochester, Minnesota. "Several research groups are pursuing an incremental approach to de-escalating treatment, such as using 15 percent less radiation dose. Our trial took a different approach—testing whether we could cut the dose by half. Our findings indicate that this more aggressive approach toward treatment reduction can be viable for appropriately selected patients."

MC1273 was a single-arm phase II trial for HPV-related OPSCC testing clinical outcomes and quality of life with a de-escalated course of radiation therapy following surgery to remove the disease. Patients received two weeks of twice-daily radiation therapy to the oropharynx for a total dose of 30-36 Gray (Gy), a 50 percent reduction of the standard radiation dose of 60-66 Gy. Patients also received two courses of chemotherapy (docetaxel 15 mg/m^2), delivered on days one and eight. The 43 patients with extracapsular extension (ECE), a marker of particularly aggressive disease, received an additional, simultaneous radiation boost to the areas with ECE, for a total dose (including primary treatment) of 36 Gy.

Eighty patients were accrued between September 2013 and June 2016 with all patients completing treatment. Eligible patients included those with HPV-related OPSCC who had no evidence of residual disease following surgery and a minimal smoking history (e.g., less than one pack per day for 10 years or less). The median patient age was 60.5 years (range 25-77 years). All patients had stage III or IV disease. The median follow-up for this report was 24 months (range 12-46 months).

At a median follow-up of two years after de-escalated treatment, the rate of tumor control in the oropharynx and surrounding region was 95 percent. Of the 80 patients in the trial, three experienced a local recurrence and one patient experienced a regional recurrence. Disease-free survival (DFS) following the dose-reduced treatment was 89 percent. By comparison, the RTOG 0234 clinical trial reported a two-year DFS rate of 86.4 percent for patients with HPV-related cancers.

Grade 2 or higher side effects were reported in one percent of patients at one year following treatment and ten percent at two years following treatment. By comparison, studies of adjuvant radiation for OPSCC generally report rates of late grade 2 or higher side effects at more than 50 percent (e.g., 55% on RTOG 0234). No patients had grade 3+ toxicity at one year or two years following treatment. Fourteen patients (18%) experienced cumulative grade 3+ toxicity within three months of treatment; all instances resolved by six months post-treatment. One additional patient experienced a temporary grade 4 event related to a chemotherapy reaction.

Patients' ability to swallow improved slightly at one year following radiation therapy compared to pre-treatment ($p = 0.03$). Swallowing function was measured using the Modified Barium Swallow Impairment Profile (MBSImP). Importantly, no patients needed to have a feeding tube placed during treatment.

Patient's quality of life largely improved or did not change following treatment, except for dry mouth. Patients reported somewhat worse salivary flow following treatment ($p < 0.0001$), as measured by the University of Michigan's Xerostomia QOL scale (XeQOLS). However, none of the other quality of life scales declined significantly—including the Functional Assessment of Cancer Therapy – Head and Neck Version 4 (FACT H&N), the EuroQol EQ-5D and the European Organisation for Research and Treatment of Cancer instrument for head and neck cancer (EORTC-HN). Each measure was assessed prior to radiation therapy and again at one, three, 12 and 24 months following treatment.

"Side effects with dose-reduced treatment were dramatically less than what we usually see in treatment of adjuvant radiation therapy for oropharynx cancer. For example, no patients in this trial needed a feeding tube placed, whereas close to a third of patients had feeding tubes placed with traditional doses on other recent clinical trials," explained Dr. Ma.

"The shorter course of treatment also has practical value for patients. If a patient has 20 twice-daily sessions instead of 30 daily treatment sessions, their financial cost is reduced by a third, and time away from work or family is reduced by a third—but the likelihood of cure remains the same."

While the results are promising, Dr. Ma emphasized that findings from a randomized study directly comparing the dose-reduced treatment with traditional treatment are needed before the new approach can be adopted widely.

"These results will require confirmation in a randomized trial, and this treatment approach should be considered investigational until confirmed in a phase III study, such as the ongoing multi-institutional DART-HPV trial that is currently open for patient accrual," he said.

The abstract, "Two-year results for MC1273, a phase II evaluation of aggressive dose de-escalation for adjuvant chemoradiation in HPV+ oropharynx squamous cell carcinoma (OPSCC)," will be presented in detail during a news briefing and the late-breaking abstracts special session at ASTRO's 59th Annual Meeting in San Diego (full details below). To schedule an interview with Dr. Ma and/or outside experts in head and neck cancer, contact ASTRO's media relations team on-site at the San Diego Convention Center September 24 through 27, by phone at 703-286-1600 or by email at press@astro.org.

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ATTRIBUTION TO THE AMERICAN SOCIETY OF RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING REQUESTED IN ALL COVERAGE.

This news release contains additional and/or updated information from the study author(s). Full original abstract and author disclosures available on the final page of this release.

Study Presentation Details

- News Briefing: Monday, September 25, 11:00 a.m. – 12:00 p.m. Pacific time, San Diego Convention Center, room 24C, webcast: http://www.bit.do/astro17-2
- Scientific Session: Tuesday, September 26, 7:45 – 9:15 a.m. Pacific time, San Diego Convention Center, room 5A

Resources on Head and Neck Cancer and Radiation Therapy

- Digital brochure: Radiation Therapy for Head and Neck Cancer
- Videos: Radiation Therapy for Head and Neck Cancer (Spanish version), An Introduction to Radiation Therapy (Spanish version)
- Additional brochures, videos and information on radiation therapy from ASTRO's patient site, RTAnswers.org
- ASTRO's clinical practice statements and guidelines

ABOUT ASTRO'S ANNUAL MEETING

ASTRO's 59th Annual Meeting, the world's largest scientific meeting in radiation oncology, will be held September 24-27, 2017, at the San Diego Convention Center. The 2017 Annual Meeting is expected to attract more than 11,000 attendees from across the globe, including oncologists from all disciplines and members of the entire radiation oncology team. More than 2,800 abstracts sharing results from clinical trials and other research studies will be presented in conjunction with educational sessions and keynote addresses that underscore the meeting's theme, "The Healing Art and Science of Radiation Oncology." Led by ASTRO President Brian Kavanagh, MD, MPH, FASTRO, the 2017 meeting will feature keynote addresses from Richard D. Zane, MD, FAAEM, Chief Innovation Officer for the University of Colorado Health System; Lucy Kalanithi, MD, FACP, widow of Paul Kalanithi, MD, the best-selling author of "When Breath Becomes Air," with Heather Wakelee, MD, Paul's oncologist; and Vinay K. Prasad, MD, MPH, an assistant professor of medicine at the Oregon Health & Science University. During the four-day meeting, more than 200 exhibitors will demonstrate cutting-edge technology and medical device innovations for radiation oncology. Visit us online for more information about ASTRO's 59th Annual Meeting or press opportunities at the meeting.

ABOUT ASTRO

The American Society for Radiation Oncology (ASTRO) is the world's largest radiation oncology society, with more than 10,000 members who are physicians, nurses, biologists, physicists, radiation therapists, dosimetrists and other health care professionals who specialize in treating patients with radiation therapies. The Society is dedicated to improving patient care through professional education and training, support for clinical practice and health policy standards, advancement of science and research, and advocacy. ASTRO publishes three medical journals, International Journal of Radiation Oncology • Biology • Physics (www.redjournal.org), Practical Radiation Oncology (www.practicalradonc.org) and Advances in Radiation Oncology (www.advancesradonc.org); developed and maintains an extensive patient website, RT Answers (www.rtanswers.org); and created the Radiation Oncology Institute (www.roinstitute.org), a nonprofit foundation to support research and education efforts around the world that enhance and confirm the critical role of radiation therapy in improving cancer treatment. To learn more about ASTRO, visit www.astro.org and follow us on our blog, Facebook and Twitter.

Abstract LBA-14: Two year results for MC1273, a phase II evaluation of aggressive dose de-escalation for adjuvant chemoradiation in HPV+ oropharynx squamous cell carcinoma (OPSCC)

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Purpose/Objective(s): Adjuvant therapy for HPV+ OPSCC has well-documented rates of grade ≥2 toxicities and 2-year disease free survival (DFS) (55% and 86.4% on RTOG 0234). The purpose of this study is to determine if dose de-escalation to 30-36 Gy for selected patients with HPV+ OPSCC can maintain historical rates for disease control while reducing toxicity and improving swallow function/QOL.

Materials/Methods: MC1273 is a single arm phase II trial testing an aggressive course of treatment de-escalation following margin-clearing surgery and simultaneous neck dissection. Eligibility criteria included patients with p16+ OPSCC, ≤10 pack-year smoking history, and negative margins. Cohort A (≥T3, ≥N2, lymphovascular invasion, or perineural invasion) received 30 Gy delivered in 1.5 Gy b.i.d. over 12 days along with weekly docetaxel (15 mg/m^2, days 1 & 8). Patients with +ECE were enrolled in Cohort B and received the same treatment plus a simultaneous integrated boost to nodal levels with ECE to 36 Gy in 1.8 Gy b.i.d. The primary endpoint was local/regional control at 2 years. Secondary endpoints included 2-yr disease free survival, toxicity, swallow function, and patient reported QOL. Each cohort was powered to detect a 10% LRF rate with 85% confidence. Patients received a modified barium swallow impairment profile (MBSImP) before, 1 month post, and 1 year post-RT. Patients also had QOL assessments consisting of the University of Michigan Xerostomia QOL Scale (XeQOLS), Functional Assessment of Cancer Therapy-HN Ver 4 (FACT-HN), European Quality of Life (Eq)-5D, and the EORTC-HN assessed at pre-RT and 1, 3, 12, and 24 months post-RT.

Results: Accrual was from 9/13 – 6/16 (n= 80, Cohort A: 37, Cohort B: 43). Median follow-up as of 8/17 was 24 months; no patient died or was lost to follow-up. Local/regional control is 95% (3 local, 1 regional), distant control 94% (n=5), disease free survival 89%. Swallowing function improved between pre-treatment and 12 mo follow-up (MBSImP 47.4±5.2 vs 48.6±4.8, p=0.03) and no patients required feeding tube placement. Grade 2/≥3 toxicity rates at pre-TX, 1 yr, 2 yr post-RT are 12%/3%, 1%/0%, and 10%/0%. All cumulative grade ≥3 toxicity occurred by 3 mo (n=14 pts, 18%) and resolved by 6 mo. One patient had a transient grade 4 hypotensive event related to a docetaxel infusion reaction. Only the XeQOLs worsened after treatment (70.3±6.7 vs 64.8±8.8, p<0.0001) while the EORTC-HN, FACT-HN and Eq-5D remained essentially unchanged or improved.

Conclusion: Aggressive treatment de-escalation resulted in locoregional control rates comparable to historical controls, low toxicity, and no decrement in swallowing function or QOL. A follow-up phase III, multi-center study is actively accruing.

Author Disclosure: D.J. Ma: None. K. Price: None. E.J. Moore: None. S.H. Patel: None. M.L. Hinni: None. A.V. Chintakuntlawar: None. J.J. Garcia: None. D. Graner: None. M.A. Neben-Wittich: None. Y. Garces: None. C.L. Hallemeier: Research Grant; Mayo Clinic. D.L. Price: None. J.L. Kasperbauer: None. J.R. Janus: None. N.R. Foster: None. R.L. Foote: Employee; Mayo Clinic. Consultant; Up to Date. Royalty; Elsevier. Responsible for

clinical practice, research and education; Mayo Clinic. Responsible for the written board examination questions for head, neck, and skin cancer; ABR.