PUO' IL CETUXIMAB SOSTITUIRE IL CISPLATINO NEL TRATTAMENTO RADIOCHEMIOTERAPICO DEI CARCINOMI AVANZATI DEL CAPO COLLO?

(a cura di V Baggio e A Gava Radioterapia Oncologica Treviso)

VOLUME 31 · NUMBER 2 · JANUARY 10 2013

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Should Cetuximab Replace Cisplatin for Definitive Chemoradiotherapy in Locally Advanced Head and Neck Cancer?

TO THE EDITOR: Definitive chemoradiotherapy is a standard of care for the treatment of locally advanced squamous cell carcinoma of the head and neck (LAHNC). A meta-analysis demonstrated a 6.5% absolute improvement in 5-year overall survival[1] with concurrent chemoradiotherapy over radiotherapy (RT) alone. Concurrent cisplatin (CDDP) was identified as the most effective agent. However, CDDP increases both short-term adverse effects and long-term toxicity from treatment.

The development of cetuximab (C225), an antibody against epidermal growth factor receptor (EGFR), seemed to offer a less toxic replacement. The study by Bonner et al[2,3] randomly assigned patients with LAHNC to C225 and RT versus RT alone and found that C225 improved locoregional control and overall survival (OS) and did not worsen quality of life. A 5-year update continues to demonstrate an improvement in OS, although locoregional control and disease-free survival data were unavailable.[4] The Bonner study,[2-4] however, was conducted before it was clear that concurrent chemotherapy was superior to radiotherapy alone, and as such, C225 was not directly compared with CDDP.

We reported our center's retrospective experience with CDDP/RT (n = 49) and C225/RT (n = 125) in LAHNC and found CDDP/RT was superior for 2-year locoregional failure (5.7% *v* 39.9%; $P < .001$), failure-free survival (87.4% *v* 44.5%; $P < .001$), and OS (92.8% *v* 66.6%; $P < .001$).[5] One criticism of this work was the lack of human papillomavirus (HPV) data; however, when we examined the third of patients (n = 62) with available HPV status, our results remained unchanged.[6] We have also reviewed patients treated with carboplatin and fluorouracil (carbo/FU; n = 52) in the time period immediately before the introduction of C225.[7] Four-year locoregional failure was similar between carbo/FU and CDDP groups (9.7 *v* 6.3%; $P = .42$) but was significantly worse for the C225 group (40.2%; $P = .002$).

Although retrospective single-institution studies need to be interpreted cautiously, prospective data has recently emerged on this question. The TREMPLIN study was a randomized trial comparing induction chemotherapy followed by concurrent chemoradiotherapy with either CDDP (n = 60) or C225 (n = 56) in patients with locally advanced squamous cell carcinoma of the larynx or hypopharynx.[8] That study found 12 patients (21%) in the C225 arm developed a local recurrence compared with five patients (8%) in the CDDP arm ($P = .08$).

Washington University also retrospectively examined their experience with concurrent CDDP (n = 33) versus C225 (n = 30) in LAHNC.[9] Patients in the two arms were well balanced for known prognostic factors. With 30 months of follow-up, both disease-free survival (79% *v* 27%; $P < .001$) and OS (72% *v* 25%; $P < .001$) were worse in patients treated with C225.

To our knowledge, only two studies suggest equivalence between the two treatments. A retrospective study from the University of Alabama demonstrated similar outcomes between concurrent CDDP and C225.[10] This study differed from ours because patients may have received additional agents besides CDDP and were treated with conventional RT instead of intensity-modulated radiation therapy. Another study by Bristol-Myers Squibb performed an indirect comparison of results from the study by Bonner et al with results of four trials evaluating CDDP and concluded that there was no difference in outcomes.[11] However, indirect comparisons are controversial and require the baseline hazard rates between studies to be similar, which is unlikely in the case of these studies.

Unfortunately, combining C225 and CDDP with RT has had disappointing results. The RTOG (Radiation Therapy Oncology Group) 05-22 trial examined the addition of C225 to chemoradiotherapy and found no improvement in any outcome, even if stratified by HPV status.[12] Ideally, biomarkers could identify which patients would benefit from the addition or substitution of C225. However, in the metastatic setting, neither gene copy number nor mutational status have been predictive of response to EGFR inhibition.[13-15]

Subgroup analysis from the study by Bonner et al[2-4] suggests that patients who derived the most benefit from concurrent C225 had an HPV-like phenotype. This led to RTOG 10-16, which directly compares C225 plus RT with CDDP plus RT in patients positive for HPV, and should definitively answer this question. However, in treatment outside of clinical trials, caution is indicated in substituting C225 for CDDP in patients positive for HPV, given recent data from the metastatic setting.[16,17] In the Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer (SPECTRUM), panitumumab improved OS when added to chemotherapy in patients negative for HPV, but not in those positive for HPV.[16] In the BIBW 2992 trial (Phase II Trial of Afatinib Versus Cetuximab in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck), patients positive for HPV had a lower response rate to EGFR inhibition compared with patients negative for HPV.[17]

In conclusion, there is accumulating evidence from both prospective and retrospective studies that suggests that it may be premature to substitute EGFR inhibitors for cisplatin outside of a clinical trial. Until there is level I evidence from a randomized phase III noninferiority trial that demonstrates equivalence in outcomes between these two agents, we believe CDDP remains the preferred concurrent treatment. Fortunately, RTOG 10-16 is addressing this question, although results will not be available for several years.

Nadeem Riaz, Eric J. Sherman, Matthew Fury, and Nancy Lee

Memorial Sloan-Kettering Cancer Center, New York, NY

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under

COMMENTO

A dicembre il gruppo di radioterapisti oncologi del Memorial Sloan-Kettering Cancer Centre di New York, in una lettera all'editore del JCO, ha commentato vari studi di confronto tra l'associazione concomitante di cisplatino e radioterapia verso l'associazione cetuximab e radioterapia nei pazienti con tumori in stadio avanzato del capo-collo, ribadendo quanto evidenziato in loro lavori retrospettivi , cioè la superiorità del CDDP o Carbo-5FU /RT nei confronti del C225/RT, in termini di controllo loco regionale a 2 anni, di sopravvivenza libera e di Overall Survival.

A conferma della loro esperienza sono citati, seppur con evidenti limiti e controversie, i risultati analoghi di altri centri americani (Washington University, Alabama University) oltre alla metanalisi di Levy.

Pertanto gli autori, in assenza di un trial randomizzato di non inferiorità di fase III, consigliano l'impiego del C225 al posto del CDDP, solo all'interno di studi clinici.

Assumeranno quindi un particolare rilievo le conclusi dello studio italiano randomizzato HeN07 del GSTTC, che potrà aggiungere una risposta significativa su questo problema ancora aperto.