Editorial

Cetuximab or cisplatin as a radiosensitizer in locoregionally advanced head and neck cancer: recent results

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Recently, Magrini *et al.* reported the results of a small randomized phase II study that included 70 patients with locoregionally advanced head and neck cancer who were randomly assigned to treatment with weekly cisplatin and radiotherapy (RT) or cetuximab and RT (1). The primary endpoint of the study was compliance and the trial was designed to accrue 65 patients per arm. However, due to poor accrual, only 70 patients were entered on the trial. Compliance was measured based on treatment breaks in radiotherapy, cetuximab or cisplatin dose reductions, adverse events and treatment discontinuation. The results demonstrated that the patients who received cetuximab were more likely to undergo breaks in radiotherapy of more than 10 days (13%) compared to the patients who received cisplatin (0%) and this difference was statistically significant (P=0.05). Also, there were more serious adverse events for those patients who received cetuximab compared to cisplatin (19% *vs.* 3%, P=0.044). Although local control and survival were not significantly different between the two arms, there was a trend towards reduced local control (P=0.073) and survival (P= not significant) for the patients who received cetuximab compared to cisplatin.

In order to access the results of Magrini *et al.*, in the context of the current management of locoregionally advanced head and neck cancer, it is important to briefly review how cetuximab and cisplatin became a part of the primary radiotherapeutic management of these patients. Prior to the turn of the century, surgery and postoperative radiotherapy or radiotherapy alone were common standard treatments for locoregionally advanced head and neck cancers. Multiple trials of chemoradiotherapy compared to radiotherapy eventually culminated in meta-analyses demonstrating that chemoradiotherapy resulted in improved overall survival compared to radiotherapy alone (2,3). Additionally, a phase III registration trial demonstrated improved overall survival for the use of cetuximab and radiotherapy compared to radiotherapy alone (4,5). Because chemoradiotherapy is supported by multiple trials, it has become the primary mode of therapy for patients who are candidates for this therapy. However, the NCCN guidelines designate cetuximab and radiotherapy as an important category 1 option for these patients (6). A phase III randomized comparison of chemoradiotherapy *vs.* cetuximab and radiotherapy has not been published. However, this later comparison is the subject of a large trial (>1,000 patients) for patients with HPV-related oropharyngeal tumors (RTOG 1016) and the trial has completed accrual, but will not be ready for analysis for more than a year (7).

Since both cisplatin chemoradiotherapy (RT/cisplatin) and cetuximab combined with radiotherapy (RT/cetuximab) have been found to be superior to radiotherapy alone for locoregionally advanced head and neck cancer, a randomized trial was performed to determine whether adding cetuximab to RT/cisplatin could enhance the effects of RT/cisplatin—RTOG 0522 (8). When the investigators originally planned this study, a third arm of RT/cetuximab was considered but concerns about accrual to a three arm trial caused the investigators to drop this arm. As the trial progressed, the accrual rate was unexpectedly robust and the required patient numbers for a third arm could have been possible if the accrual rate would have been similar for the aforementioned three arm concept. Ang *et al.* (8) reported the results of the two arm RTOG 0522 trial in which 891 patients were randomly assigned to RT/cisplatin (accelerated radiotherapy

with cisplatin—100 mg/m^2 on days 1 and 22) versus the same regimen with the addition of cetuximab (400 mg/m^2 1-week prior to RT/cisplatin and 250 mg/m^2 weekly during RT/cisplatin). The addition of cetuximab to RT/cisplatin did not result in an improvement in overall survival. Additionally, the added treatment of cetuximab resulted in an increase in grade ¾ mucositis compared to RT/cisplatin, 43.2% *vs.* 33.3, respectively (P=0.002). The higher rate of grade ¾ mucositis for patients who received cetuximab was somewhat unexpected. The previously mentioned randomized trial comparing radiotherapy alone to RT/cetuximab demonstrated no increase in the rate of grade ¾ radiation-induced mucositis with the addition of cetuximab to radiotherapy (4,5). Also, Ang *et al.* noted that the addition of cetuximab to cisplatin/RT increased the rate of RT interruptions from 15.1% to 26.9 %, P=0.001 (8). Again, in the previous study of RT/cetuximab *vs.* RT alone, there were no differences in radiotherapy variations between the two arms (4,5).

Therefore, following the report of RTOG 0522, it was apparent that the addition of concomitant cetuximab to cisplatin/RT did not benefit patients with locoregionlly advanced head and neck. However, no published phase III studies have addressed whether cisplatin or cetuximab may be the superior systemic agent during the radiotherapeutic management of locoregionally advanced head and neck cancer. Also, it has not been determined whether cisplatin or cetuximab may be superior for certain subpopulations of this larger locoregionally advanced group. The recent comparison of RT/cisplatin versus RT/cetuximab by Magrini *et al.* was not designed to assess the efficacy of these treatments, but rather compliance. (Efficacy was only examined in an exploratory fashion.) The results of Magrini *et al.*, were most noteworthy for the higher rate of toxicity that was found for RT/cetuximab compared to the RT/cisplatin. This toxicity was presumably the major factor in decreased compliance with treatment in the cetuximab/RT arm. (It is also possible that some of the unique toxicities of cetuximab were foreign to some investigators and treatment breaks were not necessarily warranted.) Traditionally, investigators have found that the addition of cisplatin to RT increases radiation-induced mucositis and therefore leads to the potential for RT treatment delays. Adelstein *et al.* (9) found greater nausea and vomiting (P=0.03) and mucositis (P=0.08) for RT/cisplatin compared to RT alone. This finding has been consistent in other trials comparing RT to RT/cisplatin (2,3,10). As noted earlier, previous studies of RT/cetuximab have not revealed greater severe mucositis/dysphagia compared to RT alone (4,5). Therefore, the findings of Magrini *et al.* are not consistent with some of these previous reports and warrant further study.

The findings of Magrini *et al.* in which cetuximab/RT resulted in increased RT treatment breaks and increased treatment-related deaths, most likely contributed to trends of decreased local control and survival for the treatment of cetuximab/RT compared to cisplatin/RT and these findings warrant further exploration. Other retrospective reviews have explored the rate of RT compliance for patients treated with RT/cetuximab *vs.* RT/cisplatin and have not found the same disparity that was noted by Magrini *et al*. Ley *et al.* found similar RT delivery for the two treatments. They noted that planned RT was delivered in 94.4% of patients who received RT/cisplatin and 93.1% for patients who received RT/cetuximab (11). Likewise, Levy *et al.* (12) found that RT compliance was similar whether patients received concomitant cisplatin or cetuximab with radiotherapy. They reported that RT compliance was "excellent" in both groups with no differences in "dose, fractionation, duration or technique". Other groups have found similar results when comparing RT compliance for RT/cetuximab *vs.* RT/cisplatin (13,14).

So, why did Magrini *et al.* find greater difficulties with RT compliance for RT/cetuximab compared to RT/cisplatin? This question cannot be convincingly solved with our current understanding of these treatments and the results of this trial. Furthermore, it is difficult to understand the episodes of severe or fatal toxicities in the study of Magrini *et al.* study. The rate of severe or fatal toxicities was 19% for RT/cetuximab *vs.* 3% for RT/cisplatin. Four patients in the RT/cetuximab arm developed infections that led to septic shock and fatalities in three patients. Also, three patients (9%) in the RT/cetuximab arm had adverse infusion reactions that resulted in discontinuation of cetuximab. In contrast, this level of cetuximab-induced hypersensitivity was seen in less than 2% of patients in the large cetuximab registration trial (4).

Therefore, it is possible that the high rate of sepsis, cetuximab hypersensitivity and the need for RT treatment breaks in the RT/cetuximab arm of the Magrini study could have occurred due to chance as the trial was a very small study. It accrued less than 20 patients a year for slightly less than a total of four years. However, it is also possible that there may have been a component of an unusual underlying geographic relationship to the RT/cetuximab-induced toxicities. It has been suggested that there are geographical differences in cetuximab-related hypersensitivity reactions (15-17). Also, these geographical-related factors may have interplay with patients' previous allergy histories and smoking habits (15-17). O'Neil *et al.* (15) have reported that there is a suggestion of a higher rate of cetuximab-related infusion reactions in certain areas within Tennessee and North Carolina compared to other areas in the United States. They

examined 88 patients entered on clinical trials involving the use of cetuximab at the University of North Carolina, Sarah Cannon Cancer Research Institute and Vanderbilt University. They found a 22% rate of grade 3 or 4 hypersensitivity reactions to cetuximab (no deaths). This rate is higher than the 2.9% rate that was found in the aforementioned cetuximab registration trial (4). Subsequently, the group from The University of North Carolina updated their results and recently reported a rate of grade 3 or 4 cetuximab-infusion reactions of 14.4% (16). These higher rates of hypersensitivity were not associated with higher death rates and hence, the findings of Magrini *et al.* remain difficult to explain even if various aspects of geographical-specific hypersensitivity were involved in the findings of their study.

Magrini *et al.* chose to use once-daily RT fractionation in their study. This choice needs to be considered when assessing their results. Their high frequency of radiotherapy interruptions for patients who received RT/cetuximab is unusual compared to the above noted comparable studies, but it is even more surprising when one considers that they utilized radiotherapy with standard fractionation. Radiotherapy with altered fractionation has been shown to lead to more local toxicities than standard fractionation (10). Magrini and colleague's use of conventionally fractionated RT should have potentially decreased toxicity and reduced their rate of RT treatment interruptions compared to other trials that utilized altered fractionated RT such as the much larger (>400 patients) registration trial (4). Ongoing studies will help better define the optimization of treatment compliance for these patients (18).

When evaluating radiotherapy fractionation in combination with cetuximab (4), it is noteworthy that more than 75% of patients in the cetuximab registration trial received altered fractionated RT (4). Previous reports have documented that altered fractionated RT improves survival compared to conventional once-daily RT for patients with locoregionally advanced disease who have received radiation alone (19). In the cetuximab registration trial, fractionation was a stratification factor in the randomization process. A retrospective analysis of the trial suggested that patients who received altered fractionated RT benefited more from the addition of cetuximab relative to those patients treated with conventional once-daily radiotherapy (5). This analysis, regarding the optimal RT fractionation with cetuximab, requires further exploration. However, it is possible that the use of conventional fractionation (as in the study of Magrini *et al.*) may result in decreased efficacy for the treatment of RT/cetuximab.

In summary, much can be learned with ongoing and future randomized investigations comparing RT/cetuximab and RT/cisplatin treatments for patients with locoregionally advanced head and neck cancer (18). It will be important to assess treatment toxicities as well as efficacy. At the present time, we have small retrospective studies that have compared efficacy. Some suggest that the treatments are comparable (13,14,20), and some suggest that RT/cisplatin may be the preferred treatment (11,12,21). All of these series are difficult to interpret due to potential biases that are inherent in retrospective studies. It will be particularly fascinated to assess these treatments in the era of genetic testing with an aim to determine subpopulations of patients that may have specific benefits with the use of cetuximab, cisplatin or other systemic treatments in combination with radiotherapy (22). It will be exciting to see these new investigations unfold.

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