ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Clinical Trials in Squamous Cell Carcinoma of the Head and Neck

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H&O How is squamous cell carcinoma of the head and neck managed?

MP Head and neck cancer arises in an area that is compact and crowded with important functions. We eat, breathe, swallow, and communicate through this very sensitive area. Trauma, damage, surgical morbidity, and radiation-induced toxicity can all result in significant decrements in function, both in speech and swallowing, as well as in comfort. Therapy for this area has been controversial, difficult, and subject to a great deal of scientific and clinical investigation. In the past, the principal treatment of squamous cell cancer of the head and neck had been surgery, or surgery and radiation. In the last 3 decades, the use of chemotherapy has been studied in clinical trials, and chemotherapy has been used now to sensitize radiation, preserve function, and increase cure rates. Chemotherapy has been used in the form of chemoradiotherapy, induction chemotherapy, adjuvant chemotherapy, and sequential chemotherapy (induction chemotherapy followed by chemoradiotherapy).

It is important to understand that squamous cell cancer of the head and neck is composed of 2 distinct diseases, which have quite different biologies and prognoses. In the United States, throughout the 1970s and early 1980s, these cancers were caused primarily by smoking, alcohol, and chewing tobacco, as well as by environmental carcinogens and other unknown factors. Another form of the cancer is caused by human papillomavirus (HPV). As the HPV epidemic has increased, there have been increasing numbers of younger, healthier patients with fewer comorbidities presenting with oropharynx cancers. These patients have active lifestyles, and they tend to be easier to manage. Patients with head and neck cancer related to the more traditional factors of smoking and drinking present with cancers throughout the head and neck and often have comorbidities, such as pulmonary and cardiac issues. They may have behavioral problems that make management difficult. They may be motivated by addictions or psychosocial problems, and they may not appreciate the danger of avoiding or delaying treatment. In addition, these patients have a 20% risk of developing a second malignancy in the first 5 years after successful therapy of their first malignancy, and they require close, lifelong surveillance. Head and neck cancer has traditionally been difficult to manage because of these types of patients, as well as the importance of the structures of the head and neck to basic quality of life.

H&O Which factors contribute to management decisions?

MP Today, we have the ability to treat these patients with surgery, radiation, and chemotherapy. The decision-making regarding management of a particular patient is subject to several factors. First and foremost is the condition of the patient. Is the individual otherwise healthy, or are significant comorbidities present? Is the patient capable of withstanding different kinds of therapy? Second, what is the nature of the disease? How extensive is it? What are the biologic parameters? Third, what treatment approach would be best: surgery, radiation therapy, chemoradiotherapy, or chemotherapy followed by chemoradiotherapy? Management decisions should be made by an experienced, multidisciplinary team familiar with the principal modalities of treatment and the expected behavior of the cancers because of the nuanced implications of stage, HPV status, and patient condition, as well as the need for very intensive management.

H&O How has management changed in recent years?

MP Changes have been made in the way treatments are delivered. Traditionally, surgery had been associated with a great deal of tissue trauma, damage, and functional organ loss. There are much better surgical options today, such as robotic surgery, transoral laser microdissection, and other tools that provide a better ability to get into the small spaces of the head and neck and avoid additional tissue trauma. We are better able to preserve swallowing and speech function and reduce collateral damage that could prolong healing and negatively impact function. Traditionally, radiation was delivered in 3-dimensional conformal doses using linear accelerators. We now have intensity-modulated radiation, which allows a reduction in radiation damage to normal tissue. With computer modeling, the ability to avoid significant damage to the normal tissues around the tumor has become more of an art and requires solid experience. Transoral robotic surgery and transoral laser microdissection are unique surgical approaches. Experience and thoughtful application of surgical technology have a big impact on outcomes. A large number of patients with oropharynx cancer are being treated with these techniques, which were not widely used even 5 years ago. There are no solid data showing how effective new surgical technologies are compared to standard or alternative non-surgical approaches. Over the next several years, a variety of studies will attempt to bring scientific evaluation to the application of these new technologies. Similarly, there is little scientific evidence showing that intensity-modulated radiation therapy (IMRT) imparts a better outcome than traditional non-IMRT radiation.

Chemotherapy has also improved dramatically. Not only do we have better drugs now than we did 10 years ago, we also have better supportive care, which allows us to deliver these drugs with less acute morbidity and mortality, and less toxicity. Understanding the biologic implications of the therapy is critically important in determining how to treat each individual patient. New drugs include epidermal growth factor receptor (EGFR) inhibitors, such as cetuximab (Erbitux, Bristol-Myers Squibb/Lilly), gefitinib (Iressa, AstraZeneca), and lapatinib (Tykerb, GlaxoSmithKline). These small molecule inhibitors have shown some activity in phase II trials in recurrent metastatic disease. Ongoing trials are examining whether they have a role as adjuvant therapy or for primary therapy in recurrent metastatic disease. Cetuximab and other anti-EGFR antibodies are clearly active, and cetuximab is approved for recurrent and metastatic disease as well as curative therapy. There are a number of new agents in the PI 3-kinase pathway that inhibit either PI 3-kinase or downstream signaling by PI 3-kinase through mTOR, or the Akt. c-Met, a tyrosine kinase, is being investigated as a target for direct inhibitors, antibodies, and for inhibitors of the ligand, which is a hepatocyte growth factor (HGF). The biology of cancer and the mechanisms of many targeted agents are not completely understood, and these agents have not been sufficiently explored in head and neck cancer. One prime example is the vascular endothelial growth factor (VEGF) inhibitors, used either alone or in conjunction with chemotherapy and radiation. There is a suggestion that they may be helpful when used in combination, although no randomized trials have been performed. An ongoing trial from the Eastern Cooperative Oncology Group (ECOG) is investigating the addition of bevacizumab (Avastin, Genentech) to cisplatin and paclitaxel (Taxol, Bristol-Myers Squibb) or cisplatin and 5-fluorouracil (5-FU). Targeted treatments will have limited efficacy as single agents in head and neck cancer, which has very few "critical targets," or so-called driver mutations, and more loss of suppression mutations. The latter are much harder to target. Therapeutic processes like synthetic lethality may prove to be useful in head and neck cancer.

H&O What types of treatment regimens have been studied in recent trials?

MP A spate of proposed and recent trials have focused on the HPV side of head and neck cancer and on de-escalation of treatment. A phase II trial by ECOG evaluated whether HPV-positive patients could be treated with less intensive chemoradiation. A sequential approach employed 9 weeks of induction chemotherapy and, if patients had a significant response, a reduced dose of radiation with cetuximab. This trial completed accrual early this year, and outcome data will be available in about 2 years.

The Radiation Therapy Oncology Group (RTOG) has produced some disappointing data that have been recently reported in an early analysis of a randomized trial, RTOG 0129. This trial compared chemotherapy (cisplatin) with accelerated concomitant boost radiation versus chemotherapy with standard radiation. Unfortunately, the report is premature, and we do not have access to the 5-year data from that trial, although it should now be available. The study investigators concluded that the 3-year data showed no difference between the treatment arms. However, if one examines the data closely, there are significant differences in toxicity and efficacy. The accelerated arm is associated with more morbidity and toxicity than the standard arm, and early data suggested that the 3 doses of cisplatin were associated with significantly better local regional control than 2 doses. With increasingly better local control and survival, later data are critical in assessing the outcomes of these randomized trials. The 5-year data are important for analysis, and it is important for all of the data to be fully reported by the RTOG.

In the same vein, a randomized trial by the Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC),

recently published in *Lancet Oncology,* compared treatment with 3 regimens: standard, once-daily radiation with 3 cycles of carboplatin and 5-FU; an accelerated treatment with 1 less cycle of carboplatin and 5-FU; and a hyperfractionated treatment. Based on the toxicity and trends in overall survival, locoregional control, and distant metastases, standard radiation with 3 doses of carboplatin and 5-FU was the preferred treatment. There was less toxicity and a positive trend in survival outcome, progression-free survival, locoregional failure, and distant metastases with 3 cycles of carboplatin and 5-FU. Taken together, these data strongly support using standard fractionation rather than accelerated or hyperfractionated regimens with chemotherapy and maintaining the full chemotherapy dose.

Another trial from the RTOG, 0522, compared 2 cycles of cisplatin with accelerated concomitant boost to 2 cycles of cisplatin plus cetuximab with accelerated concomitant boost. The authors concluded that there was no impact with the addition of cetuximab to cisplatin CRT. I believe this trial has also been prematurely reported. Although the hazard ratios suggest there are no differences in the early stages of evaluation, further follow-up, particularly at a minimum of at least 3 years and again at 5 years, will provide more robust and informative data. Very good locoregional control has been achieved with chemotherapy plus radiotherapy regimens. Patients with inapparent distant micrometastases are having longer remissions or may even be cured, which will be appreciable only after several years of follow-up. Long-term data will be needed to determine which of the tested treatment plans are effective.

The major toxicity head and neck cancer patients experience is related to radiation. If we can reduce the side effects of radiation, we would be doing our patients a great service. The RTOG is performing a trial comparing cetuximab and radiation to cisplatin and radiation in patients with HPV-negative disease, and it will be important to know whether there is a toxicity difference between cetuximab and cisplatin. The investigators are calling this approach a rollback of therapy, but I disagree with that characterization. The major toxicity these patients experience in the long term—not the acute toxicity, necessarily—is related to the dose of radiation, and there is no rollback in the radiation. It is important to look at ways to reduce radiation in the HPV-positive population, and I call on the RTOG to employ a realistic view of the effects of radiation and how radiation might be reduced.

H&O Are there any forthcoming trials?

MP Mount Sinai will be opening a randomized phase III trial, called the QUARTERBACK (A Randomized Phase III Clinical Trial Comparing Reduced and Standard Radiation Therapy Doses After Induction Chemotherapy for Locally Advanced HPV 16 Positive Oropharynx Cancer) study, in HPV-positive patients. All patients will first receive a reduced induction chemotherapy regimen. Those patients who achieve a complete or partial response will be randomized 2 to 1 to receive reduced-dose radiation (5,600 cGy) plus carboplatin and cetuximab, or radiation with carboplatin alone, to 70 Gy, which is the standard treatment based on a prior trial examining docetaxel, cisplatin, and 5-FU. This study will be a noninferiority trial in an attempt to reduce the intensity of radiation.

We are also opening a second trial, known as SIRS (Sinai Robotic Surgery). In this trial of patients with HPV-positive disease, intermediate-stage patients will be treated with surgery, and those with good prognostic features and a complete resection will not receive radiotherapy. We will reserve chemoradiotherapy for patients who relapse in order to avoid radiation completely in more than 50% of the patients. A management approach of reduced-dose radiotherapy should be performed only in a trial, so that any impact on progression and, more importantly, survival will be observable. For example, if induction chemotherapy and reduced-dose radiation cures 80% of patients, but full-dose radiation cures 90% of patients, this difference would be evident only in a randomized trial. It is unfortunate that the National Cancer Institute (NCI) does not support these types of studies, and that the RTOG and other cooperative groups will not undertake a set of randomized phase III trials to evaluate reduced-dose radiation for this increasing population of patients in the United States. I call on the NCI to allocate more funds to support clinical trials and phase III trials in this disease.

Suggested Readings

Lorch JH, Goloubeva O, Haddad RI, et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. *Lancet Oncol*. 2011;12:153-159.

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