

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Combining Radiotherapy With Systemic Therapies

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H&O How did the paradigm of combining systemic chemotherapy with radiotherapy evolve in head and neck cancer?

EV Head and neck cancer is a disease that is usually advanced but still confined locally and regionally at the time of initial diagnosis. It is possible to have large lesions or involvement of multiple large lymph nodes and not have clinically detectable systemic disease. Thus, approximately 70% of patients present with locoregionally advanced disease. Historically, such patients have been treated surgically, with postoperative radiation, a treatment administered with curative intent. Patients who could not undergo resection would be treated with radiotherapy as single modality. In the majority of patients, however, the cancer would recur locoregionally, whereas in some patients, the disease would recur systemically in the lungs, liver, or bones. The concept of adding chemotherapy to radiotherapy originated with the intent to improve local control over what surgery and radiotherapy provided. Furthermore, it was hypothesized that if local control could be improved, the need for surgery could be reduced, thereby introducing the concept of organ preservation.

Research into combined-modality therapy has focused on how best to combine chemotherapy and radiotherapy. The different methods of combination are: induction chemotherapy followed by radiation; chemotherapy given concurrently with radiation (known as sensitization); or chemotherapy plus a targeted agent given concurrently with radiation. Concurrent administration has become the favored method because head and neck cancer recurs

locoregionally, and radiation in the presence of chemotherapy can be more effective at killing tumor cells, thus providing increased locoregional control.

H&O What systemic agents are preferred in the combined-modality setting?

EV It is known that there are several very effective radiation enhancers, including cisplatin, antimetabolites such as 5-fluorouracil, and taxanes. In recent years, the epidermal growth factor receptor (EGFR) inhibitors, particularly cetuximab (Erbix, Bristol-Myers Squibb/ImClone), have been found to be effective radiosensitizers. There were comparisons of chemoradiation versus radiation alone throughout the 1990s, and the majority of these studies proved that adding chemotherapy to radiotherapy resulted in higher disease-free and local control rates, which translated to improved survival.

H&O What is the primary difference between newer, targeted agents like cetuximab and traditional chemotherapeutic agents?

EV Cisplatin, for example, has significant single-agent activity but is also associated with substantial systemic toxicities, such as nausea and vomiting, renal failure, and cumulative myelosuppression. Through the radiosensitization mechanism, there is an increase in skin and mucosal reactions. The hope with a targeted agent is to achieve better efficacy of radiotherapy, leading to increased locoregional control, with less systemic toxicity than seen following administration of chemotherapy. The current data with cetuximab show that it is possible to achieve increased locoregional control and survival with this agent added to radiotherapy over radiotherapy alone. Rash is a well-known class effect of EGFR inhibitors, but with cetuximab there may be less enhancement of mucosal reactions than with cisplatin or other chemotherapeutic agents.

H&O Is overall efficacy better when cetuximab is combined with radiotherapy as compared to chemoradiotherapy?

EV In comparisons of chemotherapy and radiotherapy given concurrently versus radiotherapy alone, the former achieves better results. A recent study demonstrated that

adding cetuximab to radiotherapy also results in better outcomes than radiotherapy alone. The larger body of evidence to date still favors chemotherapy, and we would be very interested in a comparison of chemoradiotherapy versus a targeted agent, like cetuximab, plus radiotherapy. Such research is currently ongoing. Additionally, there is interest in assessing the value of combining a targeted agent like cetuximab with chemoradiotherapy. This combination is also currently under investigation: one ongoing study enrolling patients with unresectable head and neck cancer is administering cisplatin-based chemoradiotherapy with or without cetuximab. At the present time, however, such a “trimodal” approach cannot be considered evidence-based.

H&O Is the combined-modality approach only recommended for frontline patients who are unresectable?

EV The definition of “resectable” does include some variability from patient to patient and also depends on the surgeon’s evaluation. Staging classifications take this variability into account, but if the goal of organ preservation is also considered, at least some patients who have resectable disease could be treated as if they were unresectable, ie, with chemoradiotherapy. At The University of Chicago Medical Center, this clinical scenario is common. Rather than saying surgery should never be used, we say surgery should be used if chemoradiation does not work and we administer chemoradiotherapy first. However, it is also necessary to consider patients with resectable disease who do undergo surgery and then require postoperative therapy. If patients have advanced-stage disease (ie, stage III–IV), are completely resected, but exhibit certain risk factors (eg, positive margins after surgery, involvement of more than 2 lymph nodes, or extracapsular spread of disease), postoperative chemoradiotherapy has been shown to be superior to postoperative radiotherapy alone. In this group of patients, it is unknown whether cetuximab plus radiotherapy should be administered.

H&O Are there patients in whom it would be specifically not recommended to use chemoradiotherapy?

EV In patients with stage I or II disease, it would be recommended to use either surgery or radiotherapy as a single modality, and if radiotherapy is used, concurrent chemotherapy should not be needed. Also, comorbidities must always be considered, as many patients with head and neck cancer are elderly. With the associated risk factors of smoking and alcohol use, there are sometimes other

organ dysfunctions that must be taken into account when planning a treatment strategy and judging a patient’s performance status and general ability to undergo a relatively aggressive treatment.

H&O How does the presence of human papillomavirus affect treatment for head and neck cancer?

EV In recent years, a group of patients has been identified who are younger, frequently do not have traditional risk factors of alcohol and tobacco, and have head and neck cancer related to exposure to human papillomavirus. These tumors tend to manifest in the oropharynx, mainly on the tonsil and base of the tongue. There is some evidence that these tumors are more treatment-responsive to chemotherapy or chemoradiation. It could be postulated that in this group of patients, somewhat less aggressive treatment approaches will be needed because their disease is more responsive. At this point, however, this postulation is speculative and less aggressive therapy should not be used until it is proven equally effective.

H&O What is the role of chemotherapy as induction therapy?

EV It has been known for many years that induction chemotherapy can shrink tumors, but a fairly recent discovery is that taxane-based initial chemotherapy leads to improved survival compared with radiotherapy alone. Now, as mentioned, there are three possible treatment paradigms: induction chemotherapy followed by radiotherapy, concurrent chemoradiotherapy (considered by many to be the standard therapy), and cetuximab plus radiotherapy. A further variable that could be applied to all approaches is the use, or avoidance, of surgery. There is a host of questions to ask about these competing paradigms. Should cetuximab be added to induction chemotherapy? Should cetuximab be added to chemoradiotherapy? Or, should induction chemotherapy precede either chemoradiotherapy or cetuximab plus radiotherapy. All these questions are currently being investigated in clinical trials. In the interim, we consider chemoradiotherapy the concept that is best supported by current clinical data.

H&O Because there are so many potential options, what should a medical oncologist’s standard approach be?

EV As medical oncologists, we need to realize that in head and neck cancer, we do not represent the curative aspect of therapy. The curative principle is represented by

surgery or radiotherapy. Medical oncologists have tools that allow other specialties to be more effective. We must be sure that the patient under treatment has access to experienced, expert, state-of-the-art medical, radiation, and ear, nose, and throat oncology. An experienced combined-modality team can choose the treatment option it is most comfortable using. My recommendation is that if there is not a clinical trial available, concurrent chemoradiotherapy is the most established approach. Combinations such as cisplatin and radiotherapy are quite easy to administer and evidence-based.

H&O How does the combined-modality treatment approach to head and neck cancer differ from that in lung cancer?

EV Treatment of head and neck cancer is primarily focused on local and regional control, as well as organ preservation. Lung cancer differs in that it is a much more systemic disease. Whereas in head and neck cancer, a drug such as cetuximab can be used with radiotherapy and one can expect it to enhance radiotherapy locally and regionally, in lung cancer, it is necessary to include an effective systemic-therapy component. In inoperable, stage III, regionally advanced non-small cell lung cancer, concurrent chemoradiotherapy is considered standard treatment. It has been suggested that regimens that are systemically dosed, such as cisplatin plus etoposide, may be more effective than regimens that are given at sensitizing doses, such as carboplatin plus paclitaxel. This finding is not based on direct comparison but on comparisons between trials, wherein cisplatin plus etoposide has fairly consistently shown promising data. In lung cancer, the use of systemically active chemotherapy may be more important than it is in head and neck cancer. There has been research examining whether induction or consolidation chemotherapy should be given in addition to concurrent chemotherapy and radiotherapy. Both approaches in randomized trials have not been shown to improve survival, which was a somewhat unexpected objective finding. The current approaches are thus focused on finding more modern chemoradiotherapy platforms. For example, the Cancer and Leukemia Group B is assessing the value of the combination of carboplatin and pemetrexed (Alimta, Eli Lilly), which can be given at full doses with radiation in this group of patients, as opposed to cisplatin plus etoposide. Another approach is to add agents such as cetuximab in this setting as well; the Radiation Therapy Oncology Group has completed a study that showed the feasibility of this approach. A third approach is to intensify radiotherapy to doses exceeding 70 Gy. This approach of course is primarily concerned with local rather than systemic control.

H&O Have other targeted agents been investigated in combination with radiotherapy in these settings?

EV In both head and neck and lung cancers, the tyrosine kinase inhibitors erlotinib (Tarceva, Genentech/OSI) and gefitinib (Iressa, AstraZeneca/Teva), which target EGFR, have been investigated, but there are not many data on the combination of either agent with radiotherapy. In most investigations thus far, the results have not been particularly promising. Antiangiogenic agents, such as bevacizumab (Avastin, Genentech), have been added to chemoradiotherapy in patients with lung cancer, but early results suggest added toxicity, which has led to a very slow and careful evaluation of this approach. There is no completed phase II or III study to date on the use of bevacizumab plus chemotherapy/radiotherapy in head and neck cancer. However, there are promising data on the combination of bevacizumab and erlotinib, and my colleagues and I demonstrated the addition of bevacizumab to chemoradiotherapy (using 5-fluorouracil, hydroxyurea, and radiation) to be feasible.

Suggested Readings

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