Time to Change the Treatment Paradigms in Anaplastic Thyroid Carcinoma

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Anaplastic thyroid cancer (ATC) is a rare cancer and one of the least common thyroid cancers. It is also the most aggressive and lethal of the thyroid cancers. Management with an eye towards palliative care and symptom control is an integral component of treatment because the disease is almost uniformly fatal, with death frequently associated with airway obstruction (disease-specific mortality is close to 100%). Thus, the main goal of treatment today is to prevent death from uncontrolled disease in the neck and subsequent suffocation. As meticulously presented by Drs. Burnison and Lim, better locoregional control has improved median survival in ATC. However, our future focus should not be just on the primary tumor but on the integration of treatment modalities, new biological agents, circulating tumor cells, and the tumor microenvironment and vasculature, as these may directly target the cancer and decrease the risk of distant metastases.

Unfortunately, although they are much needed, randomized clinical trials in ATC are almost nonexistent. The major obstacles for any clinical trials in ATC are the rarity of the disease and the rapidity of tumor growth and morbidity, which make patient recruitment problematic and slow. Long trial completion times increase the risk that additional new therapies will be identified before trial completion or that costs will increase unacceptably, as a product of the number of centers and the amount of time that has elapsed. In addition, studies that include numerous sites, over large regions and with low site accrual, face challenges involving consistent data collection, logistics, genetic differences in populations, differences in disease etiology, access to technology, and differences in technical standards (intensity-modulated radiation therapy [IMRT], biomarkers), as well as data dilution. As a consequence of these factors, there is a notable absence of a modern standard of care; thus, current evidence often comes from scattered, uncontrolled retrospective reviews and small-volume phase II studies. Although technology and the expansion of quality clinical research throughout the world have improved access and operations for clinical trials, we have to admit that there is no magic short-term solution for this orphan disease.

As the authors have noted, definitive local therapy is an essential component of the initial treatment of ATC. However, when either surgery or radiation is used as a single treatment modality, high rates of locoregional and distant recurrence are seen. Surgical resection followed by external beam radiotherapy (EBRT) for ATC was able to lower cause-specific mortality.[1] As with other malignancies, in order to improve outcomes in ATC, chemotherapy has been integrated into multimodality approaches.[2,3] In other malignancies, adjuvant chemotherapy not only reduces tumor volume but also makes the tumor resectable, with the additional advantage of preventing distant metastasis. Unfortunately, few agents are active in ATC. Nonetheless, the more modest outcomes in ATC have motivated clinical practice. The introduction of concurrent radiation with doxorubicin as a definitive treatment or following debulking surgery for ATC has resulted in improvements in local control and median survival, changing the natural history from local and regional recurrence to distant metastases as a leading cause of death.[4,5] In other malignant diseases—and anecdotally in ATC—with difficult and locally aggressive disease, much effort has been devoted to overcoming radioresistance by studying synergistic effects of different chemotherapy agents, combinations, and now targeted therapies (with the latter also given in combination with chemotherapy). In the case of ATC, this approach is supported by data demonstrating that paclitaxel given as single-agent chemotherapy in patients with ATC showed the highest response rate (50%) reported in a single phase II study. These results suggest that taxanes, which are also excellent radiosensitizers, could be among the most active agents for use in concurrent and combined therapies.[6] Two other studies have shown promising results with the
combination of docetaxel and radiation. In one study, with a median follow-up of 21.5 months (range, 2–40 months), five out of six patients are alive. In a second trial, median survival was 40 months, with 60% alive at 2 years. Treatment was not without a significant symptomatic price; in both studies most patients were hospitalized for severe mucositis or infection.[7,8] The incorporation of chemotherapy and targeted therapy early in treatment may also reduce rates of distant failure. Biological agents that are under development in animal models or clinical trials create an exciting new horizon for ATC. Combretastatin-A4 phosphate (CA4P) is an example. In contrast to other anti–vascular endothelial growth factor (VEGF) agents that block the formation of new vessels in tumors, CA4P stops blood flow through already existing abnormal blood vessels, which are markedly increased in ATC. CA4P was used with carboplatin-paclitaxel against ATC in a nude mouse xenograft model.[9] The combination showed significant activity, and on the basis of these findings, the triplet combination of paclitaxel and carboplatin with or without CA4P was evaluated in a phase II/III trial—the FACT (Fosbretabulin in Anaplastic Cancer of the Thyroid) trial.[10] Unfortunately, the study was closed prematurely due to slow accrual (80 patients) and inadequate funding. When the results were presented at the American Society of Clinical Oncology (ASCO) 2011 conference, the rate of patients surviving 1 year was higher in the experimental triplet arm than in the comparator arm (paclitaxel + carboplatin)—24% vs 9%—suggesting a survival benefit for CA4P. Compounds that target tumor vasculature or collapse tumor vasculature are a matter of great clinical interest and investigation. Currently, crolibulin (NCT01240590), a combretastatin derivative, and also combinations of bevacizumab (Avastin) and doxorubicin (NCT00804830), are being studied in clinical trials.

With regard to new biological agents, histone deacetylase inhibitors, tyrosine kinase inhibitors, proteasome inhibitors, farnesyl-transferase inhibitors, and PI3K inhibitors have been tested in preclinical models or clinical trials, with encouraging activity. A few will be studied in ATC in small clinical trials. It is hoped that the results from these preclinical and clinical studies will increase the limited therapeutic options for this deadly disease.[12-18] In rare diseases, evidence will be of lesser quality than that available in the more common cancers; because of the difficulty of collecting adequate numbers of patients, it will come from small trials and frequently from retrospective studies. To improve the quality of studies, new research should be conducted with high methodological standards and good data collection, and it should address specific questions. It is very difficult, in single-institution studies, to detect incremental improvement in rare and unresponsive diseases such as ATC. The long-term goals would be to identify “home runs” through new biological agents such as the PI3K, B-raf, or Akt inhibitors that address the fundamental biology of the tumor, and in the interim to work in a multidisciplinary setting. In rare diseases, the “magic” lies in close collaboration between individual investigators at academic institutions, the pharmaceutical industry, and funding institutions such as the National Cancer Institute.

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