2012 European Thyroid Association Guidelines for Metastatic Medullary Thyroid Cancer Urge Restrained Use of Novel Kinase Inhibitors

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The European Thyroid Association (ETA) launched a taskforce, chaired by Martin Schlumberger, to create guidelines on the treatment of metastatic medullary thyroid cancer (MTC) [1]. The decision to create a focused guideline, rather than an encompassing document, allowed the authors to concentrate on issues related to the treatment of MTC patients with metastases. This has been perhaps the area of greatest interest since the publication of the broader American Thyroid Association (ATA) guideline on MTC [2].

The ETA taskforce is comprised of 5 experts who represent disciplines of endocrinology, nuclear medicine, oncology, and surgery. The authors made recommendations based on expert opinion and recent literature, specifically citing the ATA guideline, with strong similarity to that guideline seen in several recommendations and areas of the text.

Perhaps the greatest strength of the document is that the authors clearly convey the opinions they held through 2011 regarding the role of the emerging systemic agents, typically oral kinase inhibitors targeting RET and VEGFR, in the treatment of metastatic MTC. This is an important message to care providers of how these international experts prioritize available treatment options, and like other guidelines, will serve as an important historical date-stamp for future generations to reflect upon. In this light, the authors clearly convey that enthusiasm for emerging systemic agents is based upon improved progression-free survival (PFS), with improved pain and diarrhea in some. Inferred, but not written, is that no agent has shown improved disease-specific survival (DSS) in

metastatic MTC. While one may expect that improved PFS would translate to improve DSS, this may not be true. In fact, recent investigations in other cancers have suggested that traditional chemotherapy may actually support tumor growth and metastasis [3]. Regarding MTC, current kinase inhibitors in MTC may prolong PFS by about 1 year, but many of us have treated patients who eventually ‘escape’ this treatment and emerge with a more aggressive tumor and we are left wondering if this was the natural course of the disease, or did the pathway-blocking therapy encourage the tumor to find ways around these blockages and thus contribute to tumor dedifferentiation. While these explicit thoughts are not expressed in the ETA guideline, the authors clearly state that given the lack of proven benefit to initiating systemic therapy early in the course of the disease, they call for the delay in starting these treatments until patients have significant tumor burden and with symptomatic or progressive disease according to RECIST criteria (recommendation 1f), and that local therapies (e.g. metastasis directed surgery, external beam radiation therapy, cementoplasty, thermal ablation, arterial embolization, chemoembolization) should be ‘first reviewed for each potential site of distant metastases’. This preference for local therapies as the patient progresses is an effort to delay the need for chronic systemic therapy and its associated toxicity and impaired quality of life. While local therapies can provide palliation and prevent local complications from continued tumor growth, they too have not been systematically shown to prolong DSS. Additionally, not all of these techniques are available at most medical centers, and expertise in their

nuanced performance and knowledge to optimally select one approach over another is often limited.

Along with a request to craft this editorial, I was asked to report my potential conflicts of interest (COI), and the Guidelines for Authors report that a COI statement will be published at the end of the article. However, the accepted-for-publication ETA MTC guideline that I was provided stated that the authors disclosed their COI, but the presence and specifics of any potential COI were not explicitly described. While I detect no commercial bias in this guideline, these disclosures should be provided to all reviewers and editorial authors, in addition to the readers. Similarly, while the task force functioned without commercial support, the ETA likely has relationships with industry that are relevant to the topic of metastatic MTC and the existence and nature of these relationships should likely be disclosed. Our colleagues in industry are motivated to develop and own effective treatments and to see them utilized in appropriate patients, all of which bring financial benefits to the company (and improves patient care). Industry requires meaningful intellectual and labor help in this task, and they seek the best and the brightest physicians to meet this need. Treating physicians and medical societies are also motivated to develop and investigate effective treatments, and medical societies seek these same physicians ('key opinion leaders') to craft and disseminate what are believed to be best practice guidelines to also improve patient care and utilize healthcare resources effectively (and instead of benefiting so directly from profit we instead benefit from name recognition and ego). It is clear that relationships between treating physicians, medical societies, and industry can be highly productive, incestuous, and potentially disastrous, and thus they need to be managed effectively. Transparent reporting of these relationships is an important part of this process.

The authors are praised for their use of an evidence-based schema to rate each of their 21 recommendations, now a standard component of modern guidelines. As outlined above, guidelines are an important effort in many organizations and medical societies, and partnered with modern technology the emergence of software (CAT-maker, BRIDGE-Wiz) to assist the process and to create uniformity of language seems to be the next step. Still, there is a tendency for guidelines to overstate the quality of evidence (QOE) in support for recommendations and the rating of +++ for recommendation 3a reminds me of the recommendation to wear a parachute when skydiving, which should be rated as grade: QOE = +; strength of recommendation (SOR) = grade 1. The SOR is grade 1 as a strong recommendation that applies to most people in

most circumstances and its benefits clearly outweigh the risk. However, the QOE is only + as the evidence is of low quality and not supported by randomized trials or significant and consistent cohort series, but rather by unsystematic observations and reasoning from first principals.

What is the take away lesson of this guideline? Patients with metastatic MTC still present an unmet therapeutic need. The pendulum enthusiastically swung to welcome kinase inhibitors as the 21st century solution to this problem, but today without evidence of a DSS benefit and with their associated side effects the pendulum has pushed our enthusiasm backwards to limit both the breadth of patients we treat and to limit how quickly we initiate these long-term therapies, now requiring (1) a significant tumor burden that is either symptomatic or progressive, and (2) not optimally treated by an alternative strategy. Treating physicians and industry partners recognize that this generation of targeted therapies has fallen short of curing metastatic MTC, or at least creating an indefinite state of asymptomatic dormancy. Still, they serve an important role for many patients, and treating clinicians and industry partners are now working to not only clarify the appropriate time and place for these new treatments, but also to improve upon them. We recognize these compounds as a welcomed step upon which to advance our progress to one day truly meet the full challenge that these unfortunate patients continue to present.

Disclosure Statement

Consulting: Astra Zeneca, American Thyroid Association (ATA) MTC Guideline Chair, Eli Lilly, National Comprehensive Cancer Network (NCCN) Guidelines, NCCN Request for Development Team, National Institutes of Health/National Cancer Institute Rare Tumor Task Force, Novo Nordisk, OptumInsight, Veracyte. Clinical Trials co-investigator: Bayer/Onyx, Eisai, Exelixis, Radiation Therapy Oncology Group.

References

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