Medical Therapy for Advanced Forms of Thyroid Cancer

Uma Rajhbeharrysingh, MD[a], Matthew Taylor, MD[b], Mira Milas, MD[c,*]

KEYWORDS

• Advanced thyroid cancer • Targeted therapy • Clinical trials • Chemotherapy
• Anaplastic • Medullary and differentiated thyroid cancer • Medical therapy

KEY POINTS

- Patients with unresectable or metastatic thyroid cancer are candidates for systemic treatment with targeted therapeutics.
- Classes of targeted therapeutic agents tested in clinical trials for thyroid cancer include selective tyrosine kinase inhibitors, multikinase inhibitors, proteasome inhibitors, inhibitors of angiogenesis, histone deacetylase inhibitors, and inhibitors of DNA methylation.
- Drugs inducing differentiation of thyroid tumors to increase susceptibility to radioiodine ablation have shown a good initial response.
- Newer trials involve combinations of drugs.
- Three drugs have received Federal Drug Administration approval: vandetanib and cabozantinib (XL184) for medullary thyroid cancer and sorafenib for papillary thyroid cancer.

INTRODUCTION

In 2013, it is estimated that 60,220 new individuals (75% women) will be diagnosed with thyroid cancer and 1850 patients will die of thyroid cancer (Surveillance, Epidemiology, and End Results Program[1]). Thyroid cancer represents 4% of all new cancer cases and is the fifth most common cancer in women. There has been an increase in the incidence of thyroid cancer since the mid 1990s, especially in the female population. This increase is partly attributed to incidentalomas found on radiology studies

Disclaimer: Drug dosages are presented to the best of current knowledge and for general illustration. Readers are advised to confirm the dosage if considering therapy.

[a] Department of Surgery, Oregon Health and Science University, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239, USA; [b] Division of Hematology & Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239, USA; [c] Department of Surgery, Knight Cancer Institute, Oregon Health and Science University, 3181 Southwest Sam Jackson Park Road, L619, Portland, OR 97239, USA
* Corresponding author.
E-mail address: milas@ohsu.edu

Surg Clin N Am 94 (2014) 541–571
http://dx.doi.org/10.1016/j.suc.2014.03.003 **surgical.theclinics.com**
0039-6109/14/$ – see front matter

used in general medical care. Primary thyroid cancer can be classified into 3 major histopathologic types: differentiated thyroid cancers (DTC), including papillary (PTC, 85% of cases) and follicular (FTC, 5%–10%); medullary thyroid cancer (MTC, 5%); and anaplastic thyroid cancer (ATC, 1%).[2] Even though the general prognosis of thyroid cancer is excellent, 10% to 20% of patients with DTC have advanced cancer either at the initial presentation or as a recurrence. Advanced presentations can be broadly defined as those with metastatic disease or extensive regional invasion of major anatomic structures, such as the aerodigestive tract (larynx, trachea, esophagus, recurrent laryngeal nerve), spine, or large cervical blood vessels. Conventional medical therapy for thyroid cancer is used in these cases, including radioactive iodine (RAI) and high-dose levothyroxine replacement therapy for thyroid-stimulating hormone (TSH) suppression. It is estimated, however, that about half of these patients with advanced disease will not respond adequately to the conventional therapy. One reason may be the dedifferentiation of the tumor, resulting in the inability to transport RAI into the tumor cell. Long-term survival for patients presenting with stage IV DTC is about 51% compared with nearly 100% for patients with stage I (American Cancer Society, www.cancer.org). The long-term overall survival decreases to 10% to 15% in patients with RAI-resistant disease.[3,4] RAI insensitivity/resistance also exists in ATC whereby cells are either dedifferentiated or undifferentiated and in MTC whereby parafollicular cells do not participate in iodine uptake. Treatment options, therefore, for thyroid tumors that cannot be managed either by surgical intervention or RAI have been very limited.

Over the last decade, there has been an exponential growth in biomolecular information focused on cell signaling pathways resulting in cell growth, proliferation, differentiation, migration, and survival. This has identified various genetic mutations in multiple pathways, which can lead to thyroid cancer. Mutations in the RAS, RET, and RAF genes were among the most common mutations noted in DTC and MTC; additionally, several somatic mutations have been described in ATC, including the genes of the MAP kinase (MAPK, more commonly referred to as MEK in published literature) and PI3K/AKT pathways and TP53. The major cell signaling pathways affected by these mutations include but are not limited to the RAS/RAF/MEK/ERK pathway, PI3K/AKT/mTOR pathway, JAK/STAT3, and NFkb pathways (**Fig. 1**), which in turn affect cell growth, proliferation, and survival. EGFR is a receptor tyrosine kinase (RTK) that acts downstream through the activation of several cascades, including MAPK, AKT, and JAK. The inhibition of one or more of the kinases in these pathways, in epigenetic mechanisms, angiogenesis, or cellular mechanics involved in cell division are likely targets that can result in tumor regression.[5] In 2004, new targeted therapies for these advanced thyroid cancers came to light, creating an upsurge in clinical trials and off-label use of these drugs soon after. Thus far, the Food and Drug Administration (FDA) has approved 2 drugs for use in advanced MTC: vandetanib (in 2011) and cabozantinib (in 2012). The purpose of this article is to provide a contemporary summary of available targeted therapies for advanced thyroid cancer, corresponding clinical trials, and innovative drugs on the horizon.

HISTORICAL OVERVIEW

There has been quite an evolution regarding innovative medical therapies for advanced thyroid cancer. The authors would like to take this opportunity to provide a timeline highlighting major events to date (**Fig. 2**). **Tables 1–7** reference specific publications with the year of publication in an effort to add to the timeline associated with a therapy. Medical therapy in the form of RAI was first reported for use in thyroid cancer