

David A. Liebner, Sigurdís Haraldsdóttir,
and Manisha H. Shah

Introduction

Chemotherapy has been used as a single-modality treatment or as part of combined-modality therapy in metastatic or locally advanced thyroid cancer when other conventional treatments (e.g., surgery and radiation therapy) have failed. Recent developments in the understanding of the molecular pathogenesis of thyroid cancer have allowed for more targeted investigations, but cytotoxic chemotherapy remains an important part of the armamentarium, particularly for anaplastic and relatively undifferentiated thyroid cancers. Numerous reports on the use of chemotherapy in a variety of thyroid cancers have been published, but only a few controlled clinical trials compare the efficacy of different drug regimens. We outline both conventional cytotoxic chemotherapeutic agents and novel targeted agents below.

D.A. Liebner, MD
Division of Medical Oncology, Department of Internal Medicine,
The Ohio State University, Columbus, OH USA

Department of Biomedical Informatics, The Ohio State University,
Columbus, OH USA
e-mail: david.liebner@osumc.edu

S. Haraldsdóttir, MD
Division of Medical Oncology, Department of Internal Medicine,
The Ohio State University Comprehensive Cancer Center,
Columbus, OH USA
e-mail: sigurdis.haraldsdottir@osumc.edu

M.H. Shah, MD (✉)
Division of Medical Oncology, Department of Internal Medicine,
The James Cancer Hospital and Solove Research Institute,
320 West 10th Avenue, A438 Starling Loving Hall, Columbus, OH
43210, USA
e-mail: Manisha.Shah@osumc.edu

Cytotoxic Chemotherapy

Prior to the early 1970s, experience with individual chemotherapeutic agents in thyroid cancer was largely limited to case reports without systematic evaluation of efficacy in clinical trials [1]. Individual cytotoxic chemotherapeutic agents with known (or proposed) antitumor activity against thyroid cancer are listed in Table 64.1. Patient nutritional status and performance statuses have been noted as important predictors of response to these agents [2, 3]. Selected agents are discussed below.

Bleomycin

Bleomycin is an antineoplastic antibiotic that impairs DNA synthesis by generating superoxide and hydroxyl radicals that cause single- and double-stranded DNA breaks. It was the first chemotherapeutic agent reported effective in thyroid cancer [4, 5]. However, due to limited activity as monotherapy with associated risk of pulmonary toxicity, subsequent study focused primarily on combination regimens. A retrospective study of doxorubicin, bleomycin, and vincristine (ABC) in thyroid cancer reported responses in 5 of 13 patients (38 %) [6], and a phase II study of ABC-melphalan reported short-term responses in 4 of 11 patients (37 %) [7]. A retrospective study of bleomycin, doxorubicin, and cis-platinum (BAP) in 21 patients noted responses in 9 patients (42 %); the best responses were seen in individuals with medullary thyroid cancer (MTC) or anaplastic thyroid cancer (ATC) [8].

Doxorubicin

Doxorubicin is an anthracycline derivative that has been the most widely used and studied cytotoxic chemotherapeutic agent in thyroid cancer. On the basis of observational experience and initial results from phase I and II studies [1, 9],

Table 64.1 Cytotoxic chemotherapeutic agents

Drug	Class	Toxicities
Doxorubicin	Anthracycline	Cardiotoxicity, mucositis
Epirubicin	Anthracycline	Cardiotoxicity, myelosuppression
Mitoxantrone	Anthracenedione, DNA intercalator	Myelosuppression, risk of cardiotoxicity
Bleomycin	Antitumor antibiotic	Pulmonary toxicity
Cisplatin	Heavy metal, DNA cross-linking	Nephrotoxicity
Carboplatinum	Heavy metal, DNA cross-linking	Myelosuppression
Etoposide	Topoisomerase II inhibitor	Myelosuppression
Topotecan	Topoisomerase I inhibitor	Myelosuppression, mucositis
Irinotecan	Topoisomerase I inhibitor	Myelosuppression, diarrhea
Dacarbazine	Alkylating-like agent	Myelosuppression, gastrointestinal toxicity
Cyclophosphamide	Alkylating agent	Myelosuppression, hemorrhagic cystitis
Paclitaxel	Taxane	Myelosuppression, peripheral neuropathy
Vincristine	Vinca alkaloid	Peripheral neuropathy
Methotrexate	Antimetabolite	Gastrointestinal toxicity, hepatotoxicity
Capecitabine	Oral fluoropyrimidine	Hand-foot syndrome, diarrhea
Gemcitabine	Antimetabolite	Myelosuppression

further investigation of doxorubicin monotherapy was pursued. Gottlieb and Hill enrolled patients with all histologic subtypes of thyroid cancer and reported that 11 of 30 patients treated with 45–75 mg/m² doxorubicin every 3 weeks had greater than 50 % reductions in the size of their metastases [10]. Responses appeared to be best in patients with pulmonary metastases followed by bone metastases, and several patients with bone metastases reported subjective improvements in bone pain with treatment. Subsequent studies of doxorubicin monotherapy were undertaken, and a summary of these early studies suggested a response rate of 38.5 % in patients with differentiated thyroid cancer (DTC) ($n=109$) and 41 % in patients with Hürthle cell carcinoma ($n=41$) [11]. However, these studies were not placebo controlled and had varying inclusion criteria and definitions of response, which limited extrapolation. A more recent retrospective study of 22 patients with progressive, metastatic, unresectable DTC or medullary thyroid cancer (MTC) treated with either doxorubicin 60 mg/m² every 3 weeks for 3–6 cycles or 15 mg/m² weekly for 8–16 cycles documented WHO partial responses (PR) in 5 % of patients and stable disease in 42 % (median 7 months) [12]. A comparison of the two dosing regimens in DTC suggested better responses with 60 mg/m² every 3 weeks compared to 15 mg/m² weekly (PR: 11 % vs. 0 %, SD: 67 % vs. 20 %, PD: 22 % vs. 80 %). Common side effects are neutropenia, nausea, emesis, and alopecia. The recommended dose is 60–75 mg/m² every 3 weeks, with cumulative dosing not recommended to exceed 450 mg/m² due to the risk of anthracycline-associated cardiomyopathy.

Epirubicin

Epirubicin is an anthracycline analog of doxorubicin, with dose-limiting myelosuppression and less cardiotoxicity than doxorubicin [13]. Santini and colleagues investigated the combination of the epirubicin with carboplatin in a small single-arm study of patients with progressive, metastatic poorly differentiated thyroid cancer [14]. A total of 14 patients were treated with carboplatin 300 mg/m² and epirubicin 75 mg/m² every 4–6 weeks. These patients also underwent TSH stimulation in an attempt to improve response to therapy. Responses were comparable to other historical regimens (CR: 6 %, PR: 31 %, SD: 44 %).

Cisplatin

Cisplatin is an inorganic platinum agent which forms intra- and interstrand DNA cross-links, leading to tumor cell death. Several early studies documented the activity of cisplatin as a single agent in advanced thyroid cancer. Hoskin and Harmer [6] reported objective responses in 5 out of 13 patients treated with cisplatin; responses were noted in all tumor histologies, including DTC, MTC, and ATC. Similar response rates were noted in subsequent studies [15], though response rates appeared lower in patients with DTC who had progressed following treatment with doxorubicin [16]. Toxicities include myelosuppression, nephrotoxicity, and ototoxicity.

Table 64.2 Selected targeted agents approved for or in development for the treatment of thyroid cancer

Drug	Target(s)	Toxicities
Axitinib	VEGFR-1–3, PDGFR, KIT	Hypertension/vascular events, fatigue, gastrointestinal toxicity
Cabozantinib (XL184)	VEGFR-2, Met, KIT, FLT3, Tie-2	Hand-foot, fatigue
Gefitinib	EGFR	Rash, gastrointestinal toxicity
Imatinib	Bcr-Abl, PDGFR, KIT, RET	Rash, gastrointestinal toxicity
Motesanib	VEGFR-1–3, PDGFR, KIT, RET	Hypertension/vascular events, fatigue, gastrointestinal toxicity
Pazopanib	VEGFR-1–3, PDGFR, KIT	Hypertension/vascular events, fatigue, gastrointestinal toxicity
Sorafenib	VEGFR-2–3, PDGFR, KIT, RET, BRAF, Raf-1, FLT3	Hand-foot, rash, fatigue, gastrointestinal toxicity
Sunitinib	VEGFR-1–2, PDGFR, KIT, RET, FLT3	Hand-foot, rash, fatigue, gastrointestinal toxicity
Tipifarnib	Farnesyltransferase	Rash, elevated lipase
Vandetanib	VEGFR-2, EGFR, RET	Hypertension/vascular events, fatigue, gastrointestinal toxicity
AZD6244	MEK	Rash, fatigue, diarrhea
Fosbretabulin	Tubulin (tumor microvasculature)	Myelosuppression, tumor pain, QTc prolongation
Plitidepsin	JNK activator (pro-apoptotic)	Anemia, thrombocytopenia, fatigue, elevated transaminases/creatinine kinase
Vorinostat	Histone deacetylase	Thrombocytopenia, hyperglycemia, hypertension
Thalidomide	TNF α , VEGF, immunomodulator	Fatigue, peripheral neuropathy, thromboembolism
Lenalidomide	TNF α , VEGF, immunomodulator	Myelosuppression

Paclitaxel

Paclitaxel is a compound derived from the Pacific yew tree which stabilizes microtubules and inhibits cell division. Higashiyama and colleagues [17] reported objective responses in 4 out of 13 patients with anaplastic thyroid cancer treated with paclitaxel administered weekly as a 1-h infusion. A second study of paclitaxel administered as a continuous 96-h infusion in anaplastic thyroid cancer reported responses in 10 out of 20 patients [18]. Common toxicities include peripheral neuropathy and myelosuppression.

Targeted Agents

The last decade has witnessed an impressive expansion in our understanding of the disease pathobiology of advanced thyroid cancer and the advent of several novel targeted therapies. Several of these agents are summarized in Table 64.2. Selected agents are discussed below.

FDA-Approved Targeted Therapy

Vandetanib

Vandetanib (Zactima, Caprelsa) is an orally bioavailable tyrosine-kinase inhibitor of RET, VEGFR-2, and EGFR [19, 20]. The results of a randomized, double-blinded, multicenter placebo-controlled phase III trial of vandetanib in patients with locally advanced or metastatic MTC (ZETA

trial) were reported in 2011 [21]. A total of 331 patients were enrolled in the trial. Progression-free survival at 6 months was 83 % in the vandetanib arm, compared to 63 % in the placebo arm (HR for progression 0.45, CI 0.30–0.69). Improvements were also noted in the overall response rate, disease control rate, and biochemical response rates. Overall survival was not significantly different between the two groups, but this was confounded in part by the crossover design of the study. Common side effects included diarrhea, rash, nausea, hypertension, and headache. It is currently one of two targeted therapies approved by the US Food and Drug Administration (FDA) for advanced, unresectable, or metastatic MTC.

Investigational Targeted Therapies

Cabozantinib

Cabozantinib (XL184) is a potent, orally bioavailable receptor tyrosine-kinase inhibitor of Met, VEGFR-2, KIT, RET, FLT3, and Tie-2. The results from a large, phase III, randomized, placebo-controlled study in patients with MTC were published in 2013 [22]. A total of 330 patients were enrolled in the trial; median PFS in patients treated with placebo was 4.0 months, compared to 11.2 months in patients receiving cabozantinib (HR 0.28, $p < 0.001$). Unlike the ZETA trial, patients on this trial were not allowed to cross over on progression. Overall survival data were analyzed in an interim analysis when 44 % of 217 required events had occurred and no difference was seen between the two arms (HR 0.98; 95 % CI 0.63–1.52).

All patients were required to have evidence of disease progression within the last 14 months prior to enrollment. The most frequent grade 3 events included diarrhea (15.9 % vs. 1.8 %), hand-foot syndrome (12.6 % vs. 0 %), fatigue (9.3 % vs. 2.8 %), hypocalcemia (2.8 % vs. 0 %), and hypertension (7.9 % vs. 0 %) in the two groups, respectively. This agent was the second FDA-approved therapy for use in progressive, metastatic MTC.

Pazopanib

Pazopanib (Votrient) is an orally bioavailable inhibitor of VEGFR-1–3, PDGFR, and KIT [23] that is FDA-approved for the treatment of advanced renal cell carcinoma. Results of an NCI-sponsored multicenter, phase II trial of pazopanib in patients with locally advanced or metastatic, radioiodine-resistant DTC were reported in 2010 [24]. Despite the fact that all patients had evidence of progressive disease at enrollment, partial responses were seen in 18 of 37 patients, and there was a reported median progression-free survival of 11.7 months. Adverse events were common and similar to other VEGFR-targeted tyrosine-kinase inhibitors, including fatigue, skin and hair hypopigmentation, diarrhea, nausea, and hypertension. Two deaths occurred during treatment, including one fatal myocardial infarction and a bowel perforation following a complicated case of cholecystitis.

Sorafenib

Sorafenib (Nexavar) is a multi-kinase inhibitor with activity against VEGFR-2–3, PDGFR- β , FLT3, KIT, Raf-1, BRAF, and RET kinases and was approved by the FDA in November 2013 for use in metastatic differentiated thyroid cancer based on the results of the DECISION trial [25]. It is also approved for the treatment of hepatocellular carcinoma and renal cell carcinoma. The phase III randomized placebo-controlled DECISION trial enrolled 417 patients with radioactive iodine-refractory locally advanced or metastatic differentiated thyroid cancer that had progressed within the past 14 months and randomized them on a 1:1 basis. Median PFS was significantly longer in the sorafenib-treated group compared to the placebo-treated group (10.8 months vs. 5.8 months, HR 0.59, $p < 0.0001$). Seventy-one percent of placebo-treated patients crossed over to open-label sorafenib upon disease progression. Overall survival did not differ significantly between the groups (HR 0.80, $p = 0.14$), and the median survival had not been reached at the time of primary analysis data cutoff. The most frequent adverse events included hand-foot skin reaction (76.3 %), diarrhea (68.6 %), alopecia (67.1 %), and rash or desquamation (50.2 %). Five phase II clinical trials have evaluated sorafenib in patients with all histologies of thyroid cancer [26–30]. Objective response rates range from 11 to 25 % with clinical benefit rates (objective responses or stable disease of at least 6 months) of 59–74 %. Toxicities were similar in the four

trials, with the most common adverse events being hand-foot syndrome, rash, fatigue, diarrhea, bloating, musculoskeletal pain, weight loss, and mucositis. Roughly one-third of patients also required adjustments in their thyroid replacement.

Sunitinib

Sunitinib (Sutent) is a multi-kinase inhibitor with activity against VEGFR-1, VEGFR-2, PDGFR, c-KIT, FLT3, and RET that is approved for treatment of renal cell carcinoma, gastrointestinal stromal tumors resistant to imatinib, and pancreatic neuroendocrine tumors. Four phase II studies have investigated sunitinib in advanced differentiated or medullary thyroid cancer [31–34]. Objective responses were seen in 13–33 % of patients. Common side effects include fatigue, lymphopenia, nausea, diarrhea, mucositis, and hand-foot syndrome.

Summary

Cytotoxic chemotherapeutic agents have historically been the backbone for treatment of advanced, unresectable thyroid cancer. Cytotoxic agents remain important as a component of multimodality therapy for anaplastic thyroid cancer. However, targeted agents have emerged as frontline therapy for the majority of patients with advanced differentiated or medullary thyroid cancers [35]. See Chaps. 71, 83, and 94 for further discussion of chemotherapy in DTC, MTC, and ATC, respectively.

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