8 Systemic Treatments and Related Side Effects in Thyroid Cancer

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Thyroid cancers are the most common cancers of the endocrine system. Especially in recent years, its incidence has been increasing in women and developed countries [1]. Most thyroid cancers are caused by follicular epithelium. These are papillary, follicular, Hurthle cell, and anaplastic thyroid cancers, respectively. More rarely medullary thyroid cancer (MTC) and lymphomas are observed. The first two of these, papillary and follicular type thyroid cancers, are called differentiated thyroid cancers (DTCs). The prognosis is better in differentiated thyroid cancers, with 10-year survival rates exceeding 90%. The basic treatment approach in differentiated thyroid cancer consists of surgical and radioactive iodine (RAI) treatment and approaches that suppress thyroid-stimulating hormone (TSH) [1–5]. Although these approaches provide long-term disease control even in metastatic disease, the disease may become resistant to RAI treatment after a while. In this case, the available treatment options are follow-up, anti-angiogenic kinase inhibitors, and chemotherapy. The place of radiotherapy is quite limited. On the other hand, anaplastic thyroid cancer is a highly aggressive tumor and its prognosis is poor in general and its main treatment is systemic chemotherapy.

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8.1 Therapy in Differentiated Thyroid Cancers

The basic treatment approach in early-stage DTC is surgery. However, total thyroidectomy±therapeutic neck dissection is recommended in the presence of any of the risk factors such as known distant metastasis, extrathyroidal spread, tumor diameter greater than 4 cm, cervical lymph node involvement, poor differentiation, bilateral nodularity, and known radiation exposure; otherwise, subtotal thyroidectomy + isthmusectomy may also be performed. Adjuvant radioactive iodine (RAI) ablation treatment and TSH suppression treatment are applied according to postoperative risk factors [3].

Recurrences may occur in approximately one-third of differentiated thyroid cancers in the following period. Local recurrences occur mostly in cervical lymph nodes, while the most common distant metastasis is the lung. Repeat surgery is recommended in local recurrence, if possible. If imaging is positive in local recurrences that cannot be resected, firstly RAI and radiotherapy are recommended [3]. The basic treatment approach in metastatic DTC is RAI treatment with TSH suppression. However, some patients become

R. Bekiş et al. (eds.), *Radionuclide Therapy*, https://doi.org/10.1007/978-3-030-97220-2_8

resistant to RAI treatment during the course of the disease. Resistance to RAI treatment is mentioned in the absence of RAI uptake in any of the metastatic lesions, in the absence of uptake in one or more of the lesions, or in the case of RAI uptake but progression with treatment. Other treatment options in this group of patients include chemotherapy, radiotherapy, metastasectomy in appropriate cases, and molecular targeted treatments. In this sense, anti-angiogenic multiple kinase inhibitors constitute the most commonly used and most up-to-date treatment approach today. In particular, kinase inhibitors targeting the vascular endothelial growth factor receptor (VEGFR) pathway are the most commonly used agents. These drugs provide tumor stabilization and can provide long-term disease control. But today there is not enough data to suggest that it increases overall survival. With the introduction of this group of drugs, the role of chemotherapy in the treatment of DTC is quite limited [3–7].

The treatment recommendation of the American Thyroid Association (ATA) guidelines [4] in differentiated thyroid cancer is as follows: Multiple kinase inhibitors are recommended in patients with RAI resistant DTC, tumor >1–2 cm and growth rate at least 20% per year, or symptomatic metastatic disease. Among these, lenvatinib and sorafenib are the primary drugs. Other multiple kinase inhibitors and BRAF inhibitors are recommended in patients who are progressing or intolerant to multiple kinase inhibitors. Cytotoxic chemotherapy remains in the background. In addition, supportive therapies such as radiotherapy and bisphosphonate therapies are recommended for bone metastasis while continuing treatment suppressing TSH [3, 6].

8.2 Multiple Kinase Inhibitors

VEGF expression and peritumoral angiogenesis are increased in thyroid cancer cells [8, 9]. In addition, studies have found genetic alterations in MAPK (mitogen-activated protein kinase) and PI3K-AKT/mTOR pathway, PTEN mutation in Cowden syndrome, BRAF-V600E mutation in papillary thyroid cancer, and activating mutations in RAS (KRAS, HRAS, NRAS) oncogen. RAS mutation and increased VEGF expression are associated with poor prognosis. Other important signal transmission pathways are fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) [10–12]. Among these, most frequently, increased VEGF expression and activation in the MAPK pathway are retained responsible. Kinase inhibitors developed for these goals have found an important place in the treatment of DTC as in many tumors. Some kinase inhibitors selectively block one of these targets, while others block multiple targets (multiple kinase inhibitors). The main ones with clinical trials in thyroid cancers are sorafenib, lenvatinib, sunitinib, pazopanib, vandetanib, and cabozantinib, and their clinical activities will be briefly discussed.

Sorafenib is a multiple kinase inhibitor that blocks VEGFR 1, 2, and 3, platelet-derived growth factor receptor (PDGFR), common RET subtypes, c-kit, and to a lesser extent BRAF [13]. The efficacy of sorafenib in RAI-resistant DTC has been investigated in a randomized phase 3 study. In the study of a total of 417 patients, patients were randomized to sorafenib or placebo arms. In conclusion, sorafenib was superior to placebo in median progression-free survival (10.8 months vs. 5.8 months). Overall survival was longer in the sorafenib arm than in the placebo arm, but no statistical significance was achieved (HR 0.8; $P = 0.14$). Similarly, the 12% response rate obtained with sorafenib was not found to be significant. Generally, grade 1 and 2 side effects were observed. Hand-foot syndrome, diarrhea, alopecia, and rash were reported at a frequency of 76%, 68%, 67%, and 50% in the sorafenib arm. Toxicity rates leading to dose reduction and treatment discontinuation were reported as 78% and 14%, respectively [14] (Table 8.1). Sorafenib received FDA approval in 2013 for the treatment of RAI-resistant, recurrent, or metastatic progressive DTC [15].

Lenvatinib is a multiple kinase inhibitor that inhibits VEGFR, RET, and fibroblast growth factor receptor kinases 1–4 [16]. The efficacy of lenvatinib in RAI-resistant DTC has been investigated in a randomized phase 3 study. In the

Table 8.1 Phase 3 studies in local advanced or metastatic radioiodine-resistant thyroid cancers

Study	Drug	Phase	Histology	Previous treatment	Number of patients	Response rate	PFS (months)	*p*	OS (HR)	*p*
Decision [14]	Sorafenib Placebo	3	DTC	None	207 210	12% 0.5%	10.8 5.8	<0.001	0.80	0.14
Select [17]	Lenvatinib Placebo	3	DTC	Yes	261 131	64% 1.5%	18.3 3.6	<0.001	0.73	0.10
Zeta [29]	Vandetanib Placebo	3	MTC	Yes	231 100	45% 13%	30.5 19.3	<0.001	0.89	NS
Exam [30]	Cabozantinib Placebo	3	MTC	Yes	219 111	28% 0%	11.2 4.0	<0.001 <0.001	0.89 0.98	NS NS

SELECT study of a total of 392 patients, patients were randomized to lenvatinib or placebo arms. In conclusion, lenvatinib was superior to placebo in median progression-free survival (18.3 months vs. 3.6 months) and response rate (64.8% vs. 1.5%). The most common adverse reactions of grade 3 and above were reported as hypertension (42%), proteinuria (10%), fatigue (9%), diarrhea (8%), and venous and arterial thrombosis (3.8% and 2.7%).

Severe adverse reactions such as gastrointestinal perforation/fistula were reported as 2% in the lenvatinib arm and 0.8% in the placebo arm. 14% (37 patients) discontinued due to adverse events [17] (Table 8.1). This benefit with lenvatinib was observed in both the age group below 65 years and the age group above 65 years [18]. Lenvatinib received FDA approval in 2015 for the treatment of RAI-resistant, recurrent, or metastatic progressive DTC [19].

Sunitinib is a multiple kinase inhibitor that blocks VEGFR 1, 2, and 3 and RET subtypes 1 and 3 [20]. Partial response and stable disease were found to be 13% and 68%, respectively, in a phase 2 study in patients with DTC who progressed under RAI treatment and used sunitinib at a dose of 50 mg/day (28 days treatment and 14 days off) [21]. In another phase 2 study using sunitinib at a dose of 37.5 mg/day (continuous use) (35 patients with DTC and 7 patients with medullary thyroid cancer), 3% had a complete response, 28% had a partial response, and 46% achieved a stable disease response [22].

Pazopanib is an anti-angiogenic kinase inhibitor that blocks all VEGFRs [23]. It does not distinctively inhibit RET. The efficacy of pazopanib (800 mg/d) was investigated in a phase 2 study in 37 patients with RAI-resistant DTC. As a result, 49% partial response and 47% 1-year progression-free survival were found [24].

Vandetanib is a multiple kinase inhibitor that blocks VEGFR, RET, and epidermal growth factor receptor (EGFR) [25]. The efficacy of vandetanib in RAI-resistant DTC was investigated in a randomized study. In the study of a total of 145 patients, patients were randomized to vandetanib or placebo arms. In conclusion, median progression-free survival was longer in the vandetanib arm (11.1 months vs 5.9 months), with no significant difference in response rate (8% vs. 5%). The efficacy was reported to be higher in the papillary Ca subtype. Toxicities of grade 3 and above in the vandetanib arm were reported as QTc prolongation 14%, diarrhea 10%, and asthenia 7% [26]. Vandetanib is also highly effective in medullary thyroid cancer and is a kinase inhibitor recommended by treatment guidelines [3] (Table 8.1).

Cabozantinib is a multiple kinase inhibitor that blocks VEGFR, RET, and c-MET [27]. The efficacy of cabozantinib was investigated in a phase 2 study in 25 patients with RAI-resistant DTC who had previously used 1 or 2 lines of other kinase inhibitors. As a result, 40% partial response and 52% stable disease response were achieved. Median progression-free survival was 12.7 months [28]. Cabozantinib is also highly effective in medullary thyroid cancer like vandetanib and is a kinase inhibitor recommended by treatment guidelines [3] (Table 8.1).

Although multiple kinase inhibitors generally do not provide cure for the disease, they show significant clinical efficacy and delay progression. These drugs have their own class side effects. Optimal treatment management is very important when using multiple kinase inhibitors due to the unique clinical behavior pattern of DTCs. In this sense, both optimal dose use and good side effect management are necessary in order not to decrease efficacy [3, 5].

8.3 Side Effects of Multiple Kinase Inhibitors Targeting Vascular Endothelial Growth Factor Receptor

Major side effects include fatigue, diarrhea, hypertension, hand-foot syndrome, myelosuppression, bleeding, thyroid dysfunction, arterial thromboembolism, and Q-T prolongation [13, 16, 20, 23, 25, 27, 29–38].

8.4 BRAF Inhibitors

Another oncogenic abnormality that plays a role in the development and invasion of differentiated thyroid cancers is the presence of BRAF mutation. BRAF V600E mutation reaches 80% in papillary thyroid cancers. In this respect, phase 2 studies were conducted with BRAF inhibitors vemurafenib and dabrafenib. Fifty-one patients with papillary thyroid cancer with BRAF V-600 mutation resistant to RAI were treated with vemurafenib in a study. As a result of this study with approximately half of the patients having previously received anti-angiogenic kinase inhibitors, the response rate in the group that had not previously received anti-angiogenic kinase inhibitors was 38.5%, and median progression-free survival was 18.2 months, while these rates remained 27.3% and 8.9 months in the anti-angiogenic kinase inhibitor group, respectively [39]. In a phase 2 study with dabrafenib, another BRAF inhibitor, the efficacy of dabrafenib was investigated in 14 patients with BRAF (V600E)-mutant metastatic thyroid cancer, achieving a partial response of 29% and median progression-free survival of 11.3 months [40]. It is also stated that BRAF inhibitors can stimulate re-differentiation and thus RAI uptake in RAI-resistant patients [41, 42]. Studies on BRAF inhibitors and MEK inhibitors are ongoing.

8.5 Side Effects of BRAF Inhibitors

Major side effects include rash, fatigue, weight loss, alopecia, squamous cell carcinoma, and skin tumors in the form of non-squamous cell carcinoma [23, 43–45].

8.6 Cytotoxic Chemotherapy

Due to the introduction of kinase inhibitors in differentiated thyroid cancers and the long-term disease stabilization effects they provide, the role of cytotoxic chemotherapy is quite limited. However, it is stated that it can be considered as salvage treatment in the selected patient group with high performance status. Today, it is recommended as an alternative option in patients progressing or intolerant to kinase inhibitor treatments in DTC [46]. Doxorubicin is the most investigated and widely used agent among chemotherapeutic drugs. Doxorubicin, the main treatment agent for anaplastic thyroid cancer, is the only chemotherapeutic agent approved by the FDA in DTCs with a partial response rate of 30–40% in phase 2 studies in RAI-resistant cases [46–50]. Studies on the use of doxorubicin in DTC have reported that it is more effective every 3 weeks than weekly use and is more useful especially in patients with lung metastasis and patients with good performance status [46, 51]. It is stated that combination treatments do not significantly increase efficacy [49].

Main side effects of doxorubicin include cardiotoxicity, myelosuppression, alopecia, secondary malignancy, amenorrhea, infertility, mucositis, abdominal pain, anorexia, and urinary

discoloration. Rare but serious side effects affecting treatment with doxorubicin are dose-dependent cardiotoxicity and are generally irreversible, and patients should be monitored by echocardiography at the beginning of and during treatment [52, 53].

8.7 Therapy in Medullary Thyroid Cancers

Medullary thyroid carcinoma is one of the rare thyroid malignancies and is also a member of the group of neuroendocrine tumors. It is the third most common thyroid malignancy and constitutes 3% of thyroid cancers. It develops from parafollicular C cells of the thyroid that produce calcitonin. It is divided into three groups as sporadic, hereditary, and familial. Calcitonin is a very important biomarker in diagnosing and determining recurrences and distant organ metastases. Carcinoembryonic antigen (CEA) is also used as a biomarker in MTC follow-up and evaluation of treatment response, although it is not specific. Its prognosis is worse than other subtypes because it causes distant organ metastases more frequently than papillary and follicular thyroid carcinomas. Approximately 13% of patients have distant organ metastases at the time of diagnosis. The mean overall survival in patients with metastatic MTC is 3 years [54–57].

The standard treatment for MTC is surgery. Thyroidectomy and prophylactic central lymph node dissection are performed surgically. Radiotherapy can be applied in incomplete surgery or surgical margin positivity. Cytotoxic chemotherapy has a limited role in recurrent and metastatic disease. With advances in molecular oncology, tyrosine kinase inhibitors (TKIs) come to the forefront in treatment. RET mutation is seen in sporadic MTC (30%–50%) as in hereditary MTC (95%) accompanying multiple endocrine neoplasia (MEN) syndromes [58]. RAS mutations occur in a group of patients (10%) without somatic RET mutations. MTC tumor cells and vascular endothelial cells overexpress VEGF receptors (VEGFR-1–VEGFR-2) [59]. In recent years, tyrosine kinase inhibitors (cabozantinib, vandetanib, sorafenib, sunitinib) targeting RET and VEGFR kinases have been used in many studies in patients with advanced MTC. Two TKIs (Vandetanib-2011, Cabozantinib-2012), whose phase 3 studies have been completed and demonstrated to prolong progression-free survival, have been approved by the FDA for use in patients with advanced MTC.

8.8 Multiple Kinase Inhibitors

There are two phase 2 studies and several retrospective studies involving a small number of MTC patients with sorafenib [60]. A meta-analysis of sorafenib studies evaluated 219 patients (159 patients with DTC, 52 patients with MTC, 8 patients with anaplastic thyroid carcinoma) and found partial response in 22% and progressive disease in only 6.5% of MTC patients. Hand-foot syndrome and diarrhea were observed in 70% of patients receiving sorafenib; fatigue, weight loss, and skin rash in 50%; hypertension in 36%; acute myocardial infarction in 3.8%; and severe hypokalemia in 2.5% (grades 3–4). Caution should be exercised with hypoparathyroidism after thyroidectomy in terms of secondary hypokalemia and other electrolyte imbalance. Cutaneous squamous cell carcinoma was observed in 6.8% of patients (6 patients in total, 4 patients with keratoacanthoma).

In the study, it was reported that 16% of the patients could not tolerate the drug due to toxicity and 56% had a dose reduction [61].

Thirty-five patients with advanced MTC were included in a phase 2 study with pazopanib in MTC. 35% of patients had a partial response lasting 29 weeks, 23% had a stable response, and 14% had progression, while 63% of the patients died during treatment. Tumor response rate was 14.3% and median PFS was 9.4 months. The most common side effects reported were fatigue, impaired liver function tests, hand-foot syndrome, diverticulitis, diarrhea, hypertension, and mood changes. Dose reduction is recommended for grade 3 and above side effects in patients using pazopanib. It should be retained in mind that there may be side effects such as proteinuria,

gastrointestinal perforation, grade 3–4 hemorrhage, and severe thrombosis due to the use of pazopanib [62].

Fifty-nine patients with surgically unresectable progressive MTC were treated with lenvatinib in a phase 2 study. While the best response rate was 35% in all partial response patients, stable disease was detected in the other 44%. Similar response rates were observed in patients with or without prior VEGFR-targeted therapy. Median progression-free survival and overall survival were reported as 9.0 months and 16.6 months, respectively. Side effects such as diarrhea, hypertension, and decreased appetite were observed [63].

The efficacy of vandetanib in MTC has been investigated in phase 2 and phase 3 studies. In the phase 3 prospective, multicenter ZETA study, 331 locally advanced MTC patients with metastatic or progression were included, and patients were randomized 2:1 to vandetanib or placebo arms. In conclusion, vandetanib demonstrated superiority over placebo in PFS (30.5 vs. 19.3 months), with no overall difference in survival. However, patients with CEA doubling times greater than 24 months were unlikely to benefit from treatment, while the presence of somatic RET M918T mutation was predicted to increase progression-free survival [29] (Table 8.1). With this study, vandetanib received FDA approval in MTC. Diarrhea, fatigue, skin rash, folliculitis, photosensitivity, hypertension, and QT prolongation at grade 1–2 level have been reported as the side effect profile of vandetanib. 12% of patients in the vandetanib arm were unable to continue treatment due to toxicity, and the dose was reduced in 35% [29]. In planning treatment with vandetanib, dose adjustment according to renal function and routine blood tests, especially ECG, sodium, potassium, calcium, and magnesium monitoring, are recommended at 2, 4, 8, and 12 weeks after initiation of treatment. This interval can be extended if there is no problem. In addition, close monitoring of diarrhea is recommended [37].

Another multiple kinase inhibitor investigated in MTC is cabozantinib. In the phase 3, randomized, prospective, multicenter EXAM study with which cabozantinib received FDA approval, 330 advanced stage MTC patients were randomized 2:1 to cabozantinib or placebo arms. In conclusion, cabozantinib demonstrated superiority over placebo in PFS (11.2 vs. 4.0 months) (Table 8.1). Diarrhea, malaise, palmoplantar erythrodysesthesia, and gastrointestinal fistula were observed in the side effect profile. It was reported that 16% of patients could not continue treatment due to toxicities and 79% had a dose reduction [30]. In the subgroup analyses of this study, PFS was found to be significantly superior to placebo, especially in patients with M918T mutation (61 vs. 17 weeks) and RET mutation (47 vs. 8 weeks). Electrolyte, calcium, and TSH monitoring is also required at certain intervals in cabozantinib use [38].

8.9 Cytotoxic Chemotherapy

With the widespread use of targeted therapies in MTC, the use of cytotoxic drugs has been seriously reduced. Among chemotherapeutic drugs, single-agent doxorubicin, platinum-doxorubicin combination, 5-FU-dacarbazine, and cyclophosphamide-vincristine-dacarbazine combinations are the most commonly studied ones. Doxorubicin is FDA approved for all histological types of thyroid cancers, including MTC. However, less than 30% of patients achieved an objective response and the response time was very short. There are positive results with the use of capecitabine at the case level in resistant metastatic MTC cases [64]. After positive results in a prospective phase 2 CAPTEM study with the concomitant use of temozolomide and capecitabine in well-differentiated neuroendocrine tumors, there are cases in which partial response is achieved with the use of these two agents in metastatic MTC patients [65].

Studies with radioimmunotherapy and bispecific monoclonal antibody and iodine-labeled bivalent hapten use in patients with advanced MTC have shown promising results. However, there are no prospective, randomized clinical trials with other treatments or with comparison to placebo. Time is needed for the use of these treatments [66, 67].

8.10 Side Effect Management in Drugs Used in the Treatment of Thyroid Cancer

The severity of toxicities observed during treatment is usually graded according to assessment methods such as the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CCTCAE) [68]. Approaches such as discontinuation, postponement, dose reduction, as well as specific approaches specific to toxicity are made depending on the type and degree of toxicity observed.

8.11 Management of Common Side Effects in Chemotherapeutics

Although the role of cytotoxic chemotherapy gradually decreases with longer-term responses with kinase inhibitors in differentiated thyroid cancers, it is stated that it can be considered as salvage treatment in patients with good performance status. Doxorubicin, the only chemotherapeutic agent approved by the FDA with a partial response rate of 30–40% in phase 2 studies, is used in this group of patients [46–50].

The main side effects of doxorubicin include cardiotoxicity, myelosuppression, alopecia, secondary malignancy, amenorrhea, infertility, mucositis, abdominal pain, anorexia, and urinary discoloration. Rare but severe side effects affecting treatment with doxorubicin are dose-dependent cardiotoxicity and are generally irreversible (type 1 cardiotoxicity). Although the guidelines do not yet recommend routine basal echocardiography (ECHO) at the beginning of the treatment, most experts believe that basal ECHO should be performed in order to facilitate the detection of newly developing adverse events during the treatment process. In addition, echocardiography should be monitored at regular intervals during treatment [52, 53]. Anthracyclines should be avoided in patients with low ejection fraction (EF) along with heart failure or left ventricular EF (LVEF) ≤40% on the basal ECHO. In asymptomatic patients with 40–50% basal LVEF and without heart failure, it is recommended that the treatment decision be made according to the profit/loss ratio. If anthracycline is to be used, it is recommended to provide blood pressure control in patients with hypertension; to initiate β blockers (recommended carvedilol, nebivolol) with ACE inhibitors/ARB before starting anthracyclines, for close ECHO monitoring; and to discontinue anthracycline if there is a 10% decrease compared to basal LVEF. Blood pressure control and ECHO monitoring are sufficient in patients with LVEF ≥50% and without heart failure [69]. For patients on doxorubicin, it is generally recommended to limit the lifetime dose to 450–550 mg/m^2. Some experts start dexrazoxane when lifetime anthracycline doses exceed 300 mg/m^2. Dexrazoxane is the only drug approved by the FDA to prevent anthracycline-mediated cardiotoxicity.

Another important and frequent side effect of doxorubicin is myelosuppression. It may be accompanied by leukopenia (≤75%; often develops within 10–14 days; recovery: on day 21), neutropenia (≤75%; often develops within 10–14 days; recovery: on day 21), anemia, and thrombocytopenia. Close monitoring is required. Acceleration of the exit time from neutropenia with granulocyte colony-stimulating agents (G-CSF) such as filgrastim according to the degree of neutropenia, close follow-up in terms of neutropenic fever, hospitalization if necessary, antibiotherapy, and platelet and erythrocyte transfusion replacements should be performed as needed. G-CSF prophylaxis should be performed, and dose modification should be performed according to the degree of toxicity in recurrent courses (Table 8.2) [52, 53, 68].

Doxorubicin may cause discoloration in the urine. Patients should be informed about this in order to prevent unnecessary fears. Another point to be considered in doxorubicin use is extravasation because it is a vesicant agent. It may result in severe local tissue damage and necrosis, which may require extensive excision of the affected area and skin graft. If extravasa-

Table 8.2 Hematological toxicity NCI-CTCAE v5.0 [68]

Blood element	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	Between LLN and 1500/microL	1000–1500/microL	500–1000/microL	<500/microL	
Platelets	Between LLN and 75,000/microL	50,000–75,000/microL	25,000–50,000/microL	<25,000/microL	
Hemoglobin	Between LLN and 10.0 g/dL	8.0–10.0 g/dL	<8.0 g/dL	Life-threatening consequences; requiring urgent intervention	Death
Febrile neutropenia			Absolute number of neutrophils <1000 microL and presence of body temperature > 38.30 °C at a single measurement or ≥ 38.00 °C lasting longer than 1 h	Life-threatening consequences; requiring urgent intervention	Death

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; LLN, lower limit of normal; Cell/microL, cell/mm^3 or cell × 10^9/L

tion is suspected, the infusion should be terminated immediately and ice applied to the affected area. It is very important to ensure and control the placement of appropriate needles or catheters before and during infusion to avoid extravasation [52, 53].

8.12 Management of Common Side Effects in Tyrosine Kinase Inhibitors

Thyroid kinase inhibitors, which are more commonly used today in metastatic differentiated thyroid cancers, have group side effects and agent-specific side effects. First of all, comorbidities and risk profile should be well evaluated with detailed anamnesis before treatment. Stabilization of comorbidities, evaluation of the drugs to be taken concurrently in terms of interaction, and patient education on the side effects of the disease and the treatment agent are very important. The severity of toxicities is usually graded according to assessment methods such as the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC) [3, 5, 70–72].

8.13 Skin Toxicity Management

Several skin side effects have been reported with sorafenib, vandetanib, and lenvatinib. Hand-foot syndrome (HFSR) (37% with sorafenib, 6% with pazopanib) and rash (41% with vandetanib) are most common, followed by squamoproliferative lesions. More rarely, seborrheic dermatitis, subungual splinter hemorrhages, erythema multiforme, and eruptive melanocytic lesions are observed [73, 74].

There is no evidence yet in randomized studies that determine the best management strategy for HFSR [75]. However, expert opinions are available from an international consensus group [76]. The most important of these recommendations is the removal of existing hyperkeratotic areas and calluses using appropriately sterilized tools, avoiding exposure of hands and feet to hot water, and avoiding excessive friction on the skin in daily activities. It should be emphasized that severe exercises that exert excessive stress especially on the palms and/or soles of the feet should be avoided, especially during the first treatment period.

It should be recommended to wear padded soles throughout treatment to reduce foot pres-

Table 8.3 Grading in hand-foot syndrome [5, 68, 76, 77]

Grade	Symptoms
Grade 1	Numbness, dysesthesia, paresthesia, tingling, painless edema, erythema, and restlessness in hands and feet, not affecting daily activity
Grade 2	Painful erythema, edema, and restlessness in hands and feet, affecting daily activity
Grade 3	Peeling, cracking, erosion, severe pain, and restlessness in hands and feet, unable to perform daily activities

sure. Patients should be warned to wear thick cotton gloves or socks to prevent injury and to keep palms and soles dry [76, 77].

For patients who develop HFSR while taking sorafenib, the following management strategies are recommended by this group [70, 76] (Table 8.3):

- No dose adjustment is required for mild (grade 1) symptoms. Hot water should be avoided and the use of topical softeners should be encouraged. Keratolytics such as topical urea (20–40%) or salicylic acid (6–10%) may be recommended.
- Treatment for grade 2 HFSR should continue as in grade 1 HFSR, but with topical corticosteroids (clobetasol 0.05% ointment) added to erythematous areas twice daily. Topical analgesics such as 2% lidocaine may be sufficient. If necessary, the dose of sorafenib may be temporarily reduced by up to 50% for at least 7 days until HFSR grade 0 or 1 is reached, and then the full dose is resumed.
- For grade 3 HFSR, treatment according to grade 1 or 2 HFSR should be provided upon temporary discontinuation of the drug for at least 7 days until grade 1 or 2. Treatment should continue up to 50% of the dose. Dose increase can be attempted if the side effect is not repeated [76, 77].

Sorafenib is also associated with cutaneous squamoproliferative lesions, including keratoacanthomas (KA) and squamous cell carcinomas (SCC) [78]. Twenty-two squamoproliferative lesions were seen in 13 patients within nine months of initiation in a series after starting sorafenib. One was reported as classic invasive SCC, 5 as KA-like SCC, and 16 as classic KA [78]. In a retrospective study of 131 patients receiving sorafenib for metastatic renal cell carcinoma, 7 were diagnosed with SCC and 2 were diagnosed with KA [79]. Squamoproliferative lesions that develop during treatment with sorafenib should be treated in a similar manner to lesions that develop in patients who have not taken any drug (usually with complete surgical excision). There is no definite evidence to continue against discontinuation of sorafenib in patients who develop SCC or KA during treatment. Close clinical follow-up is required during treatment [70].

In clinical trials, skin reactions with vemurafenib were also common in metastatic/unresectable thyroid cancer, and the incidence of serious adverse effects was reported to be 26.9% for squamous cell carcinoma and 7.6% for keratoacanthoma [39]. Vemurafenib-related phototoxic reactions are thought to be associated with UVA radiation and can be prevented by the use of broad-spectrum sunscreens [80].

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving vemurafenib [81–83].

Among patients receiving dabrafenib, verrucal keratotic lesions with low to moderate epidermal dysplasia were reported up to 66%, and keratoacanthomas or well-differentiated cutaneous SCC were reported between 6% and 26% in melanoma use [84–86]. These side effects have not been reported with dabrafenib in thyroid cancer (in combination with trametinib). The risk of developing skin SCC with BRAF inhibitors increases up to 30 percent in patients older than 60 years of age [87]. Most lesions develop during the first 3 months of treatment and may occur in sun-protected areas. Cutaneous SCC developing in patients treated with these agents is treated with surgical excision, and patients can generally continue treatment without dose adjustment [88]. Trametinib and cobimetinib are mitogen-activated protein kinase (MAPK) kinase enzyme (MEK1 and MEK2) inhibitors [89, 90] approved for the treatment of metastatic melanoma, a BRAF V600E or V600K mutation, in combination with dabrafenib and vemurafenib. Trametinib

was also approved in combination with dabrafenib in unresectable-metastatic BRAF mutant anaplastic thyroid cancer [91]. Data from combination therapy studies with dabrafenib+trametinib for advanced melanoma indicate that combination therapy is associated with a marked cutaneous toxicity reduction compared to vemurafenib or dabrafenib alone [86, 92]. Patients should be managed with close dermatological follow-up during these treatments [70].

8.14 Thyroid Dysfunction Management

Thyroid dysfunction is seen more frequently in patients receiving sunitinib for metastatic RCC but also in patients treated with sorafenib [71, 93]. In the analysis of thyroid function in RCC data, hypothyroidism was observed in 7 (18%) of 39 patients and hyperthyroidism in 1 patient [94]. Two of the hypothyroidism patients (5% of the total) were symptomatic and required thyroid replacement therapy [95].

Hypothyroidism has also been reported among pazopanib-treated patients and therefore appears to be a class effect of these agents [95–97]. Regular monitoring of TSH levels at baseline and during treatment is recommended in patients treated with antiangiogenic TKIs due to the high frequency of hypothyroidism, initial evaluation of thyroid function tests, and subsequent and every 4–12 weeks monitoring in symptomatic patients. Symptomatic patients with hypothyroidism should receive thyroid hormone support. No discontinuation of the agent causing toxicity and no dose modification is usually necessary [3, 5, 71].

8.15 Gastrointestinal Toxicities Side Effect Management

Diarrhea, nausea, and vomiting have been observed in all antiangiogenic TKIs and are generally mild. In clinical trials, diarrhea was reported in 30–79% (highest with vandetanib) of all grades and severe diarrhea (grade 3/4) in 3–17% [26, 98–104]. In addition to being a VEGFR inhibitor, vandetanib is also an epidermal growth factor receptor (EGFR) inhibitor. Therefore, the higher incidence of diarrhea associated with this agent is attributed to this [26, 101].

Nausea (all grades) was reported in 23–58% of patients treated with antiangiogenic TKIs in clinical trials. Sunitinib-, lenvatinib-, and cabozantinib-treated patients had the highest rates. Vomiting of any grade was reported in 10–48% of patients treated with pazopanib and sorafenib with the lowest and highest rates with sunitinib, lenvatinib, and cabozantinib [17, 105–107].

Nausea and vomiting are rarely severe and are usually controlled with oral antiemetics. However, caution should be exercised in combining vandetanib, lenvatinib, sunitinib, and sorafenib with serotonin antagonists such as granisetron and ondansetron due to QTc interval prolongation and torsades de pointes potential (especially with BRAF inhibitors) [71].

Infectious agents should be treated in accordance with their degree after being excluded in addition to performing fluid-electrolyte replacement in case of diarrhea. It is generally sufficient to prevent food and supplements that increase symptomatic management and gastrointestinal motility with an oral antidiarrheal agent such as loperamide in the treatment of grade 1 or 2 diarrhea. Treatment should be discontinued for grade 3 or 4 diarrhea, and dose modifications may be required to control diarrhea if the drug is continued (Table 8.4) [68, 71, 108].

8.16 Hepatotoxicity Management

Serious and occasionally fatal hepatotoxicity has been observed in clinical studies with all VEGFR TKIs. The risk of elevated serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and bilirubin during treatment with VEGFR TKIs was discussed in a meta-analysis of 18,282 patients from 52 randomized controlled trials [109]. The incidence of hepatic failure in VEGFR TKIs was found to be

Table 8.4 Diarrhea NCI-CTCAE v5.0 [68]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	<4 increase in daily defecation relative to baseline	4–6 increase in daily defecation relative to baseline	≥7 increase in daily defecation relative to baseline; requiring hospitalization	Life-threatening results; requiring urgent intervention	Death
	Moderate increase in stool coming from ostomy relative to baseline	Moderate increase in stool coming from ostomy relative to baseline	Severe increase in stool coming from ostomy relative to baseline; limitation of self-care		

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events

0.8% in general. Relative risks (RRs) for elevations in all grades in ALT, AST, ALP, and bilirubin in patients receiving VEGFR TKI were 1.57 ($p < 0.001$), 1.57 ($p < 0.001$), 1.20 ($p < 0.001$), and 1.55 ($p < 0.001$), respectively, compared to patients not treated with VEGFR TKI. While there was a statistically significant increase in the relative risk of ALT and AST for high-grade elevations, the risk increase in ALP and bilirubin elevation was not statistically significant [109].

Sorafenib-induced hepatitis can be accompanied by hepatocellular hepatic injury, which is a significant increase in transaminases that can result in hepatic failure and death. There may also be increases in bilirubin and INR. It is recommended to exclude the causes such as viral hepatitis or progressive malignancy first and to discontinue the drug considering drug-related hepatotoxicity in case of a significant increase in transaminases (Table 8.5) [5, 68, 71, 109].

Polymorphisms in the enzyme diphosphoglucuronosyltransferase 1A1 (UGT 1A1), which causes Gilbert syndrome (UGT1A1 * 28 alleles), are thought to be associated with pazopanib- and sorafenib-induced hyperbilirubinemia. Isolated hyperbilirubinemia in these patients may represent a benign manifestation of Gilbert syndrome, in which case continuation of treatment is recommended [110–112].

In general, liver function tests (LFTs) should be periodically evaluated at baseline and during treatment in patients treated with any of these agents. Evaluation of liver function tests is recommended, especially for patients treated with pazopanib, at baseline and at weeks 3, 5, 7, 9, 12, and 16 and periodically thereafter, and interruption or complete discontinuation of treatment is recommended in patients with bilirubin levels 3 times and above [71, 113, 114].

8.17 Management of Cardiovascular Side Effects

The main cardiovascular side effects are hypertension, arteriovenous thromboembolisms, LV dysfunction, and QT prolongation, which are seen as group side effects in this group of drugs [72].

Hypertension: Among VEGF receptor tyrosine kinase inhibitors, it is not clear whether any agent causes hypertension more frequently. In a meta-analysis, pazopanib was reported to cause hypertension in all grades at a higher rate than sorafenib and sunitinib (36%, 23%, and 22%, respectively), while high-grade hypertension rates were reported to be similar (6.5%, 5.7%, and 6.8%, respectively) [36]. On the other hand, both all-grade (68%) and severe (42%) hypertension rates were found to be higher with lenvatinib [17]. It has been reported in some studies that there is a relationship between antiangiogenic TKIs and antitumor efficacy during treatment and the development of systolic or diastolic hypertension [115–117].

Active control of hypertension in the use of these agents allows patients to tolerate effective treatment doses for a long time [118]. Recommendations in this regard include risk assessment for potential cardiovascular complications, identification and treatment of existing

Table 8.5 Hepatobiliary toxicity NCI-CTCAE v5.0 [68]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ALP increase	If baseline is normal, ULN to 2.5 × ULN	If baseline is normal, 2.5–5 × ULN	If baseline is normal, 5–20 × ULN	If baseline is normal, >20 × ULN	
	If baseline is abnormal, 2–2.5 × baseline	If baseline is abnormal, 2.5–5 × baseline	If baseline is abnormal, 5–20 × baseline	If baseline is abnormal, >20 × baseline	
ALT increase	If baseline is normal, ULN to 3 × ULN If baseline is abnormal, 1.5–3 × baseline	If baseline is normal, 3–5 x ULN If baseline is abnormal, 3–5 × baseline	If baseline is normal, 5–20 × ULN If baseline is abnormal, 5–20 × baseline	If baseline is normal, >20 × ULN If baseline is abnormal, >20 × baseline	
AST increase	If baseline is normal, ULN to 3 × ULN; if baseline is abnormal, 1.5–3 × baseline	If baseline is normal, 3–5 × ULN; if baseline is abnormal, 3–5 × baseline	If baseline is normal, 5–20 × ULN; if baseline is abnormal, 5–20 × baseline	If baseline is normal, >20 × ULN; if baseline is abnormal, >20 × baseline	
Serum bilirubin increase	If baseline is normal, ULN to 1.5 × ULN	If baseline is normal, 1.5–3 × ULN	If baseline is normal, 3–10 × ULN	If baseline is normal, >10 × ULN	
	If baseline is abnormal, 1–1.5 × baseline	If baseline is abnormal, 1.5–3 × baseline	If baseline is abnormal, 3–10 × baseline	If baseline is abnormal, >10 × baseline	
GGT increase	If baseline is normal, ULN to 2.5 × ULN	If baseline is normal, 2.5–5 × ULN	If baseline is normal, 5–20 × ULN	If baseline is normal, >20 × ULN	
	If baseline is abnormal, 2–2.5 × baseline	If baseline is abnormal, 2.5–5 × baseline	If baseline is abnormal, 5–20 × baseline	If baseline is abnormal, >20 × baseline	
Liver failure			Asterixis, moderate encephalopathy, liver injury due to the drug, limitation of self-care	Life-threatening outcomes, moderate-severe encephalopathy, coma	Death
Portal hypertension		Decrease in portal vein flow	Reverse/retrograde portal vein flow with varicose and/or acid	Life-threatening outcomes, requiring urgent intervention	Death

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ULN, upper limit of normal; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase

hypertension before using these agents, active monitoring of blood pressure during treatment, more frequent measurements in the first few weeks of treatment, and lower blood pressure in those with pre-existing cardiovascular risk factors such as diabetes or chronic kidney disease [5, 72].

Patients who develop hypertension during treatment (defined as hypertension; blood pressure ≥ 140/90 mmHg, or 20 mmHg increase in diastolic blood pressure compared to basal) should be treated with antihypertensives. Agent selection should be based on the severity of hypertension and the urgency of blood pressure control. It is very important to avoid drugs with verapamil or diltiazem that inhibit it with agents that undergo partial metabolism with cytochrome p450 such as sunitinib/sorafenib even though it is not an optimal antihypertensive agent recommendation [72, 119].

Arterial/Venous Thromboembolism: Venous thromboembolism (VTE) is more common in anti-VEGF monoclonal antibodies and less common in anti-VEGF TKIs. In a systematic meta-analysis of 10 studies involving 10,255 patients (87% diagnosed with RCC) treated with sunitinib or sorafenib, the risk of arterial embolism was 1.4%, with a threefold increase in RR compared to controls [120]. Similarly, arterial thromboembolisms (ATE) were observed in 3% of pazopanib-treated patients in the placebo-controlled randomized pazopanib study in advanced RCC [121]. In a placebo-controlled lenvatinib study, ATEs occurred in 5% of the treated group and 2% of the placebo-treated group [122].

There is no adequate information to recommend the use of routine anticoagulation to prevent VTE in patients receiving or starting treatment with antiangiogenic TKIs. The NCCN Oncology Clinical Practice Guidelines recommend aspirin or anticoagulant prophylaxis based on the presence or absence of risk factors for VTE. NCCN has not defined the use of angiogenesis inhibitors for VTE in cancer patients as a risk factor, but expert opinions support prophylaxis with ponatinib, which is used in chronic myeloid leukemia due to the high risk of arterial and venous thromboembolism [3, 5, 72].

Both prevention and rapid management of arterial thromboembolic events are important. Cardiovascular risk factors (hypertension, hyperlipidemia, and diabetes) should be predetermined and aggressively managed prior to initiating treatment with antiangiogenic TKIs. Baseline blood pressure should be monitored, and the drug should preferably not be administered within 6 to 12 months in patients with severe cardiovascular events. Low-dose aspirin prophylaxis is appropriate in patients with ATE or other high-risk patients [123, 124]. Antiangiogenic treatment should be discontinued and ATE should be managed in other patients who develop ATE while receiving antiangiogenic TKI.

Left Ventricular Dysfunction/Myocardial Ischemia: Left ventricular (LV) function may decrease in patients treated with any of the VEGF-targeted treatments. A meta-analysis of 21 randomized studies using various VEGFR TKIs evaluated 10,647 patients. In the group without TKI, 37 of 4895 patients and 138 of 5752 patients receiving VEGFR TKI developed heart failure of any grade (0.75% versus 2.39%). In the group without TKI versus TKI, the RR of high-grade heart failure in all grades was 2.69 ($p < 0.001$; 95% CI 1.86–3.87) and 1.65 ($p = 0.227$, 95% CI 0.73–3.70), respectively [125]. In a placebo-controlled study in patients with advanced thyroid cancer, 7% cardiac dysfunction was reported in the lenvatinib arm versus 2% in the placebo arm. In most of the cases, ejection fraction was found to decrease on echocardiography [122].

It is recommended that LVEF of the patients be screened with ECHO or MUGA and basic evaluation with ECG [72]. Some sources have suggested that patients receiving these drugs should be treated as "stage A" heart failure patients (but without structural heart disease or symptoms, i.e., at risk of heart failure) [126]. The American Heart Association guideline states that it may be reasonable to consider those who receive potentially cardiotoxic agents for LV dysfunction as stage A heart failure in 2013 [127]. Monitoring of LVEF is generally recommended in patients treated with VEGFR TKI. US prescribing information for sunitinib recommends dose reduction or discontinuation in patients with clinical signs of cardiac failure and no clinical evidence of cardiac failure, but with an ejection fraction <50% and/or > 20% below baseline [128].

QT Prolongation/Cardiac Arrhythmia: Many drugs delay cardiac repolarization. This is an effect reflected on ECG in the QTc interval. Although a long QTc interval is not immediately harmful, it can be associated with potentially fatal cardiac arrhythmias. Triggered ventricular tachyarrhythmia (VT) is the most typical and most common, also known as torsades de pointes. It is often transient but can be fatal if it persists, causing impaired cerebral circulatory symptoms or ventricular fibrillation. The risk of other VEGFR TKIs, including sorafenib and pazopanib, is lower while vandetanib and sunitinib, inhibitors of VEGFR tyrosine kinase, are more

Table 8.6 NCI CTCAE v5.0 ECG QTc interval prolongation grading [5, 68, 72]

Adverse effect	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Prolonged	QTc 450–480	QTc 481–500	QTc ≥501 ms;	Torsades de	Death
QTc interval on ECG	ms	ms	>60 ms change relative to baseline	pointes; polymorphic VT; serious arrhythmia symptoms	

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QTc, corrected QT interval

associated with QTc prolongation [129, 130]. In addition, QTc prolongation and cardiomyopathy can also be seen in BRAF inhibitors [5, 72].

Specific guidelines for the evaluation and monitoring of the QTc interval and recommendations for managing the drug by toxicity grade are available, especially for vandetanib and lenvatinib (Table 8.6). Guidelines for other antiangiogenic TKIs are not yet available. Concomitant drugs should be carefully reviewed, especially drugs that increase QTc should be evaluated for any patient receiving treatment with antiangiogenic TKI. Those with a history of QT interval prolongation, a history of arrhythmia, and preexisting heart disease, bradycardia, or electrolyte disorder may be more prone to develop QTc prolongation. Dose reduction for TKI may be required if antiangiogenic TKIs are to be taken concomitantly with strong CYP3A4 inhibitors that may increase plasma concentrations.

Patients who develop arrhythmia should be evaluated and treated separately with cardiological consultation according to the definition of arrhythmia [5, 16, 25, 72].

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