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Targeted Therapy in Management of Advanced Follicular Thyroid Carcinoma

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ABSTRACT

Follicular thyroid carcinoma (FTC) is the second most common malignancy involving the thyroid glands. Early stages of FTC are managed with total thyroidectomy followed by 131I ablation and external beam radiation therapy. Targeted therapy with tyrosine kinase inhibitors (TKIs) is an essential therapeutic option for the management of advanced cases of radioactive iodine refractory. This review will investigate the clinical data for the therapeutic use of targeted therapy in advanced FTC and compare the efficacy of different targeted therapy used in managing the patients.

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Introduction

Follicular thyroid carcinoma (FTC) is the second most common malignancy involving the thyroid glands and accounts for 10-20% of differentiated thyroid carcinomas (DTC). The relative rate of FTC tends to be higher which account up to 40% of all cases of DTC in areas which are iodine deficient [1]. FTC is a malignant epithelial tumor which has a capsule around the well-differentiated follicular cells and involve vascular invasion. FTC is more commonly metastasize to distant organs through hematogenous dissemination due to its tendency to invade blood vessels [2].

Mutations in the proto-oncogenes of RAS family (*H-RAS, N-RAS, K-RAS4A and K-RAS4B*) are associated with AKT phosphorylation which results in activation of PI3K/AKT pathway and promote cell growth and proliferation. Ras mutations are prevalent in FTC [3]. Somatic mutation profiling performed by Swierniak et al, suggested that FTC mutations were found in FOXO4 (transcription suppressor), CHEK2 (protein kinases), NCOA2 (epigenetic modifier), MITF (transcription factor) and KTN1 genes (transmembrane kinesin receptor) [4]. PAX-8 genes are necessary for normal thyroid development while PPARγ is a nuclear receptor for terminal differentiation of cells. Gene fusion of PAX8/ PPARγ is one of the most common genetic events in FTC [5].

FTC is usually found in individuals without any symptoms and the diagnosis is made accidentally after intrathyroid nodules are discovered on routine imaging [6]. Fine needle aspiration cytology cannot differentiate between FTC and follicular thyroid adenoma due to the similarities of angiogenesis and biological behavior. Frozen section of a thyroid tumor during surgery can obtain tissue and more cells for definitive diagnosis of FTC [7]. The diagnostic accuracy of frozen section is around 97.8% with multiple frozen sections taken from the tumor [8].

Patient age is an important prognostic factor and FTC is commonly found in older patient, the 10-year survival rate is 98% to 99% in patients younger than 45 years while 20% to 25% among patient older than 70 years. Histologic grade and tumor size are also important factors for prognosis.

Targeted Therapy

FTC is usually treated by total thyroidectomy followed by iodine (^{131}I) ablation and treated with thyrotropine hormone-suppressive levothyroxine which generally have a good outcome. Targeted therapy with tyrosine kinase inhibitors (TKIs) is an essential therapeutic option for the management of advanced cases of radioiodine (RAI) refractory DTC which includes FTC [9]. Abnormal expression of protein tyrosine kinase causes tumor invasion, metastasis and tumor angiogenesis due to cell proliferation disorders. TKIs inhibit tyrosine kinase phosphorylation by competing with ATP for the ATP binding site of PTK and eventually inhibiting cancer cell proliferation [10].

Sorafenib

Sorafenib is a multiple kinase inhibitor approved for treatment of advanced and progressive differentiated thyroid carcinoma (DTC) which include FTC which has a potential of inhibiting tumor growth and downregulating mechanisms that protect tumors from apoptosis. Sorafenib is given 400 mg orally twice per day and the drug is absorbed at a moderate rate where maximum concentration is observed at 2.5 – 12.5 hours after administration [11].

Several clinical trials and observational studies suggest that sorafenib is efficient in treating advanced thyroid carcinoma. A phase II clinical trial by Gupta-Abramson et al. showed a partial response in 23.3% of the patients and 53.3% of the patients had

a stable disease with a clinical benefit rate of 77%. 95% of the patients showed mean decrease of 70% in the thyroglobulin levels [12].

A phase II prospective clinical trial by Schneider et al. demonstrated that sorafenib has antitumor activity in progressive metastatic or locally advanced RAI-refractory DTC which can be considered treatment of choice. 31 patients in the study received sorafenib 400 mg orally twice and 26 patients were eligible for efficacy analysis. The mean duration of the treatment is 15 months. The median progressive free survival (PFS) is 18 months and median overall survival (OS) is 34.5 months. The most common adverse effects associated with sorafenib are hand foot syndrome, weight loss, diarrhea and rash which are commonly Grade 1 or Grade 2 [13].

A double- blinded, randomized, phase III trial, DECISION demonstrated the efficacy of sorafenib as a new treatment option for patients with progression RAI-refractory DTC. The trial is placebo-controlled where randomized patients is assigned to either placebo or starting dose of sorafenib 400 mg orally twice-daily. 417 patients from 77 centers in 18 countries with locally advanced or metastatic RAI-refractory DTC were randomized into 1:1 into either sorafenib or matching placebo where both given orally twice. The patients on placebo who progressed were switched to the open-label sorafenib. 164 of 210 patients who initially were on placebo switched to open-label sorafenib [14].

The median PFS for patients on sorafenib was 10.8 months compared to 5.8 months for patients on placebo which shows significant improvement. Besides that, patients who were on sorafenib therapy shows a 41% reduction in the risk of progression or death. RAS mutation frequency was highest in poorly differentiated histology and FTC. RAS mutations seemed to associate with prognosis but the mutation status was not predictive of sorafenib benefit for PFS [14].

Patients remained on sorafenib for a median of 10.6 months and 6.5 months for patients on placebo in the DECISION study. Adverse effects occurred in 98.6% patients receiving sorafenib and the adverse effects tended to occur early in the treatment. 66.2%, 64.3% and 18.8% of the patients required dose interruptions, reductions or withdrawals respectively because of the significant side effects. Side effects such as hand-foot skin reaction, diarrhea, alopecia, rash, fatigue, weight loss and hypertension occurred more than 40% of patients who were on sorafenib therapy. Serious adverse effects occurred in 37.2% of the patients which include secondary malignancy (squamous cell carcinomas of the skin, acute myeloid leukemia and bladder cancer), dyspnea and pleural effusion.

Lenvatinib

Lenvatinib is a multiple kinase inhibitor that inhibit tyrosine kinases that associated to pathogenic angiogenesis, tumor growth and cancer progression and inhibits the kinase activities of vascular endothelial growth factor [15].

A phase III, randomized, double-blind trial, SELECT by Schlumberger et al. studied the efficacy of lenvatinib in patients with progressive thyroid cancer that was refractory to ^{131}I. The trial involves 261 patients and they were randomly assigned to receive oral lenvatinib at a dose of 24 mg once daily or placebo in 28-day cycles in 2:1 ratio. 109 of the 114 patients who were initially assigned to placebo elected to receive open-label lenvatinib [16].

The median PFS was 18.3 months for lenvatinib arm and 3.6 months for placebo arm. The patient's RAS mutation status has no significant difference on the PFS associated with lenvatinib or placebo. The patients received lenvatib for a mean duration of 13.8 months and 3.9 months among patients who received placebo. 14.2% of the patients discontinued the treatment most commonly due to the adverse effects of fatigue and hypertension. More than 40% of the patients on lenvatinib experience the side effects of hypertension, diarrhea, fatigue, decreased appetite, decreased weight and nausea.

Furthermore, a phase II study by Takahashi et al. assessed the safety and efficacy of lenvatinib in advanced thyroid cancer. The study involved 51 patients where 25 patients had RAI-refractory DTC was given oral lenvatinib at a dose of 24 mg once day until disease progression or occurrence of unacceptable toxicity. The median PFS of patients with RAI-refractory DTC receiving lenvatinib was 25.8 months and the median OS was 31.8 months. The disease control rate was 100% and the clinical benefit rate was 84%. Some degree of tumor shrinkage was noted in most of the patients after started with treatment. The most common side effects associated with the treatment were hypertension, palmar-plantar erythrodysesthesia, decreased appetite, fatigue, proteinuria, stomatitis and diarrhea. 100% of the RAI-refractory DTC patients required lenvatinib-dose reduction due to treatment-emergent adverse effects [17].

Comparison of Sorafenib and Lenvatinib

Both randomized control trials (RCTs) in sorafenib (DECISION) and lenvatinib (SELECT) showed significant improvements of the secondary endpoints such as PFS and OS. However, RCTs showed that the median PFS for lenvatinib is longer than sorafenib (18.3 months and 10.8 months). Both RCTs of sorafenib and lenvatinib suggested that Ras mutation status of the patient has no significant impact on the median PFS of the patients on either sorafenib or lenvatinib therapy [14, 17].

Sorafenib targets C-RAF, B-RAF, VEGF receptor-1, -2, -3, PDGF receptor-β, RET, c-kit, and Flt-3 while sorafenib, a tyrosine kinase inhibitor that inhibits VEGFRs 1, 2, and 3, PDGFR β, Raf-1, RET, and BRAF. Both RCTs of sorafenib and lenvatinib showed that patients on therapy has high percentage of adverse effects which were 98.6% and 97.3% respectively. The most common adverse effects associated with sorafenib were hand-foot skin reaction, diarrhea and alopecia while the adverse effects reported in lenvatinib were hypertension, diarrhea, fatigue.

Both sarafenib and lenvatinib are effective TKIs in managing advanced FTC based on the data of RCTs. Lenvatinib may show a better prognostic than sorafenib based on the median PFS of the patients reported in the DECISION and SELECT trial. However, there is a need for additional clinical trials to compare the efficacy of sorafenib and lenvatinib. Most of the studies involved the patients of RAI-refractory DTC which includes both FTC and papillary thyroid carcinoma. Therefore, further studies need to address the efficacy of targeted therapy in patient cohort consists of FTC patients only.

Conclusion

Advanced and RAI-refractory FTC previously have limited treatment options but advancement of targeted therapies improves the survival and outcome of the patients. With further understanding of mechanism of targeted and targeted therapies, development of new drugs can be explored to reduce the adverse effects experienced by the patients.

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