TARGETED THERAPY
FOR LOCALLY ADVANCED UNRESECTABLE OR
METASTATIC MEDULLARY THYROID CARCINOMA

Effective Date: November 2012

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Carcinoma of the thyroid gland is the eighth most common type of cancer among Canadians; an estimated 5,600 Canadians (460 Albertans) were diagnosed with thyroid carcinoma in 2012. Among males and females diagnosed with cancer in 2012, the proportion diagnosed with thyroid cancer was 1.3% and 4.9%, respectively. Although thyroid cancer is relatively uncommon, the incidence rate of thyroid cancer is the most rapidly increasing of all cancers (6.8% per year in males since 1998 and 6.9% per year in females since 2002). 

Thyroid cancer can be classified into three subtypes: papillary or follicular, medullary, and anaplastic. Papillary or follicular are differentiated tumours and have a good prognosis, while medullary and anaplastic have a poor prognosis, due to the high rate of metastases for each. The majority (68%) of patients are diagnosed with localized disease, which has a five-year survival rate of 99.9%. Moreover, patients diagnosed with regional disease can expect a five-year probability of survival of 97.1%. However, for the 5% of patients diagnosed with distant disease, the five-year survival rate drops to 53.9%. The focus of this guideline will be medullary thyroid carcinoma (MTC), which comprises less than 10% of all thyroid cancer. The five-year survival for patients with MTC is 86%; however advanced age, advanced stage, prior neck surgery, and associated multiple endocrine neoplasia 2B contributes to poorer prognosis. American Joint Committee on Cancer Staging for MTC can be found in Appendix A of this document (page 6).

New drugs have been developed and tested for endocrine tumours recently, and may be efficacious in certain patients diagnosed with advanced MTC. One such drug, vandetanib, works by targeting vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR) and RET (rearranged during transfection) signaling. Inhibition of VEGFR and RET signaling contributes to an antitumor effect that slows the growth of certain tumours. The purpose of this guideline is to provide evidence-based recommendations on the use of vandetanib for MTC and to define which patients are acceptable candidates for treatment with this agent.

GUIDELINE QUESTIONS

- Is vandetanib more effective than placebo in delaying progression among patients with medullary thyroid carcinoma? If so, what selection criteria should be considered when identifying patients who are appropriate for treatment with vandetanib?
- What is the appropriate dosing regimen for vandetanib?

DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team. Members of the Alberta Provincial Neuroendocrine Tumour Team include medical oncologists, endocrinologists, surgeons, and nurses. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Endocrine Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.
SEARCH STRATEGY

The Medline database was searched (1965 through 2012 March) for relevant publications using the following search terms: vandetanib AND medullary thyroid. Results were limited to randomized controlled trials and phase II-III clinical trials. In addition, the National Guidelines Clearinghouse database was searched (2006 through 2012 March) for existing guidelines and the American Society of Clinical Oncology (ASCO) meeting abstracts database was searched (2009 through 2012 March) for relevant abstracts. Finally, chemotherapy protocols for vandetanib were searched on the Cancer Care Ontario (CCO) and British Columbia Cancer Agency (BCCA) websites. A total of three citations were returned from Medline, all of which were relevant, and one ASCO abstract was selected. Evidence is summarized in the table in Appendix B.

TARGET POPULATION

The recommendations in this guideline apply to patients diagnosed with locally advanced unresectable or metastatic medullary thyroid carcinoma.

RECOMMENDATIONS

1. Vandetanib has been shown to slow symptomatic or anatomic progression (versus placebo) in patients with progressive medullary thyroid carcinoma. Therefore, vandetanib is recommended for patients with symptomatic or progressive medullary thyroid carcinoma with unresectable locally advanced or metastatic disease.

2. Vandetanib should be given at a dose of 300 mg, orally, daily.

DISCUSSION

For localized MTC, total surgical resection of the thyroid with neck dissection, as indicated, is the standard of care and results in excellent prognosis. \(^2,8,14\) Node dissection can also be considered. \(^14\) In addition, EBRT may be used for disease that extends beyond the thyroid with positive margins after resection or for locally recurrent tumours. \(^14,15\) For advanced, metastatic disease, not amenable to resection, other options may include ablation (i.e., radiofrequency, embolization, etc.) or palliative chemotherapy, or biologic therapy, such as vandetanib. \(^4,14\)

This guideline focuses on the role of vandetanib, an inhibitor of VEGFR, EGFR, and RET, in the management of unresectable MTC. Two phase II clinical trials employed vandetanib at dose of 100 mg orally per day \(^16\) and 300 mg orally per day \(^17\) in patients with advanced MTC. Data from these trials showed that a dose of 300 mg per day was able to achieve a better response rate than a dose of 100 mg per day; the partial response rate was 20% and 16%, respectively (there were no complete responses). Biochemically, the proportion of patients with a decrease of at least 50% in the level of in calcitonin was 80% and 16%, respectively, and the proportion of patients with a decrease of at least 50% in the level of carcinoembryonic antigen was 53% and 5%, respectively. Median progression-free survival in the 300 mg per day group (n=30) was 27.9 months. \(^17\)

A phase III trial comparing vandetanib (300 mg per day, orally) with placebo in patients with advanced MTC (n=331) demonstrated an objective response rate of 45% with vandetanib versus 13% with placebo (p<.001). Median progression-free survival for the vandetanib group was not reached at the time of
publication but could be approximated at 30.5 months, while that of the placebo group was 19.3 months, giving a six-month progression-free survival rate of 83% for vandetanib versus 63% for placebo (HR=0.46, 95% CI 0.31-0.69; p<.001). 18,19

To date, no randomized controlled trials, comparing vandetanib with other systemic agents, in the setting of progressive unresectable MTC, have been published and there are currently no clinical trials of this nature in progress. 20 Current work in on vandetanib in the setting of MTC focuses on comparing 300 mg per day with 150 mg per day in patients with unresectable locally advanced MTC. It will also help the investigators understand the side effects of different doses in these patients (NCT01496313). 20

In terms of toxicity, the most frequently reported adverse events (any grade) associated with vandetanib are diarrhea (56% versus 26% placebo), rash (45% vs. 11% placebo), nausea (33% versus 16% placebo), hypertension (32% versus 5% placebo), and headache (26% versus 9% placebo). The most frequent grade 3 or higher events were diarrhea (11% versus 2% placebo), hypertension (9% versus 0% placebo), and ECG QT prolonged (8% versus 1% placebo). 18,19 Patients, especially those with a history of cardiovascular disorders, for whom vandetanib is planned should be monitored closely by physicians for cardiovascular events. 21

The recent development of targeted therapies such as vandetanib has led to an increase in the expected survival for some patients with MTC. In order to predict which patients might benefit most from vandetanib, an analysis of the plasma levels of VEGFR, as a biomarker, may be useful. 22,23 However, these potential biomarkers have only been studied in lung cancer, not MTC. Future research will need to focus on finding predictive markers to help determine which MTC patients can benefit from vandetanib and other promising biologic agents.

GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>EBRT</td>
<td>external beam radiotherapy</td>
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<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
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<tr>
<td>MTC</td>
<td>medullary thyroid carcinoma</td>
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<tr>
<td>NETs</td>
<td>neuroendocrine tumours</td>
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<td>RET</td>
<td>rearranged during transfection</td>
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<tr>
<td>VEGFR</td>
<td>vascular endothelial growth factor receptor</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2013. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Endocrine Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Endocrine Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


APPENDIX A: AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM (7th EDITION, 2010) FOR THYROID CANCER

Primary Tumor (T)
TX: Primary tumor cannot be assessed.
T0: No evidence of primary tumor.
T1: Tumor ≤2 cm in greatest dimension limited to the thyroid.
T1a: Tumor ≤1 cm, limited to the thyroid.
T1b: Tumor >1 cm but ≤2 cm in greatest dimension, limited to the thyroid.
T2: Tumor >2 cm but ≤4 cm in greatest dimension, limited to the thyroid.
T3: Tumor >4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues).
T4a: Moderately advanced disease. Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve. Intrathyroidal anaplastic carcinoma.
T4b: Very advanced disease. Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels. Anaplastic carcinoma with gross extrathyroid extension.

Regional Lymph Nodes (N)
NX: Regional lymph nodes cannot be assessed.
N0: No regional lymph node metastasis.
N1: Regional lymph node metastasis.
N1a: Metastases to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes).
N1b: Metastases to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII).

Distant Metastasis (M)
M0: No distant metastasis.
M1: Distant metastasis.

Anatomic Staging for Medullary Thyroid Carcinoma
Stage I: T1, N0, M0
Stage II: T2, N0, M0
Stage III: T1-3, N1a, M0
Stage IVA: T4a, N0-1a, M0 and T1-4a, N1b, M0
Stage IVB: T4b, Any N, M0
Stage IVC: Any T, Any N, M1
## APPENDIX B: CLINICAL STUDIES USING VANDETANIB IN PATIENTS WITH MEDULLARY THYROID CANCER

<table>
<thead>
<tr>
<th>Author (trial)</th>
<th>Design</th>
<th>Treatments</th>
<th>Patients (n)</th>
<th>Response</th>
<th>Survival</th>
<th>Adverse events (vandetanib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells SA Jr. 2012 (JCO article + ASCO abstract)</td>
<td>phase III</td>
<td>1. vandetanib 300 mg/d PO 2. placebo</td>
<td>advanced medullary thyroid carcinoma (n=331)</td>
<td>objective response: 45% vandetanib 13% placebo (p&lt;.001)</td>
<td>PFS (med): not reached (~30.5 mos) V vs. 19.3 mos P PFS (6-mos): 83% V vs. 63% P HR 0.46 (95% CI 0.31-0.69)</td>
<td>Any grade: diarrhea (56% vs. 26%); rash (45% vs. 11%); nausea (33% vs. 16%); hypertension (32% vs. 5%); headache (26% vs. 9%)</td>
</tr>
<tr>
<td>Robinson BG. 2010</td>
<td>phase II</td>
<td>vandetanib 100 mg/d PO</td>
<td>advanced medullary thyroid cancer (n=19)</td>
<td>CR: 0% PR: 16% (n=3) SD (&gt;24 wk): 53% calcitonin ↓50%: 16% (n=3) carcinoembryonic antigen ↓50%: 5% (n=1)</td>
<td>n/a</td>
<td>Mostly grade 1-2: diarrhea 47% (n=9); fatigue 42% (n=8); rash 26% (n=5); constipation 21% (n=4); anorexia 16% (n=3); back pain 16% (n=3); nausea 16% (n=3); photosens. rxn 16% (n=3)</td>
</tr>
<tr>
<td>Wells SA Jr. 2010</td>
<td>phase II open label</td>
<td>vandetanib 300 mg/d PO</td>
<td>locally advanced or metastatic medullary thyroid carcinoma (n=30)</td>
<td>PR: 20% (n=6) med dur 10.2 mos SD (&gt;24 wk): 53% calcitonin ↓50%: 80% (n=24) carcinoembryonic antigen ↓50%: 53% (n=16)</td>
<td>PFS (med): 27.9 mos</td>
<td>Mostly grade 1-2: diarrhea 70% rash 67% fatigue 63% nausea 63% headache 47% anorexia 43% vomiting 40%</td>
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