Anaplastic Thyroid Cancer:

A Doctor’s Perspective for Patients and Families Living with the Disease

By Maria E. Cabanillas, M.D., F.A.C.E.
Associate Professor and Faculty Director of Clinical Research
Department of Endocrine Neoplasia & Hormonal Disorders
University of Texas M.D. Anderson Cancer Center

Anaplastic thyroid cancer (ATC) is the least common type of thyroid cancer and meets the definition of a rare tumor.¹ ATC affects about 500-800 patients per year in the United States. To put the rarity of ATC into perspective, gallbladder cancer (considered a rare type of cancer) affects 10,910 men and women in the U.S. every year (www.cancer.org/research/cancerfactsstatistics).

Why is this important? Because the extreme rarity of ATC means that few doctors have treated patients with this cancer and there is very little good information available to patients.

However, ATC patients and their loved ones should know that some progress has been made recently and there are new treatments that may be of benefit and may offer some options for a disease that has historically had relatively few.

What is ATC and what are the symptoms?

ATC is a cancer that comes from thyroid cells, affecting mostly older patients (on average those 60 years and older) but it can affect even very young patients too. It is very aggressive, growing rapidly, causing the airway to become narrowed, and resulting in hoarseness and shortness of breath.

ATC not only grows rapidly, it also metastasizes (spreads to other organs) in most patients. This type of thyroid cancer is always classified as stage IV because of the high mortality (high rate of death) associated with it.

How is ATC diagnosed?

ATC is diagnosed by removing cells or tissue and examining them under a microscope. This can be done by performing a biopsy (usually a fine needle aspiration (FNA)). Sometimes it is diagnosed after the thyroid or an affected lymph node is removed by surgery. Again, ATC is an extremely rare disease and it is also a difficult diagnosis due to the many different shapes and forms the cells can take.

The pathology report may not always use the words “anaplastic thyroid cancer.” Synonyms (words that have similar meaning) for ATC include undifferentiated, dedifferentiated, sarcoma of the thyroid, sarcomatoid, squamous, spindle cell, and giant cell. Thus, a second opinion from an expert thyroid cancer pathologist is advisable.

¹ The definition of a RARE DISEASE, according to the Rare Disease Act of 2002 is “any disease or condition that affects fewer than 200,000 people in the United States.”
What are the mutations and which are commonly seen in ATC? Should I have my tumor tested?

Some genetic mutations\(^2\) can cause cells to grow out of control, leading to cancer. In ATC, the common genetic mutations in these tumors are BRAF, RAS, p53, and PI3K. These are only some of the mutations in ATC. Many more have been reported and some tumors have multiple mutations. The reason testing your tumor is important is that the tumor may have a targetable mutation. This means that there is a drug designed to target that particular mutation.

It is important to note that genetic testing on tumors takes a long time (2 weeks to 2 months) and requires enough tumor to be available. It is also very expensive. However, some insurance companies pay for the testing and some academic hospitals may test your tumor at no cost to you.

How is newly diagnosed ATC treated?

ATC is not only a difficult disease to diagnose, but it is also a complex disease to treat. First, the extent of disease—in which organs is the cancer present—must be determined. This can be done with different types of imaging such as ultrasound, CT scans, MRI, and PET/CT scans.

Ultrasound of the neck is a useful test to evaluate if the tumor has extended outside of the thyroid gland, to evaluate the lymph nodes in the neck, and to perform an FNA biopsy. This test is limited by the fact that the ultrasound probe cannot “see” behind the trachea and bones (for example, the sternum and the bones in the face).

CT and MRI scans are useful for evaluating the areas of the head and neck that an ultrasound cannot. These are also useful in evaluating other parts of the body for metastatic disease. ATC can spread (metastasize) to any part of the body (including the lymph nodes, muscles, and limbs), but most common sites include the lungs, liver, bones, and brain. In order to evaluate all of these sites, a PET scan fused with a CT (PET/CT) is incredibly useful in the first evaluation and later in follow-up to monitor the disease.

In patients whose tumor is localized to the thyroid gland and who have no evidence of metastasis, surgery may be an option and is potentially curative in a small number of patients. Unfortunately, this is not an option for the majority of ATC patients. Surgery in patients whose tumor has spread outside the thyroid gland or to other parts of the body is usually not helpful. Thus, a decision regarding whether surgery would be beneficial should be made quickly.

Radiation to the neck is the next treatment that is offered, regardless of whether the tumor is removed or not. In patients who have surgery, radiation is used to prevent the disease from returning. In patients who do not have surgery, radiation is used to shrink the tumor and prevent it from growing further and causing symptoms of choking from closing of the trachea (asphyxiation). Chemotherapy at low doses is usually given with radiation in order to make the radiation more effective.

---

\(^2\) MUTATIONS occur when a gene is damaged or changed resulting in an error in the genetic message. This change may cause the cells to continue to divide and make more cancerous cells or they may not result in any disease. These mutations are often caused by exposure to something harmful in the environment such as radiation. In many cases, it is not known what causes the mutation. In ATC, mutations occur in the actual tumor and cannot be passed on to the next generation.
It is important to note that ATC patients should not be given radioactive iodine since ATC cells do not respond to this treatment.

Tracheostomy (also called tracheotomy) is an opening created through the neck into the trachea to allow a breathing tube to be inserted below the tumor. This is done in patients whose tumor is not allowing them to breathe well. Avoiding a tracheostomy is best if possible because the recovery time will delay the start of radiation treatment.

Patients who present with disease that has spread outside of the neck pose an even more serious challenge. Balancing the immediate need to prevent the cancer from causing asphyxia and the need to treat the metastases is a dilemma and requires an individualized plan developed with the physician, patient, and family.

Hospice or comfort care is often offered to ATC patients. In cases where patients are too ill to have any effective treatment, this may be appropriate. For example, a patient who is critically ill in the hospital is too sick to undergo radiation or chemotherapy and should be considered for comfort care.

However, since new treatments are being discovered, ATC patients who are offered hospice but who have a good performance status\(^3\) and are well enough to be outside of the hospital may consider getting a second opinion.

**How is ATC that has not responded to standard therapy or ATC with distant metastases\(^4\) treated?**

Distant metastatic disease or disease localized to the neck (“locoregional metastases”) that has not responded to radiation is usually treated with cytotoxic chemotherapy. Cytotoxic chemotherapy refers to traditional chemotherapy that kills rapidly dividing cells. The cytotoxic chemotherapies used for ATC are usually given by vein. Unfortunately, the response rates in ATC are unacceptably low and the drugs can be quite toxic.

The advent of the 21\(^{st}\) century has brought a new class of chemotherapy, which we refer to as molecularly targeted therapy, or simply targeted therapy. Targeted therapy drugs interfere with specific molecules that help cancer cells to grow.

One class of targeted therapy, the kinase inhibitors, has been or is being tested in ATC patients. Table 1 lists these trials and available results of several kinase inhibitors. Although none of these trials have shown consistent results in ATC, the newer generation of the kinase inhibitors may be more effective. Some of the kinase inhibitors specifically target particular mutations. Thus, it is important to know which mutations are present in the tumor. Knowing this information early will expedite finding an appropriate trial for the patient.

---

\(^3\) PERFORMANCE STATUS is an objective measure of the patient’s general well-being and ability to do their usual, daily activities. It is used to determine how well a patient will be able to tolerate cancer treatment.

\(^4\) DISTANT METASTASES refers to the spread of cancer outside of the organ of origin and the nearby structures. In the case of thyroid cancer this would refer to thyroid cancer which has spread outside of the neck (for example, to the brain, lungs, liver, bones, etc.).
While it is important for all ATC patients to consider participating in clinical trials, there are advantages and disadvantages to participating in them. These are summarized in table 2. Because ATC is a rare tumor, more than likely, a clinical trial will mean having to travel to a major cancer center. Table 2 lists the trials that are ongoing at the time of the writing of this manuscript. A list of the most current clinical trials can be found at clinicaltrials.gov. The contact information for the site where the study is offered and many other details are listed for each clinical trial.

Why has so little progress been made in ATC?

As opposed to the other forms of thyroid cancer, progress in finding effective treatments for ATC has been very slow. Analyzing and trying to understand the reasons we have not been successful could be valuable information. The following are reasons why little progress has been made and the possible interventions under the patient and physician’s control:

1. ATC is a rare disease that most oncologists have never treated. Obviously, we cannot make ATC more common, nor would we want to. However, seeking the opinion of ATC experts is highly recommended. It is not that ATC experts are smarter than your doctor, but with rare diseases, experience is critical. ATC experts will also have the most up-to-date information from national/international conferences and meetings that may not yet be in the public domain. The field is rapidly evolving but the knowledge often lags behind what is practiced by most oncologists.

2. ATC is a rapidly progressive disease—time is not on the patient’s side and action on the part of the patient should be undertaken very quickly. Due to the aggressive nature of the disease, selecting the best treatment strategy and getting it started is critical. Furthermore, knowing which genes are mutated may be valuable information for the treatment plan. Genetic testing of the tumor could take anywhere from 2 weeks to 2 months; therefore, this test should be done as soon as the diagnosis of ATC is made.

3. ATC trials are uncommon and eligible patients are rare. The only way that a drug can be approved for a disease is to show it is effective. This is done by performing clinical trials. Clinical trials for rare diseases that are rapidly fatal are obviously problematic to enroll patients on; therefore, progress has been slow. For example, a quick search for all trials (regardless of their status) in lung cancer—a very common cancer—on clinicaltrials.gov brings up 5873 studies. The same search for trials in thyroid cancer brings up only 523 studies. Of those studies, only 8% are ATC related, of which an even smaller fraction are trials which are open to enrollment.

Pearls of wisdom for patients and loved ones battling ATC:

- Speed is critical—diagnosis should be confirmed and the best possible treatment should be started quickly. Be a firm advocate for speed so that all options can be examined and the best treatment decisions made.

---

5 A CLINICAL TRIAL is a research study that assigns patients to a treatment to evaluate whether the treatment is effective against the disease.
• Ask your doctor if he/she is an ATC expert and how many ATC cases he/she has treated. If your doctor has seen fewer than 20 cases of ATC, seek a second opinion from an ATC expert. Can’t travel? Seek an online second opinion consult (a consult that is done by reviewing outside records and pathology slides, without the patient’s presence). Pathology second opinions (without review of the medical records) are also available from major cancer hospitals. Some insurance companies will pay for these second opinions. If you seek out an online second opinion, make sure the person qualifies as an ATC expert.

• Ask your doctor to send your tumor for genetic mutation analysis.

• Ask your doctor about clinical trials. Trial is not an option? Ask about which drugs are most promising from the current trials and that are commercially available. Some insurance companies will allow the use of “off label” drugs. This means that the drug is approved for a different type of tumor but there is reason to believe it could work for your tumor type.

• Find a cancer patient advocate/advocacy group. Having a family member or friend as your advocate is critical. Treatments can be difficult on the patient. It is highly recommended that when possible, the patient have a family member or close friend be involved in treatment decisions. If the patient has no support, consider seeking support through an advocacy group. Advocacy groups provide services and information to assist patients and caregivers fight their cancer. ThyCa: Thyroid Cancer Survivors’ Association, Inc. (www.thyca.org), is a great advocacy group for thyroid cancer patients.
**TABLE 1. ATC clinical trials with greater than 10 participants**

<table>
<thead>
<tr>
<th>Targeted Therapy Drug</th>
<th>Number of patients participating</th>
<th>Mutation requirement</th>
<th>Median survival time</th>
<th>Response rate (how many patients had significant tumor shrinkage)</th>
<th>Was the drug under evaluation considered effective?</th>
<th>Reference and ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib 400mg twice per day</td>
<td>20</td>
<td>None</td>
<td>3.9 months</td>
<td>2 patients partial response 5 patients stable disease</td>
<td>No</td>
<td>Savvides et al, 2012 NCT00126568</td>
</tr>
<tr>
<td>Pazopanib 800 mg once daily</td>
<td>15</td>
<td>None</td>
<td>3.6 months</td>
<td>0 patients partial response 12 patients stable disease</td>
<td>No</td>
<td>Bible et al, 2012 NCT00625846</td>
</tr>
<tr>
<td>Efaltutazone + paclitaxel (cohort 1=0.15mg twice daily; cohort 2=0.3mg twice daily)</td>
<td>13</td>
<td>None</td>
<td>Cohort 1= 3.2 months Cohort 2=4.5 months</td>
<td>Cohort 1= 0 patients partial response;4 patients stable disease Cohort 2= 1 patient partial response;3 patients stable disease</td>
<td>Maybe (phase II trial ongoing)</td>
<td>Smallridge et al, 2013 NCT00603941</td>
</tr>
<tr>
<td>Paclitaxel and carboplatin (CP) vs. CP + fosbretabulin</td>
<td>80</td>
<td>None</td>
<td>4 months vs. 5.2 months</td>
<td>Not reported</td>
<td>No</td>
<td>Sosa et al, 2013 NCT01701349</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>17</td>
<td>None</td>
<td>10.6 months</td>
<td>4 patients partial response 12 patients stable disease</td>
<td>Yes</td>
<td>Takahashi et al 2016 (JCO abstract) NCT01728623</td>
</tr>
</tbody>
</table>

**Ongoing trials with no results reported as of 7/13/2016**

| | | | | | | |
|-------------------|----------------------------------|----------------------|------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------|
| Lenvatinib | 76 | None | - | - | - | NCT02657369 |
| Dabrafenib 150mg twice per day + trametinib 2 mg daily | 15 in ATC cohort | Yes (BRAF) | - | - | - | NCT02034110 |
| MLN0128 (mTOR inhibitor) | 25 | None | - | - | - | NCT02244463 |
| Pembrolizumab | 20 25 | None | - | - | - | NCT02688608 NCT02721732 |
Table 1 Continued - Ongoing trials with no results reported as of 7/13/2016

<table>
<thead>
<tr>
<th>Trial Description</th>
<th>No.</th>
<th>Yes</th>
<th>NCT Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cribulin + cisplatin vs. cisplatin alone (phase II)</td>
<td>70</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Efatutazone + paclitaxel vs paclitaxel alone</td>
<td>50</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>LOXO-101</td>
<td>151</td>
<td>Yes</td>
<td>(NTRK fusion)</td>
</tr>
<tr>
<td>Ceritinib 750mg daily</td>
<td>10</td>
<td>Yes</td>
<td>(Alk abnormality)</td>
</tr>
</tbody>
</table>

TABLE 2. Advantages and disadvantages to clinical trial participation

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to an investigational drug(s) that may not be available otherwise</td>
<td>Unforeseen risks to use of investigational drugs. These may actually not be better than the standard of care.</td>
</tr>
<tr>
<td>Investigational drug may be better than the standard of care drugs</td>
<td>You might be randomized to the standard of care plus placebo (depending on the type of clinical study). This will be disclosed in the consent form.</td>
</tr>
<tr>
<td>You may help future patients</td>
<td>Frequent visits are required. This could be time consuming and expensive. Ask if there will be any compensation for travel.</td>
</tr>
</tbody>
</table>

*Always check with your insurance before participating in a trial and read the consent form carefully

**Disclaimer:** The information presented here is intended for educational purposes only. It is not intended, nor should it be interpreted, as medical advice or directions of any kind. Any person viewing this information is strongly advised to consult their own medical doctor(s) for all matters involving their health and medical care.

— February 4, 2017