Treatments for Medullary Thyroid Cancer Compared to Metastatic Medullary Thyroid Cancer

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Abstract

Medullary thyroid cancer, or MTC, is a subtype of thyroid cancer that originates from the C-cells in the thyroid. This type of thyroid cancer is not the most common or the most deadly, however, little is known about MTC as compared to the more common types of thyroid cancer. Once MTC has metastasized it can be called metastatic medullary thyroid cancer. The most common sites of metastasis are nearby the thyroid, such as the lymph nodes, but there have been cases of MTC traveling further into the body. This paper was created to explore the differences between treating medullary thyroid cancer and metastatic medullary thyroid cancer. When cancer metastasizes, it does not lose its cellular identity, therefore the treatments should be similar. An extensive analysis of scientific research was used to compare treatment options for MTC and metastatic MTC. Having extensive knowledge of the variability of treatments for MTC and metastatic MTC can help medical professionals better treat patients in the future. It can also help researchers and drug companies develop newer more effective pharmaceuticals. Using this knowledge can help future scientists develop more advanced treatments for other types of metastatic cancers as well.

Introduction

Medullary thyroid cancer is a unique type of cancer that originates from the C-cells in the thyroid. This is different from more prevalent types of thyroid cancer that originate from follicular cells (Figure 1). Since medullary thyroid cancer is less prevalent, there is less known about it and its treatments. Scientists should continue to research this cancer in order to best treat patients with this specific subtype of thyroid cancer. C-cells, also known as parafollicular, are a cell type in the thyroid that make calcitonin, which is a hormone that helps control calcium levels in the blood. Abnormal calcitonin levels can be an indicator of MTC [1].

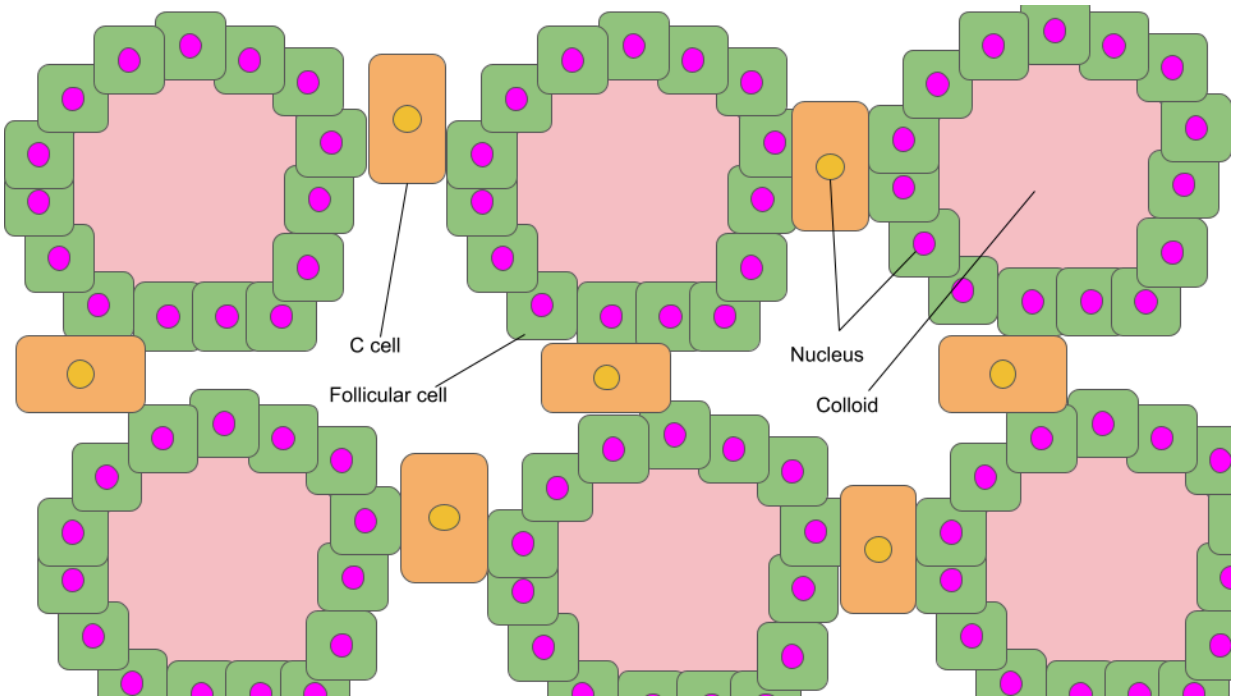

Figure 1: Arrangement of Follicular cells and C cells. Parafollicular Cells (C cells) painted in orange, C cell nuclei painted yellow, Follicular cells painted green, follicular cell nuclei painted pink, and colloids painted peach.

Only 1.2% of cancer diagnoses are thyroid cancer, of these thyroid cancer diagnosis, 1-5% are medullary thyroid cancer. The most common way to treat MTC is a thyroidectomy which is where the whole thyroid or half of it is removed. Treatment can also include various drugs such as Vantalabib, or Cabozantinib, these two drugs are types of RET (REarranged during Transfection) inhibitors. RET is a proto-oncogene that when mutated can cause medullary thyroid cancer. RET inhibitors target the mutated RET gene and stop it from helping to produce more cancer cells [2]. The most common place for MTC to metastasise to is the lymph nodes. Only about 25% of thyroid cancer diagnoses are hereditary. Factors such as age, sex and family history are risk factors of developing thyroid cancer [3]. Research on medullary thyroid cancer and its metastasis can give scientists insight on metastasized cancers and how it's treated compared to non-metastasized cancers.

Medullary thyroid cancer symptoms include a nodule on the upper part of the thyroid, most patients have this when they are diagnosed. Many patients will also have swollen lymph

nodes and rarely, an enlarged thyroid gland, causing hoarseness, difficulty swallowing and discomfort. In some rare cases, no symptoms are shown because the nodule is so small, less than 1cm [4]. MTC, like other cancers, has stages from 1 to 4 in order of least to worse severity. Stages 1 and 2 are the least severe and have no regional or distant metastasis [5]. Stages 3 and 4 will have regional or distant metastasis. Metastasis is defined as, “The spread of cancer cells from the place where they first formed to another part of the body” [1]. In regional metastasis, the cancer has spread to nearby lymph nodes, organs or tissues and in distant metastasis, the cancer has spread to distant parts of the body [6]. Stage 1 has a tumor size of less than 2 cm while stage 2 has a tumor size of 2-4 cm. Stage 3 MTC includes regional metastasis to areas such as the pretracheal, paratracheal, and prelaryngeal lymph nodes. The size of a stage 3 MTC tumor is usually 2-4 cm but can be larger than 4 in the thyroid area only. Stage 4 MTC includes multiple substages. Stage 4a includes no distant metastasis, it does include regional metastasis to the lymph nodes and unilateral, bilateral, or contralateral cervical. At this point the disease is moderately severe. At stage 4b, there is still no distant metastasis but the disease is considered very advanced as the cancer can spread to the prevertebral fascia or encases carotid arteries or mediastinal vessels during this stage. The last stage is stage 4c, during this stage there is distant metastasis, the cancer could also have regional metastasis as well, which would make the cancer very advanced [5]. Fortunately, MTC usually responds well to treatments if caught early enough and tends to progress relatively slowly [4]. The average tumor volume doubling time for MTC is about 1.6 years [7]. While this is true, the prognosis of MTC depends on many factors such as age, overall health and how far the cancer has spread throughout the body. For example, older patients with distant metastasis will have a worse prognosis than a young healthy person with little metastasis. In this paper topics such as treatments, causes and outcomes will be used to determine the differences and similarities in the treatments of medullary thyroid cancer and metastatic medullary thyroid cancer [4]. It is hoped that this research can be a catalyst to others in the scientific community to continue to research these topics as the information gained can be useful to finding treatments to other forms of cancers.

Demographics and Risk Factors

It is not clear why but the occurrence of thyroid cancer in women is three times more likely than that of men. The majority of women who are diagnosed were in their 40s to 50s, while the majority of men who are diagnosed are older, in their 60s or 70s [8]. Currently, there is no data exploring the distribution of MTC based on racial demographics, which is a critical gap in our current understanding of the prevalence of this disease. Exposure to radiation is also a factor that can cause thyroid cancer, this was shown in some people who lived around the cite of the Chernobyl nuclear power plant meltdown. A study that was done, measured thyroid cancer cases and those at risk for thyroid cancer and found that there is a relationship between the two [3]. About 25% of MTC cases are due to a hereditary gene mutation. Cases like these are known as familial medullary thyroid carcinoma (FMTC). FMTC and tumors on other endocrine glands together are called multiple endocrine neoplasia type two. Which can also be called MEN2a and MEN2b. Both of these subtypes are caused by mutations in the RET gene. The subtype MEN2a is much more common than the subtype MEN2b [8]. The other 75% of medullary thyroid cancer cases are sporadic. This is a random mutation that is not hereditary. Many patients with sporadic MTC also have RET mutations. Patients with MTC can also have mutations within the RAS gene family, but this is less common than a RET mutation [9].

When cancers metastasize, they spread through either the blood vessels or lymph nodes. MTC has local metastasis in 50% of the diagnoses and in about 10-15% of the diagnosis MTC has distant metastasis [10]. When MTC metastasizes the most common sites for it to spread to are regional places such as the lymph nodes. It is also common for that cancer to spread to the liver, lungs or bones when metastasized [11]. According to a study published by Sanziana Roman, Rong Lin, and Julie Ann Sosa, the two largest predictors of prognosis are age and stage of the disease [12]. The earlier MTC is discovered, the better chance the patient has of surviving. This also means that the prognosis for someone with metastatic MTC will likely be worse than someone with nonmetastatic MTC.

Surgical Treatments

Currently, there are three main treatment categories for MTC (Figure 2). These include surgical and drug treatment options. The most popular way to remove MTC is to get a total thyroidectomy [4],this surgery removes all of the thyroid from the body. If a patient has metastasis to the lymph nodes or a doctor suspects that they do, they can also perform central or lateral compartment dissections depending on what part of the lymph nodes the cancer has spread to [3]. This surgery would remove the cancerous lymph nodes from the neck. In the case that the cancer has not spread to the whole thyroid, part of the thyroid can be removed as well, this is called a thyroid lobectomy. The only actual curative therapy for MTC is surgery as it removes all of the cancer from the body [13]. The only issue with this is that when the cancerous thyroid is removed, the regulatory effects of the thyroid are also lost. Because of this, people who have to get a total thyroidectomy or thyroid lobectomy need to take medication for the rest of their lives in order to keep up with the things that their thyroid was doing such as producing calcitonin and regulating BMR (basal metabolic rate).

Drug Treatments

Chemotherapy (Chemo), is a treatment that uses chemicals to kill off fast growing cells in the body, this works to treat cancer because cells are marked by uncontrolled cell growth. There are many different types of chemotherapeutic drugs used to treat MTC, some of these drugs include, Dacarbazine, Vincristine, Cyclophosphamide and Doxorubicin [14]. These drugs attack cells that divide at rapid rates by targeting the cell cycle. Cells such as hair follicles, bone marrow, and cells in the lining of the mouth or intestines also divide at rapid rates. Because of this side effects of chemotherapy can include, hair loss, mouth sores, loss of appetite, nausea and vomiting [15]. Side effects usually only last until treatment has subsided and there are some medications available to take for certain side effects. Chemotherapy has only been used in MTC with marginal benefit. For instance, a study done in 2000 that used the combination of multiple different chemo drugs showed that out of 20 advanced MTC patients, only 3 had partial responses to the drugs and 10 were stabilized [16]. Therefore, chemotherapy usually works best with dual therapy [17]. New research on targeted drug therapy has shown to work much more efficiently than chemo, because of this chemotherapy is only recommended for metastatic MTC's not eligible for or resistant to tyrosine kinase inhibitors [18].

One way to treat MTC that is on the rise is the use of targeted drug therapy. In virtually every familial case and about 50% of sporadic cases MTC is associated with mutations in the RET proto-oncogene. RET encodes a transmembrane receptor tyrosine kinase. Tyrosine kinases regulate many cell processes including but not limited to, cell motility, cell growth and apoptosis [19] and [20]. Mutations in RET in c-cells result in over proliferation of the intracellular

space of the thyroid resulting in cancer. RET gene mutations are associated with higher risks for developing tumors in the endocrine system [21]. Since many patients with MTC have mutations in the RET proto-oncogene, scientists have come up with ways to target the source of the cancer, the RET mutation. There are many different RET kinase inhibiting drugs either on the market or going through clinical trials. The first of its kind was Vandetanib [22]. Before Vandetanib was released to the public, there was no treatment for patients with advanced MTC [22]. There are two types of RET inhibitors used to treat MTC, one is a selective RET inhibitor and the other is a multi-tyrosine kinase inhibitor [23]. Selective RET inhibitors target only the mutated RET proteins, thus they are called targeted therapies. While multi-tyrosine kinase inhibitors target multiple proteins related to cancer, including RET [23]. An example of a selective RET inhibitor is the drug Selpercatinib, which is approved to treat advanced MTC [24]. An example of multi-tyrosine kinase inhibitors are cabozantinib and vandetanib, both of which are also approved to treat metastatic MTC [24]. Both of these drugs are also able to treat RAS mutations that were mentioned earlier in the paper [19].

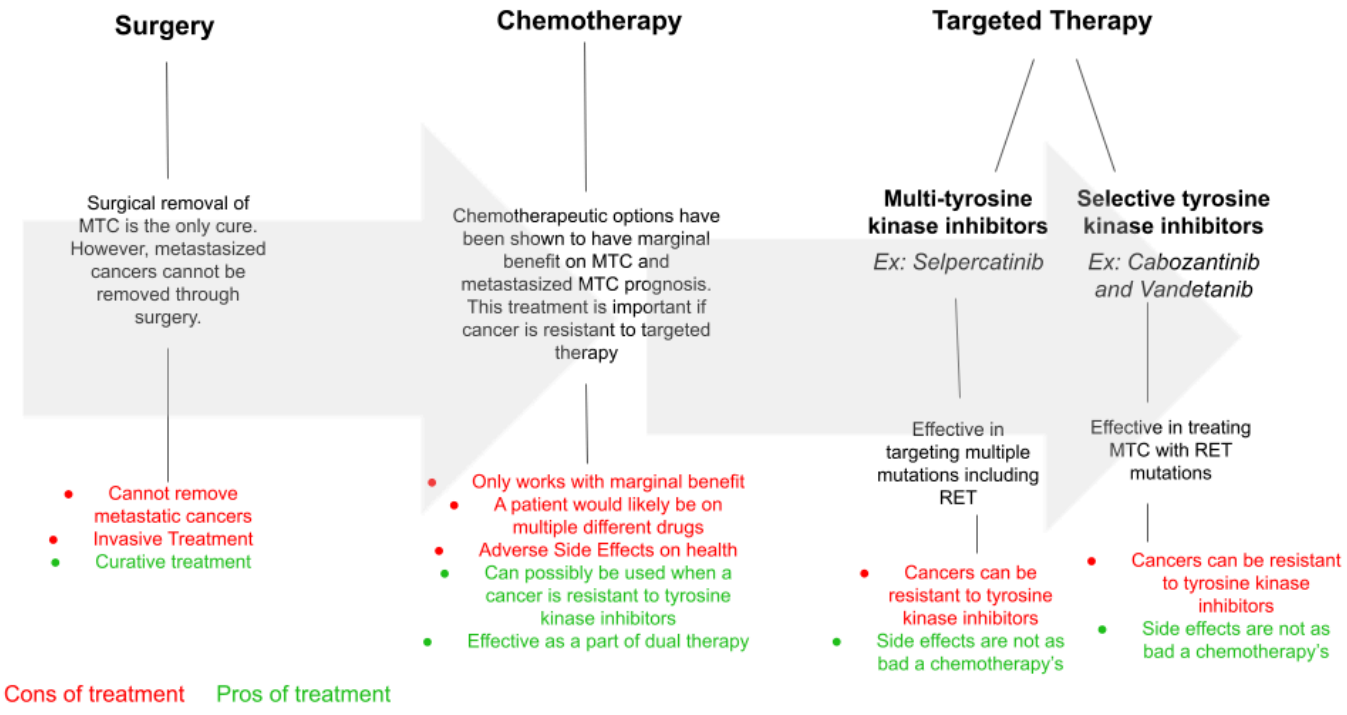

Figure 2: Treatment options and comparisons for MTC

Conclusion

A patient with MTC that has no metastasis would benefit from the surgical method of getting rid of the cancer. But if the patient's cancer has metastasized, doctors should look for a different method, such as chemotherapy or targeted drug therapy. Since chemotherapy drugs work best synergistically, a patient with MTC would likely be on many different chemo drugs at once. As mentioned before in the paper, chemo has only shown some benefit for metastasized MTC. Because of this a patient with metastasized MTC should be taking a targeted therapy

drug, unless their form of MTC has shown to be resistant to tyrosine kinase inhibitors. Tyrosine kinase inhibitors have shown great promise in treating MTC and metastasized MTC. While this is true they are not curative, and the best way to cure MTC is to remove the cancer in surgery. Metastasized cancers cannot be removed through surgery so because of this, metastatic MTC cannot be cured easily, but can still be treated to reduce that spread. As mentioned earlier in the paper, because cancer does not lose its cellular identity when it metastasizes, the treatments for MTC and metastatic MTC should be similar. While this is mostly true, there are a few exceptions for instances where metastatic cancers cannot be operated on.

Development of targeted therapies has greatly increased the positive outcome of cancer treatments. By targeting specific mutations, unique to cancer cells, there is now precision in drug treatment that was not available with chemotherapy alone. Understanding the pros and cons of each drug treatment will lead to more efficient prescription processes and allow more favorable patient outcomes (Figure 2). It is important to note the strengths and weaknesses of each drug as well as the genetic description of each patient's cancer, in order to be able to best diagnose and treat. The knowledge presented in this paper proposes an example of streamlining drug options, specifically in patients with medullary thyroid cancer.

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