

Immunotherapy and Malignant Thymus Cancer

Allen T*, Khoni NS, Razavi SE and Court NB

Global Allied Pharmaceuticals, Center for Excellence in Research and Development, Longwood, USA

***Corresponding author:** Allen T, Global Allied Pharmaceuticals, Center for Excellence in Research and Development, 160 Vista Oak Dr. Longwood, FL 32779, USA, Tel: 13219454283, E-mail: timothy.allen@gapsos.com

Citation: Allen T, Khoni NS, Razavi SE, Court NB (2019) Immunotherapy and Malignant Thymus Cancer. SAJ Cancer Sci 6: 102

Abstract

Thymoma is a relatively common tumor associated with different immunological disorders, like hypogammaglobulinemia, pure red cell aplasia, myasthenia gravis and other autoimmune diseases. Thymoma is one of the rare cause of deaths, worldwide. According to the SEER, in the United States, the overall-age standardized rate of incidence of thymoma was 0.13 per 100,000 person-years from 1973-2006. Thymus cancer accounts for only 0.06% of all the thymic neoplasms. The specific cause of thymus cancer is not known, but researchers have established that there are some mutations in DNA, which take place more frequently in cancer cells of the thymus than in the normal cells. WHO has categorized the thymus cancer is categorized into six subtypes, which are Type-A, Type-AB, Type-B1, Type-B2, Type-B3 and Type-C. Immunotherapy has shown a promising development in the past few years. One optimistic treatment modality is immunotherapy which has much progress. We review all the different classes of drugs, FDA approved or still under clinical trials directed at the therapy of the thymus cancer. The researchers are still challenged in exploring innate and adaptive immune systems because immunotherapy might be a beneficial future for the treatment of thymus cancer. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy) for thymus cancer.

Keywords: Thymoma; Epidermal Growth Factor Receptor (EGFR); Vascular Endothelial Growth Factor Receptor (VEGFR); Malignant Thymus Cancer; FDA: US Food and Drug Administration

Abbreviations: DNA: deoxyribose nucleic acid; EGFR: Epidermal Growth Factor Receptor; FDA: US Food and Drug Administration; HDAC: Hydroxamic acid type histone deacetylase; IGF-1R: Insulin-like growth factor-1 receptor; LOH: loss of heterozygosity; MABs: Monoclonal Antibody Drugs; PDGFRb: vascular endothelial growth factor receptor 2; SEER: Surveillance, Epidemiology and End Results; US: United States; VEGFR: Vascular Endothelial Growth Factor Receptor

Introduction

Thymoma is a relatively common tumor of the anterior mediastinum and is commonly associated with different immunological disorders, like hypogammaglobulinemia, pure red cell aplasia, myasthenia gravis and other autoimmune diseases [1-4]. It usually progresses with slow growth rate. It hardly produces distant metastasis and therefore, surgery remains the foundation of treatment [5]. Thymoma is one of the rare cause of deaths, worldwide. According to the SEER, in the United States, the overall- age standardized rate of incidence of thymoma was 0.13 per 100,000 person-years from 1973-2006.

The incidence of thymoma is higher in blacks and particularly Asians/Pacific Islanders, than Hispanics or Whites [6]. Similar to thymoma, myasthenia gravis is very rare with the incidence rate of 0.4-1.1 per 100,000 person-years and it is frequent in blacks than whites in the United States [7,8]. Thymus cancer accounts for only 0.06% of all the thymic neoplasms [9]. It includes different type of histopathologic and genetic characteristics. There is 1.4:1 predominance of males over females, with higher incidence observed between the age of 30 and 70 years [10].

Etiology/Predisposing Factors

Thymus cancer occurs in the epithelial cells of the thymus. The specific cause of thymus cancer is not known, but researchers have established that there are some mutations in DNA, which take place more frequently in cancer cells of the thymus than in the normal cells. According to WHO, the thymus cancer is categorized into six subtypes, which are Type-A, Type-AB, Type-B1, Type-B2, Type-B3, and Type-C (Table-1). Type-AB is also known as mixed thymoma. Furthermore, Type-C, known as thymic carcinoma, is the most aggressive type [11]. Among these subtype, Type-AB and Type-B2 are the most common types of thymus cancer.

The most common risk factors of thymus cancer are infections, genetic variants, alcohol/tobacco, environmental contaminants and ionizing radiation [6]. The symptoms, such as swelling of the neck, shortness of breath, hoarseness of the voice, chest pain, difficulty in swallowing and a persistent cough are related to the thymus cancer [12].

WHO Classification	Traditional Nomenclature
Type-A	Medullary thymoma; spindle cell thymoma
Type-AB	Mixed thymoma
Type-B1	Predominantly cortical thymoma; organoidthymoma; lymphocyte predominant thymoma; lymphocytic thymoma
Type-B2	Cortical thymoma
Type-B3	Well differentiated thymic carcinoma; epithelial predominant epithelial; squamoidthymoma
Type-C	Thymic carcinoma

Table-1: WHO classification of Thymoma Cancer [13]

Pathophysiology and Molecular Basis

In thymus cancer, the primary T-cell abnormalities appear to be associated with the acquisition of the CD45RA+ phenotype on naive CD4+ T cells throughout the terminal intra-tumorous thymopoiesis, which is followed by the export of activated CD4+ T cells into the circulation [14]. In addition to T-cell defects, B-cell lymphopenia has been observed in the thymoma-associated immunodeficiency, with opportunistic infection and hypogammaglobulinemia (Good syndrome) [15,16]. Patients with thymoma-associated myasthenia-gravis can produce auto-antibodies to a variety of neuromuscular antigens, mainly the acetylcholine receptor and titin, a striated muscle antigen [17,18].

The main genetic alteration in thymus cancer affects chromosome 6p21.3 (MHC locus) and 6q25.2–25.3 [19-21]. The identification of a frequent genetic modification on 6q25, across all histological tumour subtypes, suggests the availability of a yet undefined general tumor suppressor gene, which may ultimately play a key role in the biological mechanism of thymic medullary/cortical progenitor cell. So far, the associated genes have not been recognized. The other modifications, which commonly affects the type-B2 and B3, are situated on chromosome 5q21–22 (the APC locus), chromosome 7p15.3, and chromosome 8p11.21. The type-AB thymoma cancer exhibit loss of heterozygosity (LOH) of the APC locus and the high risk modification on chromosome 8p11.21, but it does not relate to other aggressive phenotype in these types of tumors. It was also suggested that these high risk mutations were equalized by an unidentified tumor suppressor gene. Though, type-B2 and B3 express similar genetic modification, the composition of LOH of the APC, TP53, and RB locus has so far, only been reported in B3 thymoma cancer [22].

There are several molecular pathways, which are involved in the thymus cancer and these molecular pathways are Epidermal Growth Factor Receptor (EGFR), KIT signaling pathway, Insulin-like growth factor-1 receptor (IGF-1R) and VEGFR expression.

Epidermal Growth Factor Receptor (EGFR)

The EGFR is commonly over expressed in thymic cancer (53%) and thymoma (70%) [23]. There was no relationship between EGFR mutation and EGFR expression status. Regarding EGFR downstream proteins, no mutation has been identified in the genes, such as PTEN, FRBB2, PIK3CA, MEK1, and AKT1. The three RAS mutation cases were detected among 45 thymic epithelial tumors. These were HRAS G13V, G12V KRAS, and G12A KRAS [24].

KIT Signaling Pathway

The KIT is commonly overexpressed in thymic cancer (79%) and thymoma (2%) [25-28]. The thymic carcinomas due to KIT-mutant characterize a small molecular separation of the thymic tumors. The D820E mutation was found in the thymic cancer patients, who responded to sorafenib therapy [29].

Insulin-like growth factor-1 receptor (IGF-1R)

The appearance of IGF-1R was studied by immunohistochemistry in a cohort of sixty three thymic tumours [30]. Moderate to high expression of IGF-1R was more frequent in thymic carcinomas than in thymomas (86 vs. 43% respectively). It was also associated with higher EGFR staining [31].

Vascular Endothelial Growth Factor Receptor (VEGFR) expression

VEGFR -1/2 and VEGF-A are overexpressed in thymic cancer and thymoma [32]. The VEGF expression levels and microvessel density have been shown to be associated with various clinical stages and tumour invasion [33]. The increased level of VEGF can be observed in the thymic cancer patients, but it is not observed in the thymoma cancer patients (Figure 1) [34].

Immunotherapy

Monoclonal Antibody Drugs (MABs):

Non-FDA approved MAB drugs: There are some MABs that are not currently approved by FDA for thymus cancer. However, these

MABs are under clinical trials in phase I, II, and III as in the Table-2.

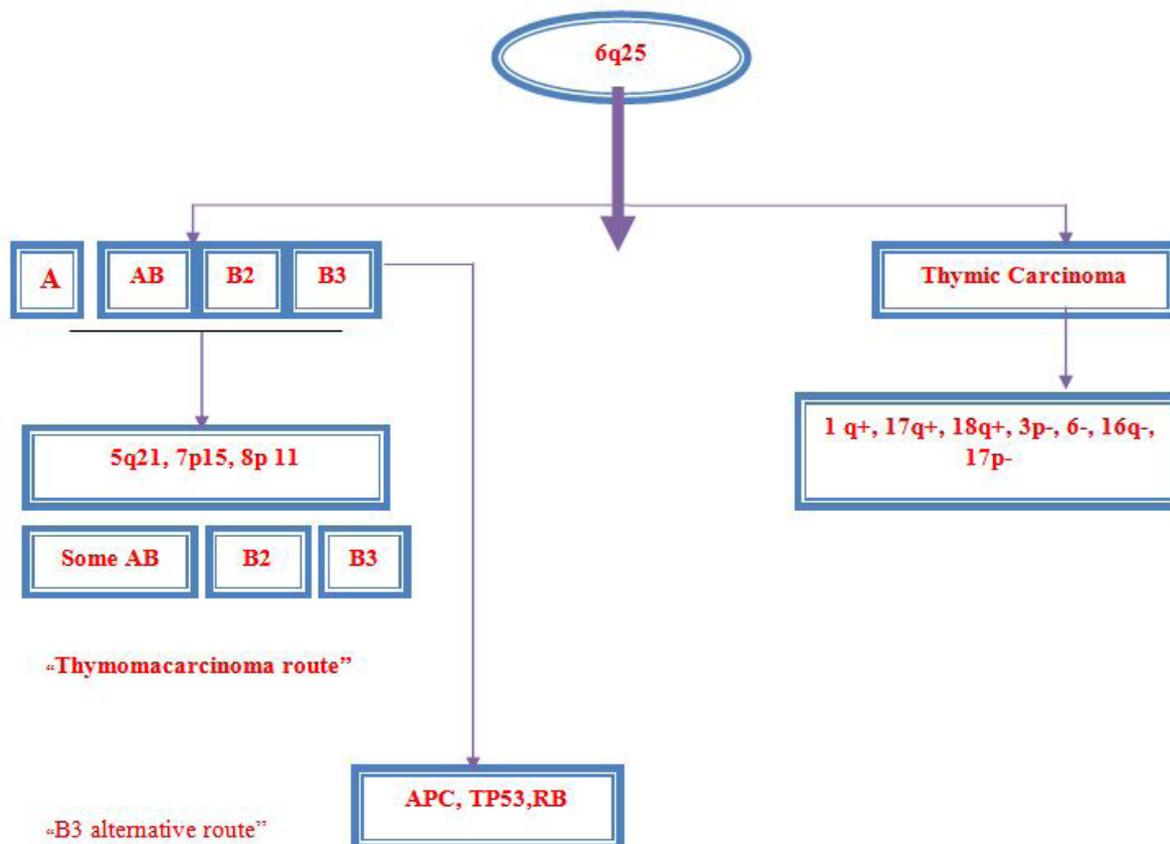


Figure 1: Molecular genetics route of Thymoma cancer [35]

Monoclonal Antibodies	Clinical trial identifier number	Phase	Study design	Target
Cetuximab	NCT01025089	Phase II	Non-Randomized, Open Label, Safety/Efficacy Study	EGFR

Table 2: Non-FDA approved Monoclonal antibodies [36]

Kinase Inhibitors

Non-FDA approved Kinase Inhibitors: There is no kinase inhibitor that is currently approved by FDA for thymoma. However, many kinase inhibitors are under clinical trials in phase I, II, and III as in the Table-3 below:

Kinase Inhibitors	Clinical trial identifier number	Phase	Study design	Target
Erlotinib + Bevacizumab	NCT00369889	Phase II	Open Label, Safety/Efficacy Study	EGFR
Sunitinib	NCT01621568	Phase II	Open Label, Efficacy Study	VEGFR2, PDGFRb, FLT3, c-kit
Saracatinib	NCT00718809	Phase II	Open Label, Efficacy Study	Src and Abl
Sunitinib	NCT01306045	Phase II	Non- Randomized, Open Label, Efficacy Study	VEGFR2, PDGFRb, FLT3, c-kit
Imatinib	NCT00314873	Phase I	Non- Randomized, Open Label, Safety/Efficacy Study	TKI KIT, Bcr-Abl, PDGFR

Table 3: Non-FDA approved kinase inhibitors [37-41]

HDAC Inhibitors

Non-FDA approved HDAC inhibitors: There is no HDAC inhibitor that is currently approved by FDA for thymoma. However, some are under clinical trials in phase I, II, and III as in the Table-4 below:

HDAC Inhibitors	Clinical trial identifier number	Phase	Study design	Target
Belinostat	NCT00589290	Phase II	Open Label, Safety/Efficacy Study	Pan-HDAC

Table 4: Non-FDA approved HDAC inhibitors [42]

Conclusion

Currently, there is no immunotherapeutic agent, which is FDA approved for the treatment of malignant thymus cancer, but there are various immunological monoclonal antibodies and kinase inhibitors, such as bevacizumab, erlotinib, cetuximab, sunitinib and

imatinib, which are under clinical trials for FDA approval. The researchers are still challenged in exploring innate and adaptive immune systems because immunotherapy might be a beneficial future for the treatment of thymus cancer. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy) for thymus cancer. Appropriate preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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