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Hypothesis: Fingolimod explores new horizons in treatment of lymphoma

Arsalan Azimi *

Histomorphometry & Stereology Research Centre, Shiraz University of Medical Sciences, Shiraz, Iran

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ABSTRACT

Lymphomas (Hodgkin's (10%) and non-Hodgkin's (90%) lymphomas) are a group of blood cell tumors arising from lymphocytes and lymphadenopathy is the most common primary presentation of the disease. In non-Hodgkin lymphomas, the prognosis is worse. As the disease initiates, neoplastic cells may spread to and involve other lymph nodes and extra nodal regions. The disease is staged based on desperation of neoplastic cells and the prognosis highly depends on the stage of the disease at the time of diagnosis. Fingolimod is an immunomodulating drug, approved for treating relapsing forms of multiple sclerosis. Fingolimod impairs migration of lymphocytes from lymph nodes and it is hypothesized that Fingolimod could alleviate and decrease disease burden of lymphoma as it sequesters malignant cells within involved lymph nodes and it decelerates progression of the disease, increases efficacy of other treatment options and it is synergistic with anti-VEGF medications, it is an anti-metastatic, anti-inflammatory, cytostatic/cytotoxic agent and it boosts function of immune system in deterioration of neoplastic cells. Therefore, the agent can be used not only to treat lymphoma, but also to control and prevent relapse of the disease in those who are remitted.

Introduction

Lymphomas are a group of blood cell tumors arising from lymphocytes. Lymphomas are lymph-node based diseases and lymphadenopathy is their most common primary presentation. The two major types of lymphoma are Hodgkin's and non-Hodgkin's lymphomas. About 90% of lymphoma patients have non-Hodgkin lymphoma (NHL). According to the U.S. National Institutes of Health (NIH), lymphomas account for about five percent of all cases of cancer in the United States. Approximately 2.1% of general population will be diagnosed with non-Hodgkin lymphoma at some point, during their lifetime. The life time risk of developing Hodgkin lymphoma is 0.2% for general population [1,2]. The incidence of HL is approximately 26.6 per 100,000 men and 18.9 per 100,000 women and in the United States it was estimated that 9290 new cases of HL would be diagnosed in 2013 [1]. Over the past two decades the incidence of non-Hodgkin lymphoma (NHL) has become doubled in the United States of America and most of other western countries [3]. The American Cancer Society had estimated that approximately 65,540 new cases of NHL would be diagnosed in 2010 [4] and more than 69,740 cases of NHL and 19,020 deaths due to NHL were predicted for 2013 [2]. By the year, about 731,277 people in the United States were either living with, or in remission from lymphoma. By the population, 172,937 people had Hodgkin lymphoma and 558,340 people had non-Hodgkin lymphoma [5].

Hodgkin and non-Hodgkin lymphomas are differed by detection of Reed–Sternberg cells, which are indicative of Hodgkin lymphoma. Although these cells comprise only 1–2% of the total tumor cell mass, Reed–Sternberg cells are the only neoplastic cells of the disease. The remainder of tumor mass is composed of a variety of reactive and mixed inflammatory cells. Most Reed–Sternberg cells are of B-cell origin and only 1–2% originate from T-cells [6,7]. There are many types of non-Hodgkin lymphoma (NHL). Most of cases with NHL have a B-cell type (about 85%). The rest are affected either by a T-cell type or an NK-cell type of NHL [5].

Whether Hodgkin or non-Hodgkin staging of malignancy is necessary to identify treatment and make a prognosis. Staging of lymphomas is made based on location and number of sites of involvement. Although Hodgkin lymphomas are potentially curable, final prognosis and five-year survival highly depends on the stage of the disease at the time of diagnosis [1].

In non-Hodgkin lymphomas, the prognosis is worse. In the United States, the five year survival rate is 69% [8]. Overall, the survival rates of patients with NHLs are less than those for Hodgkin lymphomas. For NHL, the survival rates are 77% for 1 year, 59%

* Address: Zand Blvd., Shiraz, Iran. Tel.: +98 (0) 9379876373.
E-mail address: arsalan.azimi@gmail.com

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for 5 years and 42% for 10 years. Many investigators believe that more aggressive treatments increase the cure rate [9,10].

Egress of lymphocytes from lymph nodes and lymphoid tissues is dependent to a chemical mediator called Sphingosine 1 phosphate (S1P). It is a lipid chemo-attractant, found predominantly in serum and lymph and to a lesser extent in lymph nodes. However, there is a gradient in concentration of S1P, lower in lymph nodes and higher in circulation. Engagement of Sphingosine 1 phosphate with its receptor called Sphingosine 1 phosphate receptor 1 ($S1PR_1$) on surface of lymphocytes makes them egress from lymph nodes to circulation, following gradient of S1P concentration [11–13]. $S1PR_1$ is highly expressed on surface of B and T cell lymphocytes [14,15]. Egress of lymphocytes from secondary lymphoid organs depends on concentration gradient of S1P, therefore any agent interacting with S1P concentration gradient, affects such cells and impairs their migration [16–18].

Fingolimod also known as FTY720 is an immune-modulating drug and the first FDA (Food and Drug Administration) approved oral medication to treat relapsing form of multiple sclerosis (MS) [19]. Fingolimod, when metabolized and phosphorylated by the liver, acts as a potent agonist of S1P. It binds to and activates $S1P_1$ receptor, leading to internalization of $S1PR_1$ receptors on lymph node T-cells. As a result Fingolimod impairs migration of lymphocytes from lymph nodes [15,20,21].

In the following it is hypothesized that Fingolimod may alleviate and decrease disease burden of lymphoma.

Hypothesis

It is hypothesized that both Fingolimod (FTY720) and phosphorylated Fingolimod (FTY720-P) could explore new horizons in treatment of lymphoma. To evaluate possible effects of FTY720/FTY720-P on surveillance and prognosis of patients with non-Hodgkin lymphoma, patients should be selected and divided into different groups based on their overall prognosis. For this purpose patients should be categorized based on their age, tumor histology, tumor stage, tumor bulk, performance status, serum lactate dehydrogenase (LDH) levels, beta-2 microglobulin levels, B symptoms and presence or absence of extra-nodal involvement. Then, each group should be further divided into two subgroups; one receiving current medication regimen for NHLs and the other receiving the same medication regimen together with oral Fingolimod (metabolized to FTY720-P) or intravenous FTY720. Finally patients in these two subgroups should be compared in order to evaluate possible effects of FTY720 or oral Fingolimod. Thereby, PET-scan, rate of progression and metastasis, appearance or relief of B symptoms, efficacy and duration of the therapy, side effects of the therapy, relapse of the disease and physical performance should be recorded and compared in subgroups of each group and the patients should be followed lifelong.

Evaluation of the hypothesis

Classic HL appears to be developed from a B-cell in the germinal center of a lymph node which has neither undergone immunoglobulin gene rearrangement, nor apoptosis. Impaired apoptosis results in immortalization of such cells, which gives rise to Reed–Stenberg cells (RS cells). RS cells secrete and release cytokines that account for the accumulation of a variety of reactive and mixed inflammatory cells (including lymphocytes, plasma cells, neutrophils, eosinophils, and histiocytes) inside the involved lymph node(s). Many of the characteristic clinical features of HL can be explained by the complex action of cytokines and other growth factors that are secreted by the Reed–Stenberg cells. Subsequent infiltration and proliferation of inflammatory cells result in an enlarging painless lymph node which can present as a solid mass and cause mass effect or invade local adjacent organs. NHLs are progressive clonal expansion of B cells, T cells, or NK cells. Mutations in cellular genes and damages affecting proto-oncogenes or tumor-suppressor genes result in cell immortalization and development of such malignancies. Oncogenes may be activated by chromosomal translocations whereas the tumor-suppressor loci may be inactivated by deletion or mutation in chromosomes [22].

Success of treatment is dependent on several parameters, including the type of lymphoma, stage of the disease, cell type, extra nodal involvement, age of the patient, and presence of B symptoms (e.g. fever, night sweats, weight loss, etc.) [9,10]. Extra nodal involvement and B symptoms are common in advanced stages of the disease and their presence worsens the prognosis [22].

Fingolimod (FTY720), when phosphorylated after oral ingestion, is a potent agonist of S1P and the resulted compound phosphorylated Fingolimod (FTY720-P) can engage with and alter function of four of the five known subtypes of S1P receptors ($S1PR_1$, $S1PR_3$, $S1PR_4$, and $S1PR_5$) [20,21].

$S1P_1R$ plays a key role in the regulation of lymphocyte egress from lymphoid tissues. Between T-cells only those that express CCR7 on their surface, are affected by concentration of S1P. CCR7 is a chemokine receptor for CCL19 and CCL21. Therefore, only Naive T-cells and central memory T lymphocytes are affected by the gradient in concentration of S1P. Furthermore, egress of B-cell lymphocytes from secondary lymphoid organs depends on concentration gradient of S1P [16–18].

FTY720-P sequesters malignant cells within involved lymph nodes

FTY720-P is a high affinity agonist of $S1PR_1$, yet subsequently it induces receptor down-regulation that sequesters Naive T-cells, central memory lymphocytes and B-cell lymphocyte in lymphoid tissues [23]. In most cases of lymphoma the chief neoplastic cell is derived from a primary lymph node, where it undergoes uncontrolled replication and afterwards, neoplastic cells may spread to and involve other lymph nodes or extra nodal regions. It is hypothesized that after initiation of lymphoma, Fingolimod-phosphate may inhibit dissemination of neoplastic cells to other sites of lymphatic system.

NHL is developed by progressive clonal expansion of neoplastic B cells, T cells, or NK cells. RS cells of HL are derived from a B-cell in germinal center of a lymph node [22]. FTY720-P binds to $S1PR_1$, and impairs egress of both B and T cells from lymphoid organs. It also binds to $S1PR_5$, which is expressed on surface of NK-Cells and plays an important role in their migration [23].

Therefore, Fingolimod may affect migration of every types of neoplastic cells in both Hodgkin and non-Hodgkin lymphoma.

FTY720-P increases efficacy of other treatment options

As hypothesized before, FTY720-P could sequester neoplastic cells and it may decelerate progression of lymphomas, thereby it is also hypothesized that FTY720-P can facilitate the process of therapy and increase rate of cure success. In addition, isolating neoplastic lymphocytes in lymph nodes, makes it possible for surgical resection of involved lymph nodes and increases effectiveness of radiotherapy. The remission could decelerate progression of the disease by the time between diagnosis and initiation of therapy. This buys physician(s) enough time to plan for and choose the best way to approach to the disease.