Case report

Theophylline as a therapy for chronic lymphocytic leukemia: a case report and review of literature

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Abstract—We herein, report that theophylline which can induce apoptosis in chronic lymphocytic leukemia (CLL) cells both in vitro and in vivo, also appears to be effective when used clinically to treat an advanced CLL patient.

Key words: CLL; theophylline.

INTRODUCTION

Theophylline, a methylxanthine which has been extensively used for the treatment of bronchial asthma acts by inhibiting phosphodiesterase, the enzyme responsible for degradation of cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP) thereby accumulating cAMP [1, 2]. This second messenger in turn has been found to be involved in the regulation of many genes [3]. Interestingly, there are also reports which suggest that theophylline can induce apoptosis in lymphocytes from chronic lymphocytic leukemia (CLL) patients indirectly through accumulation of cAMP both in vitro [4, 5] and in vivo [6]. This case report describes an advanced CLL patient who was treated with theophylline at a dose commonly administered for the treatment of bronchial asthma. The clinical course of this patient together with a review of the relevant literature concerning the role of theophylline in the treatment of CLL has been presented.

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CASE REPORT

A 70-year old woman was diagnosed with CLL (unknown stage) in another institute and was followed up there for 7 years until she developed rapid and progressive anemia, thrombocytopenia, leukocytosis and was admitted to our institute. On physical examination, she was found to have generalized lymphadenopathy and hepatosplenomegaly. Her blood count was 380,000/μl with 97% lymphocytes. The hemoglobin level was 6.8 g/dl with a platelet count of 120,000/μl. Bone marrow aspiration revealed complete replacement of the bone marrow with CLL. The treatment was started with chlorambucil orally at a dose of 4 mg/m², but she developed pancytopenia and neutropenic sepsis after 2 weeks and refused further treatment with anti-cancer drugs. She immediately began treatment with theophylline, at a dose of 300 mg twice daily together with supportive blood transfusion. The patient became transfusion-independent after 6 months of treatment, her lymphadenopathy resolved and there was an improvement in her hepatosplenomegaly. She also could maintain her WBC count between 53,000/μl to 80,000/μl with 89% lymphocytes. Her hemoglobin improved between 10.2 and 12.1 g/dl and there was no theophylline-associated tremor, insomnia, tachycardia, convulsions and hypotonia. She has remained on theophylline for one and a half years and is maintaining her clinical benefit.

DISCUSSION

This case demonstrates that theophylline may have a therapeutic role in advanced CLL. The blood count of our patient improved after treatment with theophylline and there was no theophylline-associated toxicity. Although there are several reports indicating definite effects of theophylline on CLL cells in vitro, there are only few clinical studies indicating the role of this drug in the treatment of CLL patients. Komlos et al. found that treatment of T and B-lymphocytes from CLL patients with theophylline led to an increased T-cell function and a decrease in the surface immunoglobulin positive cells. These findings were not seen in theophylline treated lymphocytes from normal volunteers [7]. Theophylline also could induce apoptosis in B-cells of CLL patients in a dose dependent manner and this apoptotic function of theophylline was associated with an increase in cAMP [4], an increase in the expression of c-myc which induces apoptosis [8] and a decrease in the expression of bcl-2 protein which inhibits apoptosis [9]. These effects seem to increase when these cells were treated with both chlorambucil and theophylline [4]. Mentz et al. described a patient with Rai Stage II CLL and asthma, whose CLL remained stable for 10 years without any anti-leukemic or steroid therapy. This patient was treated with theophylline at a dose of 300 mg daily [6]. Recently, Makower et al. had demonstrated the efficacy of theophylline in two CLL patients. Their patients showed clinical improvements while receiving theophylline at a dose of 300 mg twice daily as used by us in our patient and there was also no theophylline-associated toxicity [10].