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Letter to Editor

EFAVIRENZ, A WELL-KNOWN ANTIVIRAL DRUG, MIGHT BE A NEW OPTION IN THE TREATMENT OF CANCER

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ABSTRACT

Cancer is a potentially fatal disease, where cells abnormally divide which hurts the tissues. The incidences of cancer are increasing worldwide and become one of the leading causes of death. A numbers of anticancer agents are available in the market or under clinical trials used for its treatment, but unfortunately, none of them is able to treat cancer. Thus, the exploration of novel mechanistic pathways of existing molecules may help to develop more effective anticancer agents. Efavirenz, a well-known non-nucleoside reverse transcriptase inhibitor, used in the highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) infected patients with tolerable side effects. Newly emerging data revealed that efavirenz has the potential to induce toxic effects against a wide range of cancer cells by altering various cancer pathways. Thus, this existing antiretroviral drug with already known safety profiles could be rapidly utilized for the treatment of various cancers.

Keywords: Efavirenz, Endogenous reverse transcriptase, Apoptosis, Anticancer

Cancer is a leading cause of death which is characterized by uncontrolled growth and spread of abnormal cells in the body whose exact etiology is unknown, but 90-95% cases are due to the environmental factors [1, 2]. For the treatment of cancer, various options are available such as surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy and palliative care depends on the type, location, and grade of cancer as well as the person's health, but instead of that incidence of cancer keeps increasing on a global scale. Mostly all of the anticancer drugs show various side effects such as unwanted hair loss, sometimes potentially life-threatening conditions such as anemia and various infections [3, 4]. In the present situation, there is no safe and effective cancer therapy available due to lack of knowledge of the exact mechanism of anticancer agents and their side effects. Thus, there is an urgent need of novel molecules with novel mechanistic pathways which may help to develop more effective anticancer agents.

The endogenous reverse transcriptase plays an important role in the mechanism of cancer which is only activated in cancer cells and essential for their malignancy. Targeting of the endogenous reverse transcriptase specifically in tumors is the most promising approach in the field of oncology [5, 6]. Efavirenz (EFV) is a well-known antiretroviral drug (approved by FDA in 1997) widely used to treat human immunodeficiency virus (HIV) patients in combination with protease inhibitors, inhibits the endogenous reverse transcriptase in various cancer cells, thus, here I propose that efavirenz could be a potential anticancer agent.

The survival of HIV-1-infected patients is prolonged, and causes of death have changed due to the introduction of highly active antiretroviral therapy (HAART). In the literature, some reports have shown that the incidence of precancerous lesions in HIV-1-infected patients on HAART is less as compared with patients without HAART [7-9]. From these reports, it can be concluded that the decrease incidence of cancer is may be due to an anti-neoplastic effect of the drugs used in HAART.

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) which is used as part of HAART for the treatment of a HIV [10]. Emerging reports indicate that efavirenz induces the anticancer effect in various cells [11, 12]. This effect might be based on several different mechanisms such as the inhibition of endogenous reverse transcriptase, inhibition of the activity of tumor-promoting retro-elements and activation of oxidative stress mitochondrial-dependent apoptotic signaling pathways as shown in fig. 1.

The NNRTI, EFV is toxic against a wide range of cancer cells and only have a minor toxicity against normal tissue cells (fig. 1) [13]. Sinibaldi-Vallebona *et al.* [14] reported the anticancer effect of efavirenz in mice. As efavirenz is very well-tolerated in HIV treatment, so it could also be a promising for cancer treatment.

In a recent report, Patnala *et al.* (2014) demonstrated that efavirenz at low concentration (15 & 45 µM) inhibiting the activity of tumor-promoting retro elements, leading to a reduction in the rate of breast cancer proliferation. Further, this study has shown that efavirenz modulates the various genes expressions, but the underlying mechanism is still not cleared. These results indicate that efavirenz at lower concentration is a potent anticancer agent in the breast cancer [12].

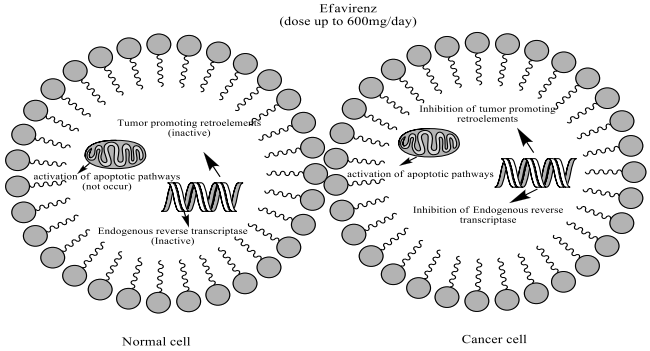

Fig. 1: Effect of Efavirenz at a lower concentration in normal and cancer cells. In normal cells, efavirenz produces tolerable damage but in cancer cells, efavirenz inhibits the endogenous reverse transcriptase, tumor promoting retroelements along with activation of apoptotic pathways which provide a new hope as anticancer agent. fig. has been drawn by Bio Chemdraw.

Among all non-nucleoside reverse transcriptase inhibitors, efavirenz has the highest antiproliferative effect with EC50s of 31.5µmol/l and 49.0µmol/l, against pancreatic BxPC-3 and Panc-1 cancer cell lines respectively. Further, this study compares the *in vitro* toxicity to

blood levels of HIV-positive patients and suggested that the *in vitro* toxic concentrations of efavirenz against cancer cells can be achieved *in vivo* in a low percentage of patients without increasing the standard dose of 600 mg EFV daily [11]. Thus, low dose efavirenz may have a beneficial effect by modulating various anticancer signaling pathways in the cancer cells which is summarized in the fig. 1.

The notion of an antiviral drug as a potential anticancer agent could be strange but we know that the therapeutic effect of many medical agents is far from their original use. For example, prontosil which is a coloring agent found to have antibacterial activities and became the first synthetic drug used in the treatment of general bacterial infections in humans. Recently, I also proposed the use of pyrethroid insecticide, deltamethrin as an anticancer agent [15]. I believe that efavirenz can also improve cancer management by inhibiting the various cancer pathways. Because it is an existing drug with known pharmacokinetics and safety profiles and is currently in use, so, it can be rapidly evaluated in clinical trials to evaluate its effect on various cancers.

The mechanisms underlying the anticancer effect of efavirenz on cancer cell are still unclear. Thus, in future studies, further exploration of the anticancer mechanisms of efavirenz should be evaluated which will be helpful for researchers to design efavirenz as a novel anticancer agent.

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CONFLICT OF INTERESTS

Author declares that he has no conflict of interest.

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