Biomedical Data Mining

Extended Abstract

Angiogenesis and cancers: Comparing the anti-angiogenic efficacy of Efavirenz to Thalidomide

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Abstract

Statement of the Problem: HIV infection has been associated with Kaposi's sarcoma (KS), cervical cancer and non-Hodgkin's lymphomas. WHO guidelines on ART recommends efavirenz as a first-line drug in HIV management therapy for all ages, gender, and gestational age. Nevertheless, Efavirenz has not been adequately studied in cases of advanced HIV disease (CD4 counts < 50 cells/ mm3) and after the failure of other regimens.

Methods: This study compares Efavirenz, marketed as Sustiva to the known anti-angiogenic and anti-cancer agent, thalidomide. With animal ethics clearance (No 2008/7/1), 30 chicks chorioallantoic membrane (CAM) was used as an in vivo vascular test environment to test the effect of Efavirenz (marketed as Sustiva) in comparison to that of thalidomide (Sigma-Aldrich, T144). CAM images were captured on day 5 and 15 of treatment. Results were analyzed using the one-way Analysis of Variance and Fischer exact test ($p \leq 0.05$).

Results: Fischer exact test showed an association between treatment drugs and CAM angiogenesis ($p<0.05$). Unlike thalidomide, efavirenz suppressed both angiogenesis and erythropoiesis, reducing mean CAM blood vessels score to 0.0.

Conclusion: Angiogenesis inhibitors are potent anti-cancer agents. This study showed Efavirenz to be a more potent anti-angiogenic agent than thalidomide, possessing an absolute anti-angiogenic effect in the developing chick CAM. And unlike thalidomide, it suppressed erythropoiesis. This awards Efavirenz an additional score when compared to thalidomide. From this work, we conclude that there is a possible future clinical use for Efavirenz as an anti-cancer drug, and with no fear of adverse effects for pregnant women and their babies, in utero.

Introduction

Human Immunodeficiency Virus (HIV) is the etiologic agent of Acquired Immune Deficiency Syndrome (AIDS), a deadly disease characterized by a profound upheaval of the immune system and the consequent increased risk of developing infectious illnesses and tumors. HIV life cycle is mediated by cellular and viral proteins: among the latter, the reverse transcriptase, integrase and aspartyl protease enzymes are key for HIV replication and infectivity.

Briefly, HIV infection begins when the gp120 protein of the viral envelope binds to the CD4 receptor on T cell surface. This is followed by gp120 interaction with a co-receptor (most often a chemokine receptor), and HIV entry into the cell. Thereafter, the HIV reverse transcriptase copies the viral RNA genome into the viral DNA, which is integrated into host cell genome by the HIV integrase, and then transcribed into messenger RNA. Subsequently, HIV transcripts are translated into HIV envelope proteins and the fused precursors of HIV capsid and polymerase proteins: this gives rise to the production of immature, non-infectious viral particles that “bud” from infected cells. Finally, the HIV aspartyl protease cleaves the fused capsid-polymerase proteins into the functional polypeptides, and HIV matures becoming infectious.

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Survival of HIV-positive individuals has been greatly extended by the combined Anti-Retroviral Therapy (cART), which has rendered HIV infection a chronic disease. cART results from the mix of drugs inhibiting the HIV reverse transcriptase, integrase or aspartyl protease.

In particular, HIV-reverse transcriptase inhibitors halt the synthesis of viral DNA, and are available in three forms: (a) nucleoside analog reverse transcriptase inhibitors, which are modified deoxynucleotides analogs competing with natural deoxynucleotides for incorporation in the HIV DNA that is being synthesized; (b) nucleotide analog reverse transcriptase inhibitors, that are phosphonate deoxynucleotides analogs again competing the incorporation of natural deoxynucleotides in the forming HIV DNA; (c) non-nucleoside reverse transcriptase inhibitors, which bind to the allosteric sites of HIV-reverse transcriptase, thereby hampering its function. Nowadays, a HIV-reverse transcriptase inhibitors-based cART containing the nucleotide analog tenofovir, the nucleoside analog emtricitabine and the non-nucleoside efavirenz is recommended as first-line treatment of HIV infection.

Conclusion

Cancer growth and dissemination are favored and sustained by the formation of new blood vessels within the tumor area. Consistently, compounds counteracting the development of tumor vasculature can limit or slow cancer clinical progression. In this regard, antagonists of the highly angiogenic VEGF have been found effective against different types of human tumors.

However, the finding that patients treated with these drugs can undergo severe adverse effects, and/or develop drug resistance, is prompting the identification of anti-angiogenesis drugs alternative to VEGF antagonists. In this context, it has to reminded that clinical trials assessing the anti-tumor efficacy of synthetic MMP inhibitors impairing tumor angiogenesis in pre-clinical models have failed: this has been due to the poor solubility, lack of specificity and/or inefficacy of the drugs.

In view of chemokine role in inflammation-driven, pathological angiogenesis, antagonists of the chemokine receptors are currently being evaluated for their efficacy in countering tumor growth and metastases. Indeed, drugs targeting single chemokine receptors have been found effective against hematological malignancies. Moreover, CXCR4 antagonists have been shown to reduce tumor angiogenesis in animal models of human tumors. However, one should consider that a given chemokine can bind to different receptors, which are all capable of triggering the AKT-MMP pathway starting angiogenesis. In this regard, HIV-protease inhibitors effectively inhibit the AKT-MMP as well as other pathways which lead to both new blood vessel formation and cancer cell survival, growth or locomotion.

In contrast, based on the reviewed literature, the anti-angiogenic actions of HIV-reverse transcriptase inhibitors appear limited: in fact, these drugs hamper some pro-angiogenic pathways, while favoring others.

Among HIV-protease inhibitors, ritonavir and nelfinavir have proven to be particularly effective in inhibiting tumor-associated new blood vessel formation. Repositioning of these anti-HIV drugs in cancer therapy has been feasible, as they are employed since many years, and their pharmacokinetic and tissue distribution are well known. Actually, clinical trials combining ritonavir or nelfinavir with standard anti-cancer therapeutics have given good results. However, as for other first-generation HIV-protease inhibitors, either nelfinavir or ritonavir increases lipid and glucose plasma

levels in treated patients. Though novel HIV-protease inhibitors such as darunavir and atazanavir do not affect lipemia or glycemia, information on their anti-angiogenic activities is narrow.

Therefore, added work should dissect darunavir or atazanavir impact on angiogenesis, and then design and test atazanavir, darunavir, ritonavir or nelfinavir analogs endowed with selective anti-angiogenic effects. To this end, further molecular modeling approaches and protein-ligand studies are needed in order to identify more precisely the targets of HIV-protease inhibitors.

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