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Drug interactions between antineoplastic and antiretroviral therapies: Implications and management for clinical practice☆

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Contents

Abstract

Despite the impact of combined antiretroviral therapy (cART) on human immunodeficiency virus (HIV)-related mortality, malignancies remain the second most common cause of death in HIV infection in developed countries. In addition to the AIDS-defining malignancies, other cancers such as Hodgkin's lymphoma and anal cancer, are more frequent in HIV-infected patients who survive longer even though they do not have complete immune restoration The use of concomitant antineoplastic chemotherapy and cART have been demonstrated to be feasible

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and effective in patients with HIV-related malignancies; however, many drugs used in cART regimens have the potential for causing drug interactions as a result of their ability to either inhibit or induce the cytochrome P450 (CYP) enzyme system. Since many antineoplastic drugs are also metabolised by the CYP system, co-administration with cART could result in either drug accumulation and possible toxicity, or rapid drug metabolism and decreased efficacy. Unfortunately, very limited prospective interaction data are available to safely guide the combined use of cART and chemotherapy. This paper reviews the potential drug interactions and therapeutic considerations of the antiretroviral agents used to treat HIV and the most common anticancer agents used in the treatment of malignancies found in patients with HIV infection.

Keywords: AIDS-related malignancies; Antineoplastic agents; Antiretroviral drugs; Cytochrome P450; Drug interactions

1. Introduction

Since the onset of the HIV/AIDS pandemic in the early 1980s, HIV infection and cancer have been closely interrelated. Several reasons explain this phenomenon: the immune suppression induced by HIV favors occurrence of cancers such as high-grade non-Hodgkin's lymphoma (NHL); the oncogenic nature of certain viruses, which directly cause cancers such as HHV8 and Kaposi's sarcoma (KS) and human papilloma virus and cervical cancer in women or rectal squamous cell cancer in men. Because many of these tumors have such a high prevalence in HIV-infected persons, they are included as part of the clinical definition of AIDS and are reported formally as "AIDS-defining malignancies". The spectacular progress demonstrated by controlling HIV replication in the vast majority of patients receiving combined antiretroviral therapy (cART) has resulted in several changes in the epidemiology of malignancies in HIV disease. First there has been a large decrease in the prevalence of AIDS-defining malignancies even though lymphomas and Kaposi's sarcoma remain the most frequent [1,2]. Secondly, the increase in survival of HIV-infected patients has led to the observation in several cohort studies that an increasing number of "non-AIDS-defining" malignancies, such as Hodgkin's disease (HD), invasive anal carcinoma, lung carcinoma, skin cancer and hepatocarcinoma, are now being reported at higher than expected frequencies compared to rates observed in the general population [1,3–6]. Not only are these tumors more frequent than they used to be in the HIV-infected population, but several epidemiological studies have now established that HIV-infected patients are at higher risk of developing these malignancies than in the non-HIV-infected population [6,7]. The risk factors for HIV-infected persons with non-AIDS-defining cancers are multi-factorial, and include lifestyle habits (smoking and sun exposure), HIV itself, co-infection with oncogenic viruses (human papilloma virus, hepatitis B and C virus, and Epstein Barr virus), and possibly drugs or medications [7,8]. HIV infection represents both a cause for immune suppression, which itself favors carcinogenesis and a major cause for deleterious chronic immune activation and inflammation which may also trigger carcinogenic pathways. Interesting data from the Cohorte Aquitaine in France suggests that the two different categories of malignancies observed throughout HIV infection may be related to two different profiles: time spent with a low CD4 cell count and exposure to a high viral load [9]. Both conditions are associated with a higher risk for developing AIDS-related cancers while the time spent with CD4 counts under 500 cells/mm^3 or with viral load greater than 500 copies/ml are associated with a higher risk for non-AIDS-defining malignancies [4]. Furthermore, cancers occurring in HIV-infected patients tends to occur at a younger age than expected and to be more aggressive [10].

These findings lead clinicians responsible for the care of HIV-infected patients to look for early cancer detection tools and adaptive therapeutic strategies. The use of concomitant chemotherapy and cART has been demonstrated to be feasible and effective in reducing morbidity associated with opportunistic infections and to improve overall survival in patients with HIV-related malignancies [9,11,12]. Treatment with cART, however is complicated by potential pharmacokinetic and pharmacodynamic drug interactions. Pharmacokinetic drug interactions are much more common because of the nature of HAART drug metabolism and particularly the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs), which are extensively metabolised *via* the cytochrome P450 (CYP450) enzyme system and may also be inhibitors or inducers of CYP450. While numerous interactions of varying clinical significance have been described with these antiretroviral drugs [13], less is known about the potential for drug interactions with antineoplastic agents. Since many anticancer agents are metabolised to some degree by the CYP system [14], concomitant cART use might result in either drug accumulation and possible toxicity, or decreased efficacy of one or both groups of agents. No specific recommendations exist and clinicians must make decisions despite the missing data by applying greater attention to the choice of chemotherapy protocols and the usual predictive surrogate markers of HIV disease, such as CD4 cell counts and viral load.

This paper reviews the potential interactions and subsequent therapeutic considerations between antiretroviral drugs and the most common neoplastic agents used in the treatment of AIDS-related malignancies assuming that specific pharmacokinetic information on the drug–drug interactions is limited, much can be predicted from the known metabolism of these agents.