Adjuvant High-Dose Interferon- α for Resected Melanoma in a Patient with HIV Infection

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ABSTRACT

Adjuvant interferon (IFN)- α remains the standard adjuvant therapy for intermediate and high-risk melanoma after definitive surgical resection. Data addressing the role and safety of adjuvant immunotherapy in HIV-infected patients with melanoma are

lacking. We report on an HIV⁺ patient who received IFN- α as adjuvant treatment for high-risk melanoma. To our knowledge, this is the first reported case of such an approach. *The Oncologist* 2010;15:695–698

INTRODUCTION

Malignant melanoma (MM) represents the sixth most common cancer in the U.S. and accounts for the highest fatality rate among all cancers in young adults [1]. Despite efforts at prevention and screening, MM incidence continues to rise without an appreciable decrease in mortality [2–4]. Although surgical excision represents the treatment of choice for early disease (stage I–IIA), with a 70%–90% cure rate, higher stages are associated with a poor prognosis [5, 6]. Adjuvant high-dose interferon (IFN)- α remains the standard of care for patients with resected stage IIb, IIc, and III tumors. It remains the only treatment to date that leads to longer relapse-free and overall survival times [7–9]. Further, a statistically significant survival benefit was con-

firmed by two recent meta-analyses of randomized controlled trials employing adjuvant IFN- α [10, 11].

Although MM is not considered an AIDS-defining malignancy, HIV infection increases MM incidence by approximately threefold [12]. MM in HIV-infected patients is generally associated with a poor prognosis, stage-for-stage, often relapsing with multifocal metastatic disease [13, 14]. Adjuvant IFN- α trials have uniformly excluded HIV-infected patients [14].

CASE PRESENTATION

The patient is a 50-year-old white male with a history of HIV who presented to his dermatologist with a 1-year history of a hyperpigmented mass on his back. Initial biopsy

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showed a MM. An excisional biopsy with sentinel lymph node sampling was then performed. Pathologic examination demonstrated a 3.01-mm thick, Clark level IV, superficial spreading melanoma with ulceration. The excisional biopsy resection margins were clear by 1 cm and a right axillary sentinel node was negative for metastatic disease. Postoperative positron emission tomography (PET) with computed tomography (CT) scanning was notable for a 2.1-cm right neck lymph node with a standardized uptake value (SUV) of 8.7 and a 1.7-cm thyroid lesion (SUV, 4.7). Fine-needle aspiration of the right neck lymph was consistent with metastatic melanoma. The patient then underwent a right neck dissection and total thyroidectomy. Final pathologic examination showed MM present in 12 of 36 right cervical nodes. Additionally, there was papillary carcinoma in the right lobe of the thyroid measuring 2.2 cm, with three of 37 lymph nodes containing papillary carcinoma. Pathologically, the patient was staged with synchronous T3bN3M0 (stage IIIC) melanoma and T2N1bM0 (stage IVA) papillary thyroid carcinoma. Eight weeks after surgery, the patient was successfully treated with radioactive iodine ablation. Highly active antiretroviral therapy (HAART) was initiated with emtricitabine, tenofovir, and raltegravir. The patient was then referred to medical oncology to consider adjuvant IFN- α .

HIV had been diagnosed 1 year prior to presentation as part of a screening program with an initial CD4 count of 500 cells/ μ L. There was no personal history of malignancy or AIDS-defining illnesses. His family history was negative for malignancy or inherited cutaneous nevi syndromes. Physical examination revealed a healthy man with well-healed surgical wounds in the upper back and right postero-lateral neck. There was no evidence of palpable lymphadenopathy in the neck or axillae. There was no abdominal organomegaly. The remainder of the skin examination was normal.

Ten weeks after surgery, a PET scan and magnetic resonance imaging of the brain were performed, which demonstrated no measurable active disease. Consent was obtained for IFN- α , and citalopram, 20 mg once daily, was initiated. High-dose IFN- α was administered at 20 million IU/ m^2 daily, 5 days per week, with a goal total dose of 20 treatments [15]. Treatment was delayed twice. Once was for noncardiac chest pressure on day 6, requiring a 3-day dose delay. The second was for grade III neutropenia on day 15 (with an absolute neutrophil count [ANC] nadir of $0.6 \times 10^3/\mu$ L); therapy was held until the ANC recovered to $1.0 \times 10^3/\mu$ L, and the remaining five doses were reduced to 15 million IU/ m^2 daily. With dose delays, therapy was administered over 5 weeks. HIV viral load, CD4 count, and liver function studies were monitored during therapy and are out-

Figure 1. Laboratory findings during and after IFN- α therapy. (A): HIV load and CD4 count during and after (up to 8 weeks) IFN- α therapy. (B): Blood cell counts. (C): Liver function tests.

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; BIL, bilirubin; IFN- α , interferon- α ; PLT, platelet count in 10,000/ μ L.

lined in Figure 1. The physical examination remained normal throughout treatment. The patient declined continued therapy with maintenance subcutaneous IFN- α .

At follow-up 2 months after completion of IFN- α , the patient developed a palpable 1-cm left supraclavicular lymph node. Fine-needle aspiration of the node revealed recurrent MM. A restaging CT scan revealed two new sub-centimeter lesions in the right middle lobe consistent with metastatic disease. Palliative temozolomide was initiated; progression of disease was noted after 2 months of therapy. The patient declined further cytotoxic treatments.

DISCUSSION

The mechanism by which HIV infection increases the risk for MM development is not well understood, but it likely is an immune-mediated phenomenon [12, 14]. MM in HIV-infected patients tends to follow an aggressive course, with significantly lower disease-free and overall survival times [13, 14]. The association between the degree of immunosuppression and the pathogenesis of MM also remains unclear, with reports demonstrating a correlation between the CD4 count and extent of disease [13].

In human and animal models, IFN- α -induced immune inhibition has been associated with HIV progression [16–18]. Conversely, a transient and significant antiretroviral effect has been observed when IFN- α is administered to treatment-naïve patients or those with Kaposi's sarcoma [19–27]. Furthermore, a rapid decline in HIV viral load following IFN- α administration in patients coinfecting with HIV and hepatitis C virus (HCV) has been demonstrated [28]. In the case described above, simultaneous initiation of HAART and IFN- α resulted in a substantial drop in HIV viral load whereas the CD4 count remained >400 cells/ μ l.

Substantial toxicity has been reported with concomitant administration of IFN- α and HAART. For example, a threefold higher incidence of HAART-related hepatotoxicity was observed when IFN- α and ribavirin were used to treat HCV in HIV $^{+}$ patients [29]. The purported mechanisms for this effect include accelerated progression to

HCV liver cirrhosis with HIV coinfection, the presence of HCV infection itself, and interactions between ribavirin and HAART [30]. Data regarding interactions between IFN- α and HAART are generally lacking, but IFN- α does decrease the metabolism of zidovudine, resulting in increased myelosuppression [27, 31, 32].

The rapid recurrence of melanoma in the case presented above may represent the lack of efficacy of IFN- α in an HIV $^{+}$ patient or the aggressive biology of the disease. Further, longer-term disease control may have been compromised by the patient's refusal to be placed on maintenance IFN- α . However, we have demonstrated that IFN- α can be safely administered to well-selected patients with HIV, and there was no short-term adverse impact on either the HIV viral load or CD4 count. The patient tolerated therapy with anticipated side effects that were effectively managed with standard dose reductions.

Adjuvant IFN- α could be considered for use in the post-operative setting, while acknowledging that efficacy data in the HIV $^{+}$ patient are lacking. Further investigation of immunomodulatory agents in HIV $^{+}$ patients with melanoma may be warranted.

AUTHOR CONTRIBUTIONS

Collection and/or assembly of data: Nakhle S. Saba

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