Cancers in Children Infected With the Human Immunodeficiency Virus

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ABSTRACT

The AIDS epidemic continues unabated in Africa, Asia, and South America, and since patients survive longer, the number of chronically immunocompromised individuals is increasing in Europe and the United States. The number of children with HIV infection who will ultimately develop a malignancy is not known. Currently, tumors represent about 2% of the AIDS-defining events in children in the United States, but the incidence might be different in developing countries. The most common tumors in HIV-infected children are non-Hodgkin’s lymphoma, smooth muscle tumors (leiomyosarcomas), and Kaposi’s sarcoma (only in Africa). This article provides an overview of epidemiology and clinical and pathological presentations, as well as preliminary data regarding treatment options in children with HIV-associated malignancies. The Oncologist 1999;4:309-317

OVERVIEW

The advent of highly active antiretroviral chemotherapy and the initiation of the use of zidovudine or other agents during pregnancy have decreased the incidence and short-term mortality of AIDS in industrialized countries. However, not only does the AIDS epidemic continue unabated in Africa, Asia, and South America, the number of chronically immunocompromised individuals is increasing in Europe and the United States, since patients survive longer. The incidence of some malignancies has not changed in HIV-infected individuals, i.e., non-Hodgkin’s lymphoma (NHL), while others appear to become less common, i.e., Kaposi’s sarcoma (KS).

As of December 1998, a total of 8,461 children under 13 years of age have been diagnosed with AIDS in the United States [1]. Worldwide, the Joint United Nations Programme on AIDS (UNAIDS) estimates that 1.2 million children are living with HIV/AIDS (reference: UNAIDS Web site). It has been estimated that in 1998 alone, 5.8 million adults and children were newly infected with HIV-1, which means 16,000 new infections every day, and among them 7,000 young people between ages 10 and 24 years (five young people every minute!). More than 2.5 million adults and 510,000 children under the age of 15 years have already died of HIV-related complications.

Each year, approximately 130 cases of cancer are diagnosed per million non-HIV-infected children (0.013%) [2]. The number of children with HIV infection who develop a malignancy is poorly defined. In 1994, the Centers for Disease Control and Prevention (CDC) published a revised classification of pediatric AIDS which lists (as in adults) primary brain lymphomas, small non-cleaved cell (Burkitt’s) NHL, immunoblastic or large-cell lymphoma of B-cell or unknown immunologic phenotype, as well as KS as AIDS-defining events (Category C) [3]. Leiomyosarcomas are included in Category B as a sign of a moderately symptomatic stage.

This classification has only limited use when trying to assess the incidence of malignancies in HIV-infected people. If a child is initially diagnosed with another Category C symptom (for example, Pneumocystis carinii pneumonia), the occurrence of a tumor will not be registered, since only the first AIDS-defining event leads to registration with the CDC. Furthermore, HIV-infected children may develop different kinds of NHLs, including tumors of T-cell phenotype, which are currently not listed, or other malignancies. Finally, lymphoproliferative disorders are clearly part of the spectrum of pediatric HIV disease and potentially represent a preneoplastic disorder. However,
only lymphadenopathy (Category A) and lymphoid interstitial pneumonia (ILIP, Category B) are currently included in the CDC definition [3].

Tumors represent about 2% of the AIDS-defining events in children as listed by the CDC. Through December 1997, 162 of 8,086 (2%) children with AIDS have been diagnosed with a tumor as their AIDS-defining event [4]. Fifty-two children had a Burkitt’s NHL, 51 an immunoblastic NHL, 31 a primary NHL of the central nervous system (CNS), and 28 KS. A survey conducted by the Children’s Cancer Group and the National Cancer Institute identified 64 children (39 boys, 25 girls) with 65 tumors that occurred between July 1982 and February 1997 [5]. Forty-two children (65%) had NHL, 11 (17%) had leiomyosarcomas (or leiomyomas), and three were diagnosed with KS. However, other malignancies (not listed in CDC definition), included acute leukemia (five children), Hodgkin’s disease (two children), vaginal carcinoma in situ (one child), and a tracheal neuroendocrine carcinoma (one child). Similar numbers have been published from Europe [6].

In developing countries, the incidence rate for HIV-associated tumors might be different. There have now been several reports of an increased incidence of KS in children from Zambia and Uganda but also a trend to an increase in the numbers of retinoblastomas, nasopharyngeal carcinomas, and rhabdomyosarcomas, tumors not commonly associated with immune deficiency states [7]. In a study from Zimbabwe, 76 consecutive newly diagnosed cases of malignancy between May 15 and November 15, 1997 were evaluated for HIV infection [8]. Twenty-seven of 64 children were HIV seropositive, giving a seroprevalence rate of 42.2% (95% CI 30.1% to 54.3%). The most common malignancies included NHL (22.4%), acute lymphoblastic leukemia (19.7%), Wilms’ tumor (19.7%), and KS (15.8%). Nine of 17 patients with NHL and all 12 patients with KS were HIV-positive.

The tumors seen in HIV-infected children are somewhat different than in adults and the spectrum appears to be age-dependent. For example, KS, a rare tumor in young children, is the AIDS-defining illness in only 3% of adolescents between 13 and 19 years of age, but this increases to 9% in young adults between 20 and 24 years of age, and to 13% in adults over 25 years of age [4, 9-11]. In contrast, smooth muscle tumors (leiomyomas and leiomyosarcomas), although clearly part of the AIDS malignancy spectrum of childhood, have only infrequently been described in HIV-infected adults [5, 12-18]. Lymphoproliferative disorders appear to occur more commonly in HIV-infected children than in adults [19-23]. It is not yet clear whether and how often these lymphoproliferative disorders will evolve into a “true” monoclonal malignancy with a rapid and invasive growth pattern.

The risk of developing a cancer is probably higher with a weakened immune system [24]. However, the absolute CD4 count alone is not sufficient to determine a child’s risk of developing a tumor, since HIV-infected children can develop a tumor while their CD4 count is only moderately depressed. Length of immunosuppression might play a role, which could have an important impact on the future number of HIV-associated malignancies.

The evaluation of an HIV-infected child suspected of having a tumor is not different from that in other children. When cancer is suspected, a careful staging should include radiological studies with computer-assisted tomography and/or magnetic resonance imaging, possibly a gallium or bone scan, a bone marrow examination, and a lumbar puncture. Many infectious processes can mimic the occurrence of a tumor and must be carefully ruled out. HIV disease often results in multi-organ problems, and it is important to assess hepatic, peripheral neurological, renal, bone marrow, and cardiac function as best as possible prior to intervention.

**NON HODGKIN’S LYMPHOMA**

**Presentation and Histology**

Because HIV infection and the occurrence of a malignancy are often associated with similar symptoms (e.g., lymphadenopathy, hepatosplenomegaly, and, on occasion, impairment of the function of the CNS), it is not uncommon that the diagnosis of an NHL is delayed in a child with HIV disease. There are also differences between NHL occurring in infected and uninfected children. Small non-cleaved tumors with a high growth fraction are the most common NHL in uninfected children, whereas the more indolent anaplastic large-cell lymphomas occur with equal frequency in HIV-infected children. Small non-cleaved tumors are of B-cell origin, while large-cell lymphomas can have either B- or T-cell phenotype, and often are characterized by the CD30 marker (Ki-1) [25-27]. In adults, most HIV-associated NHLs are of B-cell origin and of the anaplastic large-cell phenotype. As in adults, CNS lymphomas in HIV-infected children are generally high-grade tumors, mainly of B-cell origin and commonly associated with Epstein-Barr virus (EBV) [28-32].

Non-Hodgkin’s lymphoma can occur in children with relatively well-preserved immune systems as measured by CD4 counts, but the risk of developing an NHL increases with the depth and duration of very low CD4 counts. Indolent tumors, such as mucosa-associated lymphoid tumors (MALTs) of both the pulmonary or gastric mucosa, can be either a manifestation of advanced disease or the very first symptom of HIV infection [33-36]. These tumors are possibly more closely related to the lymphoproliferative disorders (LPDs) that can occur with remarkably well-preserved CD4 counts.
Viral associations All CNS tumors and about 60% of systemic NHL are associated both with the EBV and the human herpes virus type 8 (HHV-8), have to date been described in adults and in only one child [41-45].

Table 1. Non-Hodgkin’s lymphoma in HIV-infected children

<table>
<thead>
<tr>
<th>Presenting symptom(s)</th>
<th>Non-specific: fatigue, weight loss, night sweats, refusal to walk, loss of appetite</th>
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<tbody>
<tr>
<td>Site-dependent:</td>
<td>• Lymphadenopathy, localized or disseminated</td>
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<td></td>
<td>• Respiratory distress (mediastinal or pharyngeal tumor)</td>
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<td></td>
<td>• Neurological symptoms, including seizures (brain lesion)</td>
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<tr>
<td></td>
<td>• Ileus, ascites, or pain, often palpable tumor</td>
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<tr>
<td>Localization</td>
<td>Nodal or extranodal, central nervous system</td>
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<td>(especially with very low CD4 counts) with or without concurrent systemic disease</td>
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<tr>
<td>Pathological features</td>
<td>Small non-cleaved cell, B cell</td>
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<td></td>
<td>Anaplastic large cell, B or T cell (ca 40%); most common form in HIV-infected adults</td>
</tr>
<tr>
<td>Viral associations</td>
<td>All CNS tumors and about 60% of systemic NHL are EBV-positive</td>
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<td></td>
<td>HHV-8 found in primary effusion lymphomas (so far only seen in adults)</td>
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<td>Role of HIV as oncogenic factor under discussion</td>
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</table>

The clinical profile and modes of presentation of NHL in the HIV-infected child are described in Table 1. Nonspecific complaints such as fatigue, loss of appetite, and night sweats are common, and patients can have marked variability in age, CD4 count at diagnosis, and sites of presentation [5]. Many of the symptoms can also be caused by either HIV infection itself or an opportunistic infection such as Mycobacterium avium complex bacteremia, and a heightened index of suspicion must be sustained to discriminate between infectious and neoplastic etiologies.

Primary CNS lymphomas account for 4%-40% of the NHL in HIV-infected adults and have also been described in children with AIDS [28, 37-40]. Although CNS NHLs appear to be more common in patients with low CD4 counts, we and others have treated children with relatively well-preserved immune status who developed a CNS tumor. The symptoms are similar to those in adults, with cranial nerve deficits, seizures, and hemiparesis being the most common. In adolescents, infection with Toxoplasma gondii has to be considered in the differential diagnosis, but in younger children this is rare and it is more likely that the intracranial lesion represents a malignancy or lymphoproliferative process—unlike in adults, where CNS toxoplasmosis is not uncommon. The approach of using empirical antiparasitic therapy as the first intervention in a patient with a brain lesion, as recommended in adults, is less well defined in children. Since brain tumors (of non-lymphoid origin) are the second most common cancers in non-HIV-infected children [2], it is likely that they will be seen more commonly in HIV-infected children who survive longer.

Body cavity and primary effusion lymphoma, which are associated both with the EBV and the human herpes virus type 8 (HHV-8), have to date been described in adults and in only one child [41-45].

Treatment

The therapy of adults with HIV infection and systemic NHL has had a poor rate of success. Most chemotherapy protocols used to date have been fairly intensive, using modified COMP regimens (cyclophosphamide, vincristine, methotrexate and prednisone), PROMACE-MOPP (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide-mechlorethamine, vincristine, prednisone and procarbazine), or M-BACOD (methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine and dexamethasone), or various combinations thereof [46-49]. Most regimens resulted in a median survival of only five to six months, with death often due to intercurrent opportunistic infections and survival clearly dependent on several HIV-related factors (e.g., performance status, history of AIDS prior to the diagnosis of lymphoma, and CD4 cell count). Straus et al. performed an analysis of prognostic factors in patients treated on a randomized trial of low-dose versus standard-dose m-BACOD plus GM-CSF [50]. Age greater than 35 years, intravenous drug use, stages III/IV, and CD4 cell counts less than 100/mm³ were adverse prognostic factors in multivariate analyses. The median overall survival for patients with none or one of the adverse factors was 46 weeks, compared with only 18 weeks with three or four factors.

There are currently no published studies comparing the response rate and treatment-associated morbidity in children with NHL and concurrent HIV infection with that in uninfected children. Because of the preexisting organ dysfunctions (most commonly bone marrow), impaired immune system, possible opportunistic infections, and the need for multiple drugs to treat HIV infection, it is often assumed that HIV-infected children are less likely to tolerate standard chemotherapy. However, although this might be true for prolonged intensive treatment modalities, it may be possible to successfully treat them with short but dose-intensive regimens. Most HIV-infected children with NHL tolerate chemotherapy (including most commonly cytoxan, methotrexate, vincristine, and prednisone) fairly well, and a growing number are surviving for two years and longer [31, 51-53]. Concern has recently been raised about the use of protease inhibitors during chemotherapy and potential drug interactions. It has, for example, been noted that saquinavir increases mucosal toxicity in patients with HIV-associated NHL [54]. In contrast,
azidothymidine has been used in combination with methotrexate to take advantage of its potential antineoplastic activity [55].

Treatment of CNS lymphoma, unsuccessful in the majority of cases arising in the general population, is similarly ineffective in patients with HIV infection. A small series of eight patients treated with cranial irradiation demonstrated a complete response in six patients and a partial response in one patient that received at least 40 Gy [56]. However, only two of the complete responders were free of recurrence 8 and 14 months from treatment, two had relapsed, and two had died of opportunistic infections. Only case reports are available describing the treatment outcome of HIV-infected children with CNS lymphomas [5, 29]. In the very young child, chemotherapy alone is preferable because of concerns about subsequent developmental delays, but in the older child (over three years of age), radiotherapy is probably indicated in conjunction with intrathecal and systemic chemotherapy.

**Hodgkin’s Disease**

In industrialized countries, the epidemiology of Hodgkin’s disease (HD) shows a first peak in incidence in mid to late adolescence and therefore does not currently represent a major problem in HIV-infected children [57]. In contrast, in developing countries, HD occurs at an earlier age, and some cases of HD have been observed in unusually young HIV-infected children. As in adults, HD associated with HIV infection tends to present as an aggressive, lymphocyte-depleted form. In an Italian study which compared the presentation of HD in infected and non-HIV-infected adults, HIV-associated HD occurred in younger patients (29 versus 38 years), had a male predominance (90% versus 56%), and presented more often with stage IV disease (63% versus 29%), B symptoms (77% versus 35%), and extranodal disease (63% versus 29%) [58]. Mixed cellularity and lymphocyte depletion are the most common histologies in HIV-infected patients (66%), compared with lymphocyte predominance and nodular-sclerosing types in HIV-negative patients (71%). In the majority (78%) of patients with HIV-associated HD, there is evidence for latent EBV infection, and 80% of these tumors contain monoclonal EBV genomes [58].

The optimal chemotherapy for HIV-associated HD has not yet been defined. HIV-negative patients can achieve cure rates of over 70% with MOPP and/or ABVD regimens; however, HIV-infected patients often do not have the bone marrow reserves to tolerate such therapy [59]. Serrano et al. reported a decreased response to chemotherapy and a significant decrease in survival in patients with HIV-associated HD [60]. Twelve of 21 patients who received chemotherapy had a complete response (CR), four achieved a partial remission, and five had progressive disease. The average survival was 18 months for the whole group, but patients with AIDS survived only for an average duration of 13 months, a significantly shorter period (p = 0.05). In another study, 35 previously untreated patients (median age 34, range 21-53 years) were treated with epirubicin, bleomycin, vinblastine, plus prednisone (EBVP), concomitant zidovudine or dideoxynosine, as well as G-CSF [61]. An overall response rate of 91% was observed; 74% were complete responses (CRs) and 17% partial responses. However, 10 of 26 (38%) patients who achieved a CR relapsed, and the median survival was only 16 months, with a survival rate of 32% and a disease-free survival of 53% at 36 months [61]. Montalvo et al. reported a 4.5-year-old boy with HIV infection and nodular sclerosing HD who achieved and maintained complete remission with systemic chemotherapy (MOPP, ABVD) for 20 months after the chemotherapy was stopped [51].

**Lymphoproliferative Disorders**

LPDs are common in HIV-infected children and could well represent the link between increased proliferation and overt malignancy [20, 62]. The spectrum of manifestations includes the many different presentations (Table 2). Lymphadenopathy with hypergamaglobulinemia is very common in HIV-infected children, especially at the early stages of disease, and LIP is a typical feature of childhood HIV infection [63-65]. Histologically, both B- and T-cell types have been implicated, and the role of EBV remains to be determined. Several cases of pulmonary MALT have been associated with LIP, and a pathogenetic link is currently being investigated [66]. The recently described patients with multiple cystic lesions in their grossly enlarged thymus may also belong to this same group [19]. In adults, multicentric Castleman’s disease, an atypical lymphoproliferative disorder, has been associated with HHV-8 infection [67, 68].

**Table 2. Lymphoproliferative disorders in HIV-infected children.** The distinction among the different manifestations is not always well defined, and it is not clear whether any of them can and will progress to an overt malignancy.

- Polyclonal hypergamaglobulinemia or reactive lymphadenopathy; common
- Lymphocytic interstitial pneumonitis (LIP); used to be common, can lead to oxygen- and steroid-dependency
- Mucosa-associated lymphoid tumors (MALT); occurring in lungs, gastric mucosa, parotid or lacrimal gland
- Polyclonal, often indolent, cystic mediastinal tumors
- Lymphomatoid papulosis, a monoclonal, indolent, T-cell process with waxing and waning course
- Castleman’s disease, relatively common in adults (associated with HHV-8), rare in children
The treatment approach for many of these manifestations includes optimization of antiretroviral therapy, steroid therapy in the case of LIP with oxygen-dependency, and possibly surgical excision (in the case of MALTs). Because of the potential for malignant transformation and clinically significant problems in some children, we evaluated a therapeutic approach with alpha-interferon and retinoic acid for children with clinically significant LIP (e.g., no response to optimized antiretroviral therapy, large mass, or steroid-dependent LIP), and preliminary results indicate that this therapy is relatively well tolerated and in some cases will lead to marked reduction of tumor size [69].

**SMOOTH MUSCLE TUMORS**

Smooth muscle tumors are rare in children, representing less than 2% of all cancers [70]. However, an increased number of leiomyomas and leiomyosarcomas have been described in HIV-infected children, leading to their inclusion in the revised CDC classification of pediatric HIV disease as a Category B symptom [3, 12-15, 18, 71]. Granovsky et al. reported 11 cases of leiomyomas/leiomyosarcomas (17% of all tumors) [5]. Unusual localizations, such as spleen, pleural space, adrenal glands, and lungs have been described, although they present most commonly in the gastrointestinal tract [72, 73]. Several cases of intracranial or dural leiomyosarcomas have been described, and we treated a child with a primary leiomyoma of the liver and spleen who later developed another tumor in her orbit (S. Burchett, personal communication) [74, 75].

EBV has been demonstrated in situ hybridization and quantitative polymerase chain reaction, a finding that appears to be unique to tumors from HIV-infected or otherwise immunocompromised (i.e., post-transplant) patients [16, 76-78].

The course of disease is highly variable with indolent tumors (more likely leiomyomas) that probably do not necessitate intervention in some children and very aggressive, disseminated tumors in others. Since smooth muscle tumors are in general not very sensitive to chemotherapy or radiotherapy, local excision, if feasible, is the first line of therapy [70]. Intensive and prolonged chemotherapy as used in noninfected patients is rarely tolerated by HIV-infected children.

**KAPOSI’S SARCOMA**

In the United States, KS is the AIDS-defining illness in less than 1% of children <13 years of age and only 3% of adolescents between 13 and 19 years of age [4]. However, the incidence increases to 9% in young adults between 20 and 24 years of age and to 13% in adults over 25 years of age [4, 10]. However, this might be different in other parts of the world. In Zambia, KS now comprises almost 20% of all childhood cancers, compared with 6% prior to 1986 [79, 80].

But even in African countries, KS is rarely the first presentation of HIV disease in children. Most will have had a history of hepatosplenomegaly, failure to thrive, or recurrent infections [80]. Three clinical patterns were observed among childhood KS cases in Uganda: an orofacial distribution with regional (86%) or generalized (60%) lymphadenopathy and variable skin involvement (39%); an inguinal-genital distribution, with inguinal lymphadenopathy (100%), skin (57%), and anogenital (14%) involvement; and a less common pattern with solitary tumors in the extremities or visceral organs (8%) [80]. There was a trend towards an increased incidence of the nonlymphadenopathic form in HIV-infected children compared with that in non-HIV-associated pediatric cases [7]. HHV-8 was demonstrated in eight of eight archival samples from pediatric KS cases in Uganda [80]. The seroprevalence of HHV-8 was studied among a group of Zambian women of reproductive age and among mother-child pairs in which either one of them had KS [81]. A cross-sectional group of 378 pregnant women was randomly recruited into the study, and 183 (48.4%) had HHV-8 antibodies. Fifty-one percent of the HIV-infected women were HHV-8-seropositive, compared with only 47.3% of HIV-1-negative women. All children with KS had mothers who were HHV-8-seropositive, while not all children whose mothers had KS were infected with HHV-8 [81].

Because of the rarity of the disease in children, no pediatric treatment guidelines have been developed, and the reader is referred to reviews regarding treatment in adults [82, 83].

**OTHER TUMORS**

Several miscellaneous tumors have been reported to occur in HIV-infected children, including leukemia, Ewing’s sarcoma, rhabdomyosarcoma, ependymoblastoma, and others [39, 84-88]. Although the incidence for any one of these tumors does not appear to be increased, it has been notable that some children have developed distinctly unusual tumors, such as a small-cell carcinoma located between the esophagus and trachea (unpublished data) or a fibrosarcoma of the liver [85].

Based on the observation of an increased incidence of cervical pathologies in HIV-infected women, the classification for HIV-infected adults was revised in 1993 to include cervical dysplasia (moderate or severe) as well as cervical carcinoma in situ as an AIDS-defining diagnosis [89-93]. The prevalence of cervical dysplasia has increased in all adolescents, and human papilloma virus (HPV) infection is found in 15% to 38% of sexually active adolescents [94-96]. Furthermore, the incidence of anal cancers also appears to increase in homosexual males with HIV infection [97].
There is a strong correlation between infection with HPV, especially types 16 and 18, and the development of cervical or anal neoplasms [96, 98-100].

Since many adolescents are sexually active, it is important for the pediatrician to be aware of this increased risk and to actively rule out such malignancies in sexually active patients.

**Future Developments**

As children with HIV survive longer due to better antiretroviral and supportive therapies, HIV-related malignancies may become an increasingly common problem. It is important to monitor the growing population of long-term survivors and to determine whether lymphoproliferative disorders or therapies used to treat HIV infection can increase the risk for cancer in HIV-infected children. While NHL and smooth muscle tumors are the most common malignancies seen in this population, their pathogenesis remains incompletely understood. We are only just starting to understand the interactions between viruses and the immune system as they relate to neoplastic proliferations. Exploring the options of antiviral interventions (against HIV, EBV, and HHV-8), cytokines, or immune modulators offers many therapeutic options in addition to less toxic and more effective chemotherapeutic regimens. However, the biggest challenge continues to be to gain control over the epidemic that is currently devastating developing countries.

**References**


