AIDS-RELATED MALIGNANCIES

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Abstract  Immunodeficiency alters the risk of cancer. Specific types of immune
dysfunction are associated with different tumor risks, but most tumors are related to
oncogenic viruses. In acquired immunodeficiency due to the human immunodeficiency
virus (HIV), HIV itself rarely directly causes cancer; rather, it provides the immuno-
logic background against which other viruses can escape immune control and induce
tumors. The most common malignancies are Kaposi’s sarcoma and non-Hodgkin’s
lymphoma. This chapter discusses the pathophysiologic background of these tumors,
how they have been affected by the use of anti-HIV medications, and their clinical
management.

INTRODUCTION

The number of individuals infected with the human immunodeficiency virus type 1
(HIV-1) worldwide is currently estimated at 40 million. Manifestations are highly
dependent on geographic location, genetic background, and most importantly the
availability of antiretroviral therapy. Malignancy, a complication of HIV-induced
and other forms of immunodeficiency, is restricted to a limited spectrum of tu-
mors (Table 1), generally those for which an infectious cofactor has been defined
(Table 2). Although the mechanisms by which these tumors arise vary markedly
with tumor type and virus, inadequate immunologic control provides a unifying
conceptual framework among them. As opportunistic malignancies, these tumors
have the potential for responsiveness to immunologic control and the development
of novel therapeutics. The two major types of tumors seen in the setting of HIV
are Kaposi’s sarcoma and non-Hodgkin’s lymphoma. These are the focus of this
chapter.

Epidemiology

The spectrum of tumors in the context of HIV-1 infection varies according to
risk group and has been substantially influenced by the advent of combination,
highly active antiretroviral therapy (HAART). Kaposi’s sarcoma (KS) is the tumor
TABLE 1  Tumor types with increased incidence in HIV disease

<table>
<thead>
<tr>
<th>Definite</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s sarcoma</td>
<td>Seminoma</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td>Squamous cell neoplasia</td>
<td></td>
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<tr>
<td>Hodgkin’s disease</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma (in children)</td>
<td></td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td></td>
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</tbody>
</table>

most obviously affected by this potent treatment. Although the incidence of this infection-related neoplasm was already declining in the United States prior to the availability of HIV protease inhibitor therapy, the therapy has made it a relative rarity among treated HIV-infected individuals (1–3). Both regression of KS following successful HIV suppression on HAART and a marked decrease in KS incidence since the availability of HAART have been noted, with estimates of decline as high as 80-fold (2–6). In settings where HAART is not available, such as sub-Saharan Africa, KS remains a major problem and is the major cancer diagnosis in some regions (6a,b).

Like KS, primary central nervous system lymphomas (PCNS)—a subset of non-Hodgkin’s lymphomas—have undergone dramatic changes in incidence. Although this complication of far-advanced HIV disease was much less common than KS, and therefore its decline is less well documented, U.S. centers that had previously seen cases monthly are now seeing them annually. PCNS is an agonal manifestation of AIDS, and like post-transplant lymphoproliferative disease, it is virtually uniformly associated with the presence of Epstein-Barr virus (EBV).

TABLE 2  Secondary virus infections associated with AIDS-related malignancies

<table>
<thead>
<tr>
<th>Virus</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Non-Hodgkin’s lymphoma (PCNS, primary effusion lymphoma)</td>
</tr>
<tr>
<td>Kaposi’s sarcoma herpesvirus (KSHV)</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>Squamous cell neoplasia</td>
</tr>
</tbody>
</table>

*Abbreviations: ARLs, AIDS-related lymphomas; PCNS, primary central nervous system.
in the tumor tissue. Comparable to post-transplant lymphoproliferative disease, the profile of EBV latent gene expression includes EBNA1-6 and LMP-1, -2, a type III pattern seen when EBV is used to transform B cells in vitro (7, 8). Among these gene products are those readily targeted by cytotoxic T lymphocytes, which may account for the marked reduction in incidence of PCNS among patients with successful control of HIV-induced immune destruction by HAART. Of note, even among those with detectable EBV-specific cytotoxic T lymphocytes, abnormalities in cell function have been noted and associated with EBV lymphoproliferation (9).

In contrast to the PCNS subset of AIDS-related lymphomas (ARLs), the risk of systemic lymphomas is less dramatically reduced by HAART (3, 10). Overall, the estimated decline in systemic lymphomas is approximately two- to seven-fold since the introduction of HAART (1, 11–13). The largest study to date was an observational cohort analysis of 8500 HIV-positive individuals across Europe (EuroSIDA) (12). The incidence of all subtypes of lymphoma was significantly reduced after 1999, when the use of HAART was commonplace, compared with the period prior to HAART (marked in this study as beginning in September 1995). Similarly, an international multicohort study found a reduction of approximately twofold following the introduction of HAART (11). Of note, this series assessed subtypes of lymphomas and observed the greatest difference in immunoblastic lymphoma and PCNS. Burkitt’s lymphoma and Hodgkin’s disease appeared to be largely unaffected (11). The changes evident within only some lymphoma subsets does suggest possible differential involvement of immune function in tumor development.

NON-HODGKIN’S LYMPHOMA

Pathophysiology

There are ARLs, such as PCNS, in which EBV is uniformly present and for which a pathophysiologic process may be readily envisioned. In that setting, EBV latent genes are expressed in a type III pattern including expression of the latent membrane protein–2 (LMP-2), which is known to dysregulate cell growth control and can transform B lymphocytes. The systemic lymphomas appear to have a more complex pathophysiology, however. EBV is present in a subset of these tumors (33%–67% depending on the report), and the type III latent gene pattern is not consistently observed (14–16). Some of these tumors appear to express a profile of EBV genes more consistent with Hodgkin’s disease, and the large proportion of those without EBV have a range of other genetic abnormalities. Among AIDS-related large-cell lymphomas, Bcl-6 rearrangement, c-myc rearrangement, and p53 mutations occur in approximately 33%, 40%, and 25%, respectively (17). The small-cell (Burkitt’s and Burkitt’s-like) histology subset is commonly associated with c-myc rearrangements, but not Bcl-6 and rarely p53 mutations (18–21). There is no clear link between EBV and any specific genetic mutation other than those noted for the histologic subtype (18–21). Among
those tumors in which c-myc is rearranged, c-myc is transposed into the immunoglobulin gene heavy-chain switch region (20, 22–25), which strongly suggests that the rearrangement occurred at the time of class switching rather than during early B cell differentiation. Because this follows VDJ recombination of the immunoglobulin locus, the cell of origin is likely to be a post-germinal-center B cell.

B cell growth kinetics appear to be altered in the presence of HIV infection and clinically manifest as the frequent lymphadenopathy and hypergammaglobulinemia seen in this group of patients. HIV may directly contribute to the process through antigenic drive, and there are reports that HIV envelope glycoprotein may directly enhance B cell activation (26, 27). HIV gp120 envelopes capable of interacting with the CXCR-4 chemokine receptor, in particular, may effect changes in B cell proliferation, as this receptor is known to provide a growth-promoting signal to B cell subsets (28–32). Perturbation of the T cell compartment, with enhancement of TH2 subpopulations and release of B cell stimulatory interleukins, IL-10 and IL-4, probably further augments proliferation (33, 34). With control of HIV replication, the B cell stimulus may be reduced through these direct and indirect mechanisms, resulting in a decrease in hypergammaglobulinemia with successful HAART.

Genetic analyses of patient cohorts have begun to reveal host-related factors relevant to the risk of lymphoma. Individuals with polymorphisms in regulatory regions of the chemokine gene encoding stroma-derived growth factor–1 (SDF-1) were noted to have an excess risk of developing lymphoma, particularly of the Burkitt’s subtype (35). Although the specific mechanism has not been shown, SDF-1 is the cognate ligand for CXCR-4, is a known B cell growth factor, and may provide an excessive proliferative stimulus. HIV-infected individuals heterozygous for an inactivating deletion mutation of CCR5 (CCR5Δ32) were noted to have a threefold decrease in lymphoma risk (36). This abnormality may decrease the sensitivity of target cells to the chemokine RANTES, which may result in altered B cell function, either directly or through T cell–mediated events (36). Further genomic analysis of the host-pathogen interaction is clearly an area of potential for defining patients with variable risk and may ultimately lead to screening or preventative strategies.

Clinical Presentation, Evaluation, and Treatment

Systemic ARLs frequently involve tissues outside of lymph nodes and therefore have a wide array of possible clinical presentations. Common extranodal sites include the gastrointestinal tract, bone marrow, and central nervous system (CNS), though virtually any tissue may be involved (19, 38–54). Histologic subsets do have some discriminating patterns of involvement. For example, large-cell tumors preferentially involve the gastrointestinal tract and small-cell tumors the bone marrow and meninges (45, 55). The presenting symptoms of lymphoma do not appear to be appreciably affected by HAART (56, 57).
Owing to a high incidence of CNS involvement noted early in the HIV epidemic [20% in one study (43)], it has become commonplace to more aggressively evaluate the CNS in patients with systemic ARL. This has generally included imaging and cerebrospinal fluid sampling studies, and many centers prophylactically administer intrathecal therapy to all patients. Particular attention should be paid to those in whom EBV is documented in the primary tumor, since in one study its presence strongly predicted an increased risk for CNS relapse ($p = 0.003$) (58). The same study also defined extranodal involvement as a strong predictive factor ($p = 0.006$). Whether such criteria can be used to subselect patients in whom CNS prophylaxis may be restricted has not been tested formally, but the data do support targeting intrathecal chemotherapy to those with EBV in the tumor tissue and those with extranodal involvement of high-risk sites such as marrow, testis, or paranasal sinus (59).

The prognosis for patients with ARL prior to HAART was poor but appears to be changing with the overall improvement in health and tolerance of chemotherapy afforded by control of HIV. Most prognostic factors were defined before HAART and may need to be revised to accommodate broader, more current experience. However, the largest multivariate analysis to date indicated that CD4 count $<100$ cells/mm$^3$, age $>35$ years, intravenous drug use, and stage III/IV disease were negative prognostic factors (60). When one or none of these factors was present, the overall survival was 46 weeks; with two factors, 44 weeks; with three or four factors, 18 weeks.

The International Prognostic Index (IPI) (61) is a useful means of stratifying risk in aggressive lymphomas outside the context of AIDS but has not been broadly applied to date in ARL. A study of 46 patients did indicate that high IPI score was predictive of poor outcome (62), and other reports have indicated that factors used in the IPI such as elevated LDH (63) or age $>40$ years provide independent prognostic information in ARL. In the context of HAART, it is likely that IPI can be used to define risk in ARL and will be tested in current trials. Burkitt’s or Burkitt’s-like histology has not been consistently noted to be of prognostic significance. Treatment protocols to date have generally included this subset of patients with other histologic groups and not detected a distinct outcome. However, as more information is gained in the era of HAART, now that other HIV complications contribute less to outcome, this histologic subset may distinguish itself as more problematic. Whether more aggressive treatment programs should be applied to this group in the setting of HIV disease remains undecided.

Primary effusion lymphoma is a rare form of systemic lymphoma associated with AIDS. It is a liquid-phase hematologic malignancy that rarely involves the blood or lymph nodes and generally does not present with a tumor mass. Rather, a body cavity effusion (64–66) laden with large anaplastic or immunoblastic-appearing cells is the hallmark. The cells immunophenotypically mark with surface CD45 (common leukocyte antigen) but do not stain with antibodies specific for B cell (CD20 or CD19) or T cell (CD3) antigens. Molecular analysis of tumor cells does demonstrate VDJ rearrangement of the immunoglobulin locus, confirming a
B cell origin. Unique among the ARLs, primary effusion lymphoma cells also are uniformly found to contain the Kaposi’s sarcoma herpesvirus (KSHV) genome and frequently demonstrate coinfection with EBV. These tumors are not restricted to HIV-related immunodeficiency and may be found in other immunodeficient states. They provide a unique and intriguing paradigm for virus-induced human malignancy.

Therapy

The impact of HAART on lymphoma risk has been paralleled by improved treatment tolerance in patients with lymphoma. The ability of patients to receive full-dose therapy has now been well established, and the options of intensive dosing and transplantation are being explored. Prior to the availability of HAART, the limited prognosis and poor tolerance of therapy pushed experimentation to pursue minimally toxic regimens. A phase III randomized trial comparing full-dose with half-dose m-BACOD demonstrated equivalent tumor outcomes with a more favorable toxicity profile for the lower-dose regimen (67). This study set a standard for reduced-dose approaches, which has now been supplanted as HAART has improved the overall health of the patients. Low-dose regimens are now generally reserved for those with advanced AIDS who have either failed HAART or for whom HAART is not available. Studies that have not formally compared dose intensity, but in which different dose levels were used, have indicated a more favorable effect on tumor outcomes with standard-dose regimens (68). Therefore, CHOP and its equivalents have resumed their position as the up-front treatment of choice for patients with ARL.

Studies with modified dosing schedules indicate that infusional regimens may benefit ARL patients. The CDE regimen of Sparano and colleagues has yielded response rates of ~58% (69), and a study by the U.S. National Cancer Institute using dose-adjusted EPOCH (70, 71) demonstrated durable responses in >75% of patients (72). These are the most encouraging data to date and if validated may set a new standard for this patient group. Whether adding rituxan to standard chemotherapy conveys benefit in the setting of ARL is not clear. A randomized, phase III trial comparing CHOP alone with CHOP plus rituxan has recently been completed by the U.S. National Cancer Institute AIDS Malignancy Consortium and should provide important new information.

Given the improved tolerance of therapy with HAART, transplantation has again been considered for patients with ARL. This approach, which proved highly toxic and showed very poor results early in the HIV epidemic (73–81), now appears to be far more promising. Small studies in the United States and Europe have indicated that autologous transplant is well tolerated, with no delay in engraftment or undue opportunistic complications (82, 83). Furthermore, long-term survival in the context of relapsed Hodgkin’s or non-Hodgkin’s lymphoma and HIV have been reported (84).

Genetic manipulation of stem cells to render them resistant to HIV has been a conceptually appealing but thus far disappointing strategy (83, 85). Allogeneic
or minimally myeloablative approaches are now entering clinical trial. Such approaches can only be recommended in the context of clinical trials at present, given the complex interplay of immune function, viral replication, and tumor biology in these patients.

Although prior HAART can increase tolerance of antitumor medication, there is controversy as to whether HAART can be given concurrently with antitumor medication. In an effort to resolve this issue, the AIDS Malignancy Consortium studied stavudine, lamivudine, and indinivir at fixed dose in combination with CHOP chemotherapy. No untoward or unexpected toxicities were observed. The pharmacokinetics of doxorubicin and indinivir were unaffected, but a ∼50% reduction in cyclophosphamide clearance was observed without apparent clinical impact (86). Although these data indicate the relative safety of concurrent HAART and antitumor medication, they are restricted to a small subset of antiretroviral drugs and a regimen less common now than at the time of the study. Recognizing the potential complexity of regimens and potential drug-drug interactions, the National Cancer Institute stopped all antiretrovirals during its trial of modified EPOCH chemotherapy (87). As anticipated, the HIV viral load increased and CD4 cell count decreased, but both parameters normalized following reintroduction of HAART at the end of antitumor therapy. Transiently discontinuing antiretrovirals during cancer chemotherapy had no apparent deleterious effects. However, this is a heavily weighted emotional issue for many patients, and thoughtful discussion with each individual is necessary when considering whether to stop anti-HIV medications.

KAPOSI’S SARCOMA

Viral Epidemiology

Kaposi’s sarcoma (KS) is the most common neoplasm associated with AIDS, but not all HIV-infected individuals are at risk for it. It is more common in geographic regions associated with endemic KS, such as the Mediterranean basin and sub-Saharan Africa, and is particularly likely to occur in patients who acquired HIV by male homosexual activity. The disproportionate risk for KS among select immunodeficient populations raised the suspicion of a secondary infectious factor, which was confirmed by the identification of KSHV (88, 88a). Comparative genetic analysis of KS-involved tissue with normal tissue revealed DNA homologous with viral sequences from the gammaherpesvirus family. This group contains at least two other viruses capable of transforming human cells: EBV, which immortalizes human B cells, and Herpesvirus saimiri, which immortalizes human T cells (88).

KSHV is a 165-kb, double-stranded DNA virus (89) that is present in patients prior to tumor formation (89, 90), has a high seroprevalence in populations with a high incidence of KS (91), and is present in cells composing the tumors (89). These data provide compelling evidence for a causative association of KSHV with KS. Definitive seroepidemiologic studies of KSHV infection await broadly accepted assays, but data from a number of approaches have begun to outline the rates
of infection in some populations. The ORF73 gene product is the serodominant antigen. Assays for it have high specificity, but their sensitivity is only \(\sim 80\%\) in HIV-infected populations with clinical KS (91). The prevalence of KSHV in the United States as determined by this assay has been reported to be 1\%\--2\% of blood donors, 2\% of hemophiliacs, 3\%\--4\% of HIV-positive women (92), and 25\%\--30\% of HIV-positive homosexual men (93). A whole-virus lysate assay provides greater sensitivity (92% positivity among patients with KS) and detected 11\% positivity among healthy blood donors (94). Thus, in prevalence, KSHV resembles *Herpes simplex* rather than the virtually ubiquitous EBV, at least among North Americans and northern Europeans. The epidemiology is quite different in sub-Saharan Africa and the Mediterranean basin, where prevalence rates exceed 40\% in some populations.

How KSHV is transmitted remains unclear. That male homosexual activity is associated with transmission is quite clear from a longitudinal study of men in San Francisco followed over a ten-year period. That study demonstrated that KSHV seroconversion risk was linearly related to the number of male-male sexual intercourse contacts (93). Men who had in excess of 250 sexual partners in the preceding two years had a seropositivity rate of 65\%. Other modes of transmission must occur, based on the epidemiology of the disease, but are less well defined. In Africa, childhood infection occurs after the risk of vertical transmission but prior to sexual activity. KSHV has been documented in saliva and oral transmission has some epidemiologic support (95), although the spread of the virus by oral contamination is thought to be inefficient.

Pathology and Pathogenesis

KSHV infection is necessary but not sufficient for KS. Its malignant potential appears to be quite low outside the setting of immune compromise, but it is present in sporadic endemic and epidemic settings of KS. KSHV enters cells by engaging a cellular integrin receptor (\(\alpha_3/\beta_1, \text{CD49c/29}\)) (96). It can infect a range of different cell types, including B cells and dermal microvascular endothelial cells (97). It is present in KS tissues but is rapidly lost from culture when KS-derived cells are propagated in culture (97). The basis for the KSHV induction of tumor remains controversial and may be distinct from the paradigms proposed for other viral-related tumors. Although it is in the same herpesvirus subfamily as EBV, the latent genes implicated in EBV-induced transformation do not have homologues in KSHV. *Herpesvirus saimiri* encodes a transforming gene product that does have homology to a KSHV gene, \(K1\), and that gene product has transforming ability when transfected into target cells (98). However, \(K1\) is expressed in the lytic and not the latent phase of the KSHV life cycle. Other KSHV gene products have been associated with transformation in transfection assays, but their gene expression profile is not consistent with the concept that latent program genes are those likely to be involved in transformation. For example, both the KSHV gene \(K9\), which encodes a homologue of the interferon regulatory factor family, and \(K12\), which
has no clear gene family homology, can transform cells. Perhaps the most intriguing gene product is a constitutively activated chemokine receptor–like protein, ORF74, which can transform cells (103) and induce a disease closely resembling KS when expressed in mice (104). It may be, therefore, that lytic phase genes may contribute to oncogenesis in trans, influencing the function of neighboring cells while the lytically infected cell dies. Clinical data do provide some indirect support for this unconventional paradigm: Medications that affect lytic replication of herpesviruses, ganciclovir and foscarnet, have been associated with antitumor effects (105–108). Further analysis of how this virus affects tumor growth awaits definition of methods for propagating the virus.

The KSHV genome encodes a number of gene products, which have the potential for affecting cells in trans. There are two homologues for chemokine genes, vMIP-I (K6) and vMIP-II (K4), and a viral IL-6 homologue, K2. Each interacts with cell surface receptors with either agonist (K2 and K6) or antagonist (K4) effects (109, 110). The IL-6 homologue is a particularly attractive candidate for influencing normal cell proliferation, but circulating levels of vIL-6 do not correlate with tumor development (111).

Host response to the virus appears to be critical in determining the clinical outcome of infection, including tumor development. The association of KS with immunodeficiency is clear, and evidence for complete regression of tumor with either HAART or, in the setting of organ transplant, reduced immunosuppressive medication further demonstrates the importance of immune control (112, 113). KSHV, like other members of the herpesvirus family, has evolved mechanisms to avoid immune attack. MHC class I cell surface expression is reduced by the viral gene products K5 and K3 because of enhanced endocytosis (114, 115) and reduced tapasin expression (116). It has also been demonstrated that K5 downregulates ICAM and B7-2, critical immune-modulating surface molecules for activation of effector cells (117). Therefore, host and viral mechanisms may dually contribute to inadequate immunologic control of KSHV.

It is not clear why HIV infection is particularly permissive of KS compared with other immunodeficiency states, but several mechanisms have been proposed. The HIV-1 tat gene product can enhance KSHV replication (118) and increase expression of IL-6 (119) and IL-6 receptor (120). HIV-1 replication may thereby directly potentiate KSHV effects and indirectly contribute to oncogenesis.

Treatment

The diagnosis of KS should not prompt a reflexive move to treat. This tumor may progress in an indolent manner even in patients with advanced immunosuppression. The decision to treat is based on the tumor’s location, extent, and rapidity of change. For all patients, a critical aspect of tumor control is optimizing anti-HIV therapy. Response of pre-existing KS to HAART alone has been documented in up to 86% of patients (121), a rate exceeding that of most cytotoxic chemotherapy studies. These responses are generally durable and gradually
increase over time; in one multi-institutional study, only 6 of 39 KS patients treated with HAART still required KS-specific therapy 24 months after initiation of HAART (122). However, although HAART plays an important role, it is often insufficient in those with aggressive disease, and given the potential for aggressive or symptomatic KS to worsen prognosis (123), tumor-specific therapy may be indicated.

Tumor treatment may be locally applied for those with limited, accessible lesions and includes topical liquid nitrogen, intralesional vinblastine, and radiation therapy. In a randomized trial of 82 patients, topical 9-cis–retinoic acid cream demonstrated a sixfold higher response rate than placebo (124). However, local erythema and irritation were common effects that may offset the benefit in tumor control. For patients with edema, extensive mucocutaneous disease, or symptomatic pulmonary or gastrointestinal involvement, systemic chemotherapy is appropriate and generally well tolerated. Response rates in the literature are somewhat difficult to interpret because no standard measuring system has been applied, and the typical response criterion of changing bi-dimensional area may be misleading, since a residual hemosiderin stain is common even with histologic regression of KS. Single agents such as bleomycin and vincristine (125) or the combination of doxorubicin, bleomycin and vincristine (126) have demonstrated response rates of 57% to 88% (127). These drugs are often associated with toxicity, but this can be mitigated by more recent therapies of liposomal anthracyclines or paclitaxel. Because KS lesions are composed of vessels with poor integrity, liposomally encapsulated drugs are deposited in them. Drug concentrations have been found almost tenfold higher in lesions than in surrounding tissue (128). Two phase III studies, each involving ∼250 HIV-positive KS patients, have evaluated liposomal doxorubicin. Superior tumor response (1.5–2-fold improvement) was observed relative to either bleomycin plus vincristine or that combination plus Adriamycin (129, 130). A phase III study comparing liposomal daunorubicin with combined doxorubicin, bleomycin, and vincristine demonstrated a superior toxicity profile with no major difference in tumor response rates (131). No comparison of the liposomal agents has been reported. Despite the potential difference in tumor activity and minor differences in toxicity profile [for example, liposomal doxorubicin is associated with the hand-foot syndrome and liposomal daunorubicin is not (129)], the agents are often used interchangeably.

Paclitaxel, a tubulin stabilizer, has emerged as a highly active and generally very well-tolerated agent for KS. A phase I trial involving 28 patients demonstrated a major response in 71% (132), including individuals with heavily pretreated, anthracycline-treated KS. Low-dose paclitaxel (100 mg/m² every 2 weeks) is extremely well tolerated, and a phase II study reported a 59% response rate with a longer duration of response than was seen with other cytotoxic therapies for KS (133). Durability of the response to any cytotoxic agent is transient, and patients generally require chronic therapy unless anti-HIV therapy has permitted substantial immune regeneration. The cure for KS appears to be immune reconstitution, as cytotoxic agents are strictly palliative.
Antiangiogenic compounds are a natural strategy for combating this highly vascular tumor, and some trials have demonstrated encouraging results. Thalidomide is an angiogenesis inhibitor, and a phase II trial demonstrated a partial response in 4 of 13 patients over a 52-week period (134). The membrane metalloproteinase inhibitor, col-3, has been shown to be active in early-phase testing and is now entering phase II trial through the AIDS Malignancy Consortium. In contrast, Fumigillin (TNP-470) had little antitumor effect in a study of 38 patients (135), and IM862 has not demonstrated benefit in phase III testing. How the antiangiogenesis will be used, either alone or in combination, and how immunologic manipulation may ultimately contribute to the armamentarium against KS remain to be determined. However, the uniquely accessible and highly vascular nature of KS offers a particularly attractive target for testing angiogenic-modulating therapies.

CONCLUSION

The malignancies that complicate HIV disease represent a unique intersection of virology, immunology, and tumor biology. As such, they provide opportunities for furthering our understanding of cancer and for testing novel paradigms of therapy. Further study of these tumors offers insights that will reach beyond the HIV epidemic and may provide unique opportunities for evaluating new cancer treatment strategies.

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