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HIV/AIDS Associated Malignant Disorders: Role of Highly Active Antiretroviral Therapy

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1. Introduction

Persons infected with the human immunodeficiency virus (HIV) have an elevated risk for the development of Cancer. Some of the malignant processes are intrinsic to the immunological impact of the HIV infection; others are more often related to the risk scenarios associated to the viral inoculum and subsequent development of the infection. In general terms, malignant transformation is fundamentally caused by genetic alterations to individual cells, which allow the presence of the disorganized autonomous growth of cells and the development of properties associated to the survival of the cancer cells. Properties associated to successful growth of the cancer include the capacity for relative autonomous growth, evasion of the normal regulatory process present within bodies, capacity of tissue invasion, spread to other organs and disruption of the normal organ homeostasis. Predisposing conditions that lead to an increased risk for the malignant transformation include chronic inflammatory states, congenital or acquired genetic mutations, autoimmune diseases, and exposure to environmental factors. The presence of HIV infection, particularly in the context of a deteriorated immune system is associated to an increased risk for the development of Kaposi's sarcoma, high-grade non-Hodgkin's lymphomas, central nervous system lymphoma and invasive uterine cervical cancer. Collectively these entities may be the initial manifestation of HIV infection and are intimately associated to the deteriorated immune system associated to the infection. As such they are considered AIDS defining conditions. The spectrum of HIV associated malignant disorders also includes non-AIDS defining cancers. Non-AIDS defining malignancies are often seen in patients who are at younger age than usual, are associated to a more aggressive behavior and tend to be diagnosed at a more advanced stage. The most common non-AIDS defining malignancies include Hodgkin's lymphomas, non-small cell lung cancer, head and neck cancer, ano-genital cancer, hepatic cancer and possibly multiple myeloma. The role of the HIV virus in triggering the malignant transformation of cells appears to be a direct effect by promoting cancer growth, and indirect in others by disrupting the human regulatory symbiosis provided by the immune system. The introduction of multiple spectrum antiretroviral therapy (ART) and the availability of highly active antiretroviral therapy (HAART) have caused a dramatic improvement in the immunological function of infected subjects with an associated increment in the overall survival of these patients. The use of HAART has been intimately associated to a dramatic decrease in not only AIDS defining opportunistic infections but in some of the AIDS defining tumors particularly Kaposi's sarcoma and non

Hodgkin's lymphomas. Nevertheless changes in the incidence of invasive cervical carcinoma and non-AIDS defining cancers have not been so remarkable. HIV infection has become a chronic condition associated to a longer lifespan of patients and the introduction of an evolving list of co-morbid conditions, including cancer. Under this scenario, understanding the trends on cancer development in this population of patients has become of marked importance, since they represent the next boundary that is limiting the survival of the HIV infected patient. In this chapter we describe the changing trends in the incidence of malignant disorders which affect the HIV infected patients with a particular emphasis on the role of HAART in the expression of these malignant conditions (Bedimo et al, 2004; Bonne et al., 2008; Bower et al, 2006; Caceres et al., 2010; Crum-Clanflone et al, 2009; Engels et al., 2008; Gurlich et al., 2002; Long et al., 2008;Mitsuyasy et al., 2011; Newcomb-Fernandez et al., 2003; Patel et al., 2008; Simard et al., 2010) .

2. Cancer

Hereditary or acquired genetic mutations, autoimmune disorders, and exposure to certain environmental agents may singly or in a combined synergistic fashion, predispose to the development of neoplasms. The role of HIV in inducing the malignant transformation of cells appears to be an indirect effect by disrupting the human immune regulatory process. Immunological deficiency induced by HIV causes a progressive impairment of the cellular immunity responsible for the control of viral growth and the immune recognition against virus-infected or altered cells in the different stages of malignant transformation. HIV induced cytokine deregulation disrupts the host's capacity to control oncogenic viral reactivation and replication, ultimately increasing the risk for malignant transformation. Oncogenic viruses, including the Ebstein-Barr virus (EBV), human herpesvirus 8 (HHV 8), certain subtypes of the human papilloma virus, hepatitis B virus (HBV), and hepatitis C virus (HCV) have all been causally related to the increasing prevalence of cancer development in these patients. In addition the presence of certain risky lifestyle behaviors often present in the HIV infected patients such as smoking, alcohol use, use of illegal drugs and sexual promiscuity may contribute and accelerate the risk of malignant transformation in these subjects. HIV associated severe immunosuppression may be interrupted or partially restored with the use of ART. Improvement or partial restoration of the cell-mediated immunity and the suppression of the HIV viral load will not only improve the patients' immunological status but will improve the overall clinical status with an improvement in overall survival. An increment in the survival of the HIV infected patient leads to an aging patient cohort with a higher likelihood of oncogenic viruses exposure. These elements alter the clinical course of the HIV infection with the development of new morbidity patterns such as altered toxicity profiles of medications, development of metabolic disorders, long lasting co-infections (including HPV, HHV, HCV, HBV and EBV), development of an increased risk of cardiovascular diseases and non-AIDS defining neoplasms. Even though, for many of the tumors described in this chapter, there are no specific prevention guidelines, other than the need to diagnose early and institute therapy as early as possible.

2.1 AIDS defining malignances

Kaposi's sarcoma, high-grade non-Hodgkin's lymphomas, including the high-grade immunoblastic or diffuse large cell lymphoma, the small noncleaved (Burkitt, Burkitt-like or non-Burkitt) lymphoma, primary central nervous system lymphoma (PCNSL), and invasive

cervical cancer are neoplasms included as AIDS defining conditions. With the introduction of HAART the spectrum of these cancers has changed, with a dramatic reduction in the incidence of Kaposi's sarcoma and non-Hodgkin's lymphomas. However, the impact of HAART in the invasive cervical cancer had not been significant. It is relevant to mention that in spite of HAART, the risk for AIDS defining cancers continues to be significantly higher as compared to the non HIV infected general population (Simard et al., 2010).

2.1.1 Kaposi's sarcoma

Kaposi's sarcoma is an angio-proliferative disease characterized by tumors composed of new blood vessel (angiogenesis), endothelial spindle cell growth, inflammatory cell infiltration and edema. Kaposi's sarcoma is classified in four epidemiologic variants: the classic, the African endemic, the iatrogenic, and the epidemic AIDS-related. The clinical manifestation of this sarcoma in patients with AIDS is variable but usually presents as a multiple, small, innocuous pigmented cutaneous or oral-pharyngeal lesions. These may grow and spread causing symptom-producing visceral disease. Alternatively it may develop in a multifocal fashion in several sites at the same time. In both cases it may result in a life-threatening process with the need of aggressive therapy.

2.1.1.1 Pathophysiology

The pathogenesis of the condition was clarified in 1994 when human herpes virus-8 (HHV-8) also known as Kaposi's sarcoma -associated herpes virus (KSHV) was described and detected in all forms of Kaposi's sarcoma. HHV-8 is a transmissible DNA virus with a seroprevalence in the United States between 1%-5%. The pathogenesis of AIDS related Kaposi's sarcoma is multifactorial and includes HHV-8 infection, HIV induced cytokine malfunction, and stimulation transactivating transduction (TAT) protein by HIV. HHV-8 is an oncogenic virus transmitted both sexually and through body fluids such as saliva and blood, which encodes a cell protein involved in signal transduction, cell cycle regulation and inhibition of apoptosis. HHV-8 is critical in the pathogenesis of this AIDS related sarcoma, but by itself is not sufficient to cause the cancer. The risk of this cancer is directly related to the degree of immune suppression in the host and can remain in a latent phase for many years. The interaction between HIV-TAT protein and the immune suppressed state of the host allows the activation of the virus resulting in an abnormal inflammatory response and the promotion of angiogenesis by inducing lymphatic reprogramming of the vascular endothelium.

2.1.1.2 Clinical manifestation and diagnosis

The clinical presentation of Kaposi's sarcoma ranges from irregular reddish discrete lesions to violaceous or brown nodules, macules, patches, or plaques. The lesions are usually painless, do not blanch under pressure and may be associated with edema, lymph node or visceral involvement. Pathologic confirmation is required to establish a diagnosis of Kaposi's sarcoma since bacillary angiomatosis can mimic this malignancy even for the seasoned clinician. The lesions may occur in any part of the body, including the face, chest, oral mucosa, penis or scrotum, rectum, and conjunctiva. The oral cavity can be extensively involved resulting in airway obstruction. The gastrointestinal tract is a common site of the disease. These lesions are often asymptomatic but can be associated with abdominal pain, gastro-intestinal bleeding, diarrhea, abdominal cramps, and weight loss. Visceral involvement occurs in over 50% of the cases. Pulmonary involvement is the second most

common extra-cutaneous location and may present with life threatening manifestations. Pulmonary involvement is often associated with obstructive respiratory symptoms, hemoptysis and chest pain. The clinical course of this sarcoma is variable with the presence of slowly progressive lesions over the course of many years, or it may have a rapid progression over a course of weeks or months. The external appearance of the cutaneous lesions may lead to emotional distress and stigmatization. The use of corticosteroid therapy has been associated with the induction or exacerbation of this cancer in the context of the HIV infected individual (Bellan et al, 2003; Dezube, 2007).

2.1.1.3 Therapy

The decision to institute therapy needs to consider the extent, location and rate of tumor growth as well as the patient's symptoms, and immune system condition. Optimization of HAART therapy is critical in all patients with Kaposi's sarcoma since this tumor is intrinsically linked to the degree of immunosuppression and the fact that up to 91% of lesions regress with HAART. Immune reconstitution is a primordial therapeutic goal in every patient. For limited skin lesions, the application of topical therapy with liquid nitrogen, vinblastine or retinoic acid may be appropriate. External beam radiotherapy is also an option in certain cases. Interferon-α is an immunomodulator with antiviral and anti-angiogenic effect that has been used with some success in patients with the cutanous form of the disease. Its widespread use has been hampered by its toxicity profile, which is often moderate to severe in nature. For patients with edema, extensive mucocutaneous disease, or symptomatic pulmonary or gastrointestinal involvement, the administration of systemic chemotherapy is recommended. Several single agent drugs are active in this AIDS related sarcoma. These include vincristine, vinblastine, etoposide, anthracyclines, bleomycin and taxol with an overall response rate of 76%. The administration of combination chemotherapy has been utilized since early 1991 for rapidly progressive mucocutaneous or visceral disease. The most common drug combination has been doxorubicin, bleomycin and vincristine (ABV) or bleomycin and vincristine (BV). The use of liposomal anthracyclines is currently considered the optimal first line therapy for the treatment of advanced Kaposi's sarcoma. This single agent therapy has been reported to have similar or improved response rates to other drugs but less toxicity. Paclitaxel (taxol) is the most recent introduction to the systemic chemotherapeutic agents available for these patients. Its use is often prescribed as second line therapy for patients with refractory disease. The response rate with paclitaxel is between 59-71%. Additional drugs that have variable rate of success in this disease include inhibitors of angiogenesis such as thalidomide, inhibitors of tyrosine kinase or mammalian rapamycin pathways such as imatinib and sunitinib. The response rate after standard chemotherapy is usually very good, but they tend to be short lasting. The high incidence of opportunistic infections associated to the administration of chemotherapy along with the chemotherapy associated cytopenias, are major issues in the management of these patients (Berretta et al, 2003; Dezube, 2007).

2.1.1.4 Epidemiology

Kaposi's sarcoma is a rare condition in the HIV negative population; however, it is the most common malignancy associated with HIV infection. This cancer had been more often detected in HIV-positive persons with more advanced immunosuppression ($CD4^+$ T lymphocyte counts of <200 cells/μL), and especially in men who have sex with men (MSM). Among MSM the transition of the HHV-8 is predominately by deep kissing. In these

individuals the HHV-8 prevalence that is associated with their number of homosexual partners is considerably greater when compare to the other HIV risk behavior groups. The probability of developing Kaposi's sarcoma in HIV infected persons who are infected with HHV-8 is significantly high. The overall incidence of this cancer was as high as 20% among patients with AIDS before the advent of effective ART. However the incidence decreases dramatically since the introduction of HAART and remains low (Bedimo et al., 2004). The HIV/AIDS Cancer Match Study of 263.254 AIDS cases followed in 15 States of the United States between 1980 and 2008 reveals a significant reduction of this sarcoma incidence of 80% (RR, 0.2: 95% CI, 0.2%-0,2%) in the HAART era (Simard et al, 2010). This study concord with previous studies performed in United States and Puerto Rican's HIV cohorts that reported a significant reduction in the incidence or prevalence of this cancer after the antiretroviral therapies era (Engel et al., 2008; Crum-Cianflone et al., 2009; Mayor et al., 2008b). Despite the significant incidence reduction of Kaposi's sarcoma the risk of this cancer in HIV infected persons remains significantly elevated in the HAART era, when compare to the general population (Simard et al., 2010; Engels et al., 2008; Patel et al., 2008).

2.1.1.5 Prevention

Routine screening for HHV-8 by PCR or serologic testing is not indicated for HIV-infected persons. It has been advocated that HAART therapy will reduce the incidence of Kaposi's sarcoma by improving the immunological state and preventing tumor growth. Thus opportune antiretroviral therapy is an effective preventive strategy for patients who qualify.

2.1.2 Non Hodgkin's lymphoma

Non-Hodgkin's lymphomas represent a diverse group of malignant conditions of the immune system. These tumors are 60-100 times more common in the HIV infected patient as compared to the general population. There are three histological subtypes that are responsible for the majority of non-Hodgkin's lymphomas diagnosed in HIV patients and they include small non-cleaved lymphomas (Burkitts and non Burkitts like), high grade large cell, and the immunoblastic lymphomas, commonly present with the brain as primary site. With the institution of HAART the incidence of lymphomas in these patients has decreased but the decrement is much less as compared to the other AIDS defining conditions. The risk of developing non-Hodgkin's lymphomas has decreased from 1,226 to 306 per 100,000 person years after the introduction of HARRT (Simard et al., 2010). However, the prevalence of these lymphomas in HIV persons after HAART remains high when compare to HIV negative population (Engels et al., 2008; Simard et al., 2010; Bierman et al., 2004; Doweiko, 2007b).

2.1.2.1 Pathophysiology

The pathogenesis of AIDS related non-Hodgkin's lymphomas are fundamentally related to repeated stimulation and proliferation of B cells in the setting of a T–cell immunodeficiency. This results in the loss of immune surveillance and the continued proliferation of aberrant B cell clones. Etiologic agents implicated in the abnormal B cell proliferative response include HIV, Ebstein Barr virus and other infections. The presence of HIV induces the expression of cytokines (IL-6, IL-10 and TNF-α), which also contribute to B cell activation and proliferation. The process of B cell expansion results in lymph node enlargement and is usually accompanied by polyclonal hypergammaglobulinemia. The enhanced proliferative response of B cells increases the opportunity of genetic error, which may result in the

dysregulation of suppressor genes (p53) and/or activation of proto-oncogenes (c-myc, BCL-6 or ras). The majority of AIDS-related non-Hodgkin's lymphomas (75%) carry alterations in at least one proto-oncogene and more than 90% have alterations in at least one of the suppression genes. The presence of activation cytokines such as IL-6 and IL-10 contribute to the chronic B cell stimulation resulting in continued growth. Specifically, IL-6 activity that increases early in the course of HIV infection is predictive of the likelihood of lymphoma developing over time. IL10 is an autocrine growth factor for lymphoma and an inhibitor of cellular immune response. Elevated levels of IL-10 are associated to a worse prognosis in AIDS related non-Hodgkin's lymphomas (Bellan et al, 2003; Doweiko, 2007b).

2.1.2.2 Clinical manifestation and diagnosis

The presence of constitutional symptoms (fever, weight loss and night sweats) is seen in 80-90% of patients with AIDS-related non-Hodgkin's lymphomas. It is vital to exclude the presence of opportunistic infections in these patients prior to instituting antineoplastic therapy. Most patients initially present with advanced stage of lymphoma with 80% presenting as a stage IV. Common sites of extra-nodal involvement include central nervous system (30%), gastrointestinal tract (25%), bone marrow (25%) and liver (17%). Nevertheless any site of the body may be involved with AIDS-related non-Hodgkin's lymphomas including the rectum, soft tissue, oral cavity, lungs and heart. Bone marrow and leptomeningeal involvement are more often associated with small, non cleaved (Burkitt-like) lymphoma. Patients with gastrointestinal involvement may present with pain, weight loss, bleeding, obstruction and perforation in 40% of the cases. The prognosis of this group of patients tends to be better; they respond very well to therapy and have a longer survival. Patients with primary central nervous system lymphoma often present with focal neurologic deficits, seizures, and or altered mental status. A diagnosis of non-Hodgkin's lymphomas requires histological confirmation by biopsy with immunephenotypic and molecular rearrangement studies. A complete staging evaluation must be done once a diagnosis is made utilizing body imaging studies of the brain, bone marrow aspiration and biopsy, liver function studies and spinal fluids analysis if clinically indicated. The presence of Ebstein Barr virus DNA in cerebrospinal fluid by polymerase chain reaction is a high specific and sensitive diagnosis criterion for primary central nervous system lymphoma.

The majority of in HIV related non-Hodgkin's lymphomas are associated with one of three histological subtypes mentioned above. The presence of small non-cleaved lymphomas (Burkitts and non Burkitts like) accounts for 40% of them and is usually seen in patients with a higher CD4 counts than other types. They often express an abnormal p53 and c-myc or ras oncogenes. The high-grade large cell histology is seen in 40% of patients and is associated with an abnormal expression of BCL-6 in 40% of the cases. One of the particular presentations of this histology is primary effusion lymphoma. Primary effusion lymphoma occurs as a late manifestation of HIV infection and has a poor clinical outcome and a shorter 6 months survival as compared to other sites of this histology. This high-grade lymphoma originates in the pleura, pericardium, peritoneum, serosal surface or rarely in the meninges. The etiologic cause of this lymphoma is related to herpes virus-8 infection of the tumor clone. A previous history of Kaposi sarcoma increases the risk of developing primary effusion lymphoma, and often genomic material containing the imprint of KSHV/HHV8 genes is found in the malignant clone of cells. The remaining 30% of AIDS-related non-Hodgkin's lymphomas are inmunoblastic plasmocytoid lymphomas and are considered to

be related to EBV infection. The most important presentation of this histology is the primary central nervous system lymphoma, which accounts for 20% of all AIDS related lymphomas. This histology is seen in advanced stage AIDS with CD4 cell counts below 30 cells/mm, and they rarely occur outside the brain. The incidence of primary central nervous system lymphoma has decreased with the introduction of HAART but remains a disease with poor outcome. This type of lymphomas is the second most common brain space-occupying lesion in patients with AIDS after toxoplasmosis. The most common location for primary central nervous system lymphomas is cerebral hemispheres, following by basal ganglia, cerebellum, and brain stem, with less than 10% involving posterior fossa. Unlike primary central nervous system lymphoma in the general population, these tumors can have ring-enhancement due to their rapid growth. The tumors usually measure at least 3 cm and may present with central necrosis. Management of this primary lymphoma consists of radiation therapy, the use of corticosteroids and alkylating agents. This therapy will increase length of survival but they rarely induce lasting remissions (Bierman et al., 2004; Doweiko, 2007b).

2.1.2.3 Treatment

The mainstay of therapy for patients with AIDS related non-Hodgkin's lymphomas are systemic chemotherapy. The common used regimens include R-CHOP, m-BACOP, EPOCH although no regimen appears superior to the other. System prophylaxis with intrathecal cytarabine (ARA-C 50 mg) or methotrexate (10-12 mg) every week for four weeks has been shown to reduce central nervous system relapse in the high risk group of patients. The major complication of chemotherapy is myelosuppression with its associated morbidities. Several studies have shown that co-administration with hematopoietic growth factors may enhance the chemotherapy toleration. In addition, prophylaxis with trimethropim/sulfa, azithromycin, fluconazole, ciprofloxacin, and valgancyclovir can reduce the risk of infection during intensive chemotherapy regimen. Refractory or relapse systemic lymphomas have a very poor prognosis with no satisfactory second line therapy available. An important factor in the management of AIDS related non-Hodgkin's lymphomas is the use of HAART to reduce the viral load and enhance the immune system management of the malignant clone.

2.1.2.4 Epidemiology

In the United States, 3% of the AIDS cases present with lymphoma. The major risk factors include older age, magnitude and duration of the immunosuppression, no prior HAART use or insufficient immunologic or virologic response to HAART. The types of risky practices associated to HIV infections are not associated to the presence of lymphoma. AIDS related non-Hodgkin's lymphomas are seen more frequent in men than in women and is seen more often in whites than in blacks. The standardized incidence rate of AIDS associated lymphoma is significantly higher than in the general population (Grulich et al., 2007). Most of the AIDS related non-Hodgkin's lymphomas (75%) have advanced HIV disease, however 25 % of patients develop the disease when the viral load is undetectable. Different studies had reported a significant reduction in the incidence of these lymphomas with the availability of effective antiretroviral therapies, particularly HAART (Bedimo et al., 2004). For example the HIV/AIDS Cancer Match Study of Simard et al, reported a 70% decline in their incidence (RR, 0.3: 95% CI, 0.2%-0.3%) as compared to the pre-HAART era (Simard, et al., 2010). The study found significant reduction in the diffuse large B cell and in the CNS Hodgkin's lymphomas NHL, but no differences were seen in the Burkitt-like

histological lymphomas. Similar findings were documented in the other United States and Puerto Rican AIDS cohorts (Engels et al., 2008; Mayor et al., 2008b). Despite this significant reduction, non-Hodgkin's lymphomas risk remained significantly higher in HIV infected persons after HAART when compared to the general population as reported by Patle et al, Simard et al. and Engels et al.

2.1.2.5 Prevention

The risk of developing non-Hodgkin's lymphoma is directly proportional to the disruption of the immune system. The appropriate and opportune use of antiretroviral therapy (HAART) is necessary to reduce this risk. There are no specific prevention guidelines, other than the need to diagnose early and institute therapy as early as possible.

2.1.3 Invasive cervical cancer

Cervical cancer is a malignant proliferation of the squamous epithelium of the ectocervix causing squamous cell carcinoma. Malignant proliferation of the glandular lining of the endocervix carries histology of adenocarcinoma. More than 95% of cervical tumors have squamous cell histology and infection with the Human papilloma virus (HPV) is a necessary factor for the malignant transformation in the majority of these patients. Several subtypes of the HPV have delineated as responsible for the development of cervical dysplasia, which represents the usual histological antecedent to invasive tumors of the ectocervix. A higher incidence of HPV-related dysplasia, more advanced stages of cervical dysplasia and refractoriness to standard therapy is characteristic of this disease in females who also have HIV infection. The similarities in risk profiles and transmission modes between HIV and HPV explain the common and widespread presence of HPV in this group of patients. The higher risk of developing cervical dysplasia in HIV infected women initially promoted the inclusion of cervical cancer as one of the AIDS defining condition in 1993. The presence of HIV associated immunosuppression contributes to an impaired HPV clearance, facilitating progression of early stage to more advanced forms of dysplasia. The role of HIV in the ultimate transformation to cervical carcinoma is not so clearly defined. Cervical cancer is a tumor, which can be prevented and clearly curable if diagnosed at an early stage. Aggressive prevention strategies have significantly decreased the incidence and prevalence of this tumor in developed countries (Molpus &Jone, 2004; Powrie & Cu-Uvin, 2007).

2.1.3.1 Pathophysiology

The majority of squamous cell carcinomas of the cervix are preceded by a premalignant epithelial dysplasia known as cervical intraepithelial neoplasia and squamous intraepithelial lesions. These lesions slowly progress to the invasive form of cervical cancer. HPV infection has an important role in the genesis of this dysplasia and in the progression to an invasive state. This is in large part due to the chronic inflammatory insult induced by this oncogenic virus. HPV infection is the most common sexually transmitted infection in the US with an increasing prevalence seen among HIV infected individuals. HPV Types 16, 18, and 31 are the major virus associated with cervical cancer. Type 16 is more frequently associated with squamous cell histology and type 18 with adenocarcinoma. Other factors associated to the increase incidence of the cervical cancer in these patients include, the use of tobacco, younger age of first intercourse, higher number of sexual partners, immunosuppression, multiple pregnancies, use of hormonal medications, and to a lesser degree family antecedents (Molpus &Jone, 2004; Powrie & Cu-Uvin, 2007).

2.1.3.2 Clinical manifestation and diagnosis

Cervical cancer is asymptomatic in its early stage and is most often seen in patients over the age of 30 years. As the cancer progresses some patients may present with non-menstrual vaginal bleeding, post coital bleeding, postmenopausal bleeding, pain during the sexual intercourse or abnormal vaginal discharges. With more advanced stages of the cancer, the presence of back and pelvic pain, bowel and bladder malfunction, lymph nodes enlargement or urinary obstruction may be present. Cervical intraepithelial neoplasia (CIN) also knows as cervical dysplasia, and invasive stage cancer is diagnosed by histological changes, usually based on cytologic examination of the cervical cells. The Pap smear cervical cytology is the established screening test to evaluate for dysplasia or cancer. A single Pap smear has a sensitivity of 50% and a specificity of 81% when compared to a biopsy of the area. Consecutive Pap smears increase the sensitivity to 99%. In situations where the Pap smears suggests an intraepithelial lesion or the presence of carcinoma, a colposcopy and directed biopsy is usually diagnostic. Any suspicious visible lesion in this anatomic area requires a biopsy.

2.1.3.3 Therapy

The management of cervical dysplasia among HIV-infected patients does not differ from the general guidelines used for the general population. Observation without specific intervention is usually recommended for low degree of cervical dysplasia (CIN 1) unless the lesion persists over a period of 18-24 month. If the lesions evolve to a more advanced degree of dysplasia, or if there is poor adherence to routine monitoring, immediate intervention is necessary. Conventional therapies used for treatment of CIN 2 or 3 dysplasia stage include cryotherapy, laser therapy, cone biopsy, and a loop electrosurgical excision procedure (LEEP). In patients with CIN 1 that have not been treated with one of the outlined interventions, Pap smears or colposcopy should be repeated every 4-6 months to monitor for persistence or progression of lesions. Recurrence rates of 40%-60% after therapy has been reported among HIV-1 infected women undergoing these procedures. Very early stage of cervical cancer with a depth of invasion of less than 3 mm can be treated with hysterectomy or cervical conization. Lager tumors require radical hysterectomy with pelvic lymphadenectomy or pelvic radiation therapy. For advanced stages, therapy with radiation or cisplatin-based chemotherapy is indicated in a palliative or neo-adjuvant basis. Since recurrence of CIN and cervical cancer after conventional therapy is increased in the HIV-infected populations, these patients need careful and repeated follow up examinations with frequent cytologic screening and colposcopic examination if necessary.

2.1.3.4 Epidemiology

Cervical carcinoma is the second most common cause of cancer related mortality in the world. The prevalence of this tumor is much higher in countries in which primary and secondary prevention strategies are not fully implemented. It is estimated that over 12,800 new cases are diagnosed annually in the United States with an associated yearly mortality of 4,600 patients. With the introduction of cervical cytologic screening, the incidence of invasive cancer and mortality associated to this condition has decreased dramatically. Nevertheless the incidence of cervical carcinoma in HIV infected women (16 per 100.000 women) continues to be higher than in the general women population (7 per 100,000) in United States for the year 2004. Contrary to the other AIDS defining malignancies; the incidence of cervical cancer incidence has not changed (RR, 0.8: 95%CI (0.5-1.2) with the

introduction of HAART (Bedimo et al.,2004). The standardized incidence ratio (SIR) of cervical cancer continues to be significantly higher in HIV infected females when compared to the general female population (Simard et al., 2010; Engels et al., 2008; Patel et al., 2008). The immunosuppressive effects of the HIV appear to have a lesser role in the pathogenesis of this tumor as compared to the oncogenic effects of HPV. The oncogenic effects of HPV are not interrupted with HAART, limiting the impact of antiretroviral therapy on the overall incidence of cervical cancer in this population of patients. Nevertheless continued immunosupression is associated to a more aggressive disease once invasive carcinoma is present.

2.1.3.5 Prevention

Primary and secondary prevention are essential in order to reduce the incidence of invasive cervical carcinoma in HIV infected women. Early detection of dysplastic changes in the cervical cells and the use of the recently available HPV vaccine are preventive methods directed to reduce the incidence of invasive cancer. HIV infected women need to have a Pap smear on initial evaluation and six months after the initial evaluation. If both tests are negative then follow up exams every year is suggested. If there is cervical dysplasia, a history of a cervical lesion or if the patient is positive for HPV, the Pap smear should be repeated every 4 to 6 months. Some Gynecologists advocate the use of HPV DNA assays as a screening modality in HIV infected females to identify women with a higher risk of dysplasia. Other assays to detect the HPV mRNA of E6 or E7 protein are also used with similar reasons. If a Pap smear demonstrates dysplasia or atypia, colposcopic directed biopsy of the cervix is indicated. HPV vaccine is now available for the active immunization against some of the most common HPV oncogenic virus. This vaccine does not immunize against all oncogenic HPV viruses, thus repeated screening through Pap smear continue to be relevant in the immunized patient. HPV vaccine will provide immunization in females prior to the infection, thus the vaccine is recommended prior to sexual activity usually ages of 9 and 26 years. The efficacy of the vaccine in inducing an effective immune response in the HIV infected host is unknown at this time. Educational interventions on cervical cancer along with its relation with HIV and HPV infections need to be reinforced amongst all health workers and patients.

2.2 Non AIDS defining malignancies (HIV-related)

There are several malignancies that are not AIDS defining, which has a higher prevalence amongst HIV infected individuals. These HIV associated malignancies include, Hodgkin's lymphoma, non-small cell lung cancer, head and neck cancer, anal cancer, liver cancer, multiple myeloma, and central nervous system malignances (Engels, et al., 2008; Simard et al, 2010; Nguyen et al,2010). Most of these malignant conditions can be attributed to persistent infection with oncogenic viruses and are not directly associated to the HIV induced immunodeficiency. The enhanced life expectancy of HIV infected patients with the use of HAART has allowed an increased period of vulnerability where the patients can be exposed to oncogenic viruses. An increase in the period of viral latency also accompanies an increase in survival. Nevertheless, the immunological deficiency associated to HIV contributes to the progressive impairment of cellular immunity against oncogenic viruses and virus-infected tumor cells. HIV infection elicits a cytokine deregulation, which disrupts the host capacity to control the reactivation and replication of oncogenic viruses, increasing the risk of malignant transformation.

2.2.1 Hodgkin's lymphoma

Hodgkin lymphoma is one of the most common non-AIDS defining malignancy in HIV positive patients with an incidence which is 18 times more frequent than in the general population. This lymphoma is characterized by the orderly spread of disease from one lymph node group to another and by the present of systemic symptoms. This histology has been associated to intravenous drug use, but the occurrence of this lymphoma is not exclusively restricted to this risk profile. The diagnosis of Hodgkin lymphoma is usually established late in the course of the HIV infection, when patients present a CD4+ T cell count of 300 cells per mm^3 or less.

2.2.1.1 Pathophysiology

The histology presentation of Hodgkin lymphoma among HIV positive patients tends to be more unfavorable as compared to the general population. The mixed cellularity and the lymphocyte-depleted histology subtypes are more frequently found in HIV infected persons when compared to the general population. Contrary, the nodular sclerosis type is less frequent in HIV persons. The general population with Hodgkin lymphoma demonstrates tumor with an extensive infiltrate of T lymphocytes as compared with the HIV patient in which the malignant cellular infiltrate is substantially depleted of T lymphocytes. These variations in histology convey a more aggressive course for the Hodgkin lymphoma in HIV infected patient. Epstein Barr virus (EBV) is associated with Hodgkin lymphoma, and may play an important role in the pathogenesis of this disorder since 80%-90% of patients with HIV related Hodgkin lymphoma have EBV genome integrated within Reed-Sternberg cells (RSC). This proportion is higher than the one detected in the general population. The RSCs are the malignant cells seen in Hodgkin lymphoma and their presence is essential for the diagnosis of this disorder. The survival of the RSC depends on the antiapoptotic nuclear factor (NF) κB pathways. The activation of this pathway relies on the recruitment of inflammatory cells to the tumor mileu, which provide essential signals that stimulates the proliferation and inhibits the apoptosis of the RSC. In advanced AIDS stages, the incidence of Hodgkin lymphoma may decrease due to inability of the tumor mileu to recruit lymphocytes and other inflammatory cells essential for the survival of the RSC. The latent expression of EBV-associated transforming protein on the surface of the RSC may also help the proliferation of malignant cells. This latent protein mimics the activated CD40 receptor and allows the constitutive activation of the NF κB pathways, resulting in inhibition of the RSC apoptosis. Thus EBV can potentially promote oncogenesis independent of the availability of inflammatory and activated CD4 T cells. The nodular sclerosing histology appears to be less associated to EBV infection and is more likely to be seen in patients with a higher CD4 cell count. All patients with Hodgkin lymphoma require complete staging with total body imaging studies and bone marrow examinations (Portlock & Yahalom, 2004; Doweiko, 2007b).

2.2.1.2 Clinical manifestation and diagnosis

The clinical manifestations of Hodgkin lymphoma in HIV infected patients differ from the presentation seen in the general population. HIV associated Hodgkin lymphoma is more aggressive in nature, usually presents in advanced stages of the disease with more than 75% having stage III or IV at diagnosis. Liver and spleen involvement is seen in 65% of patients and bone marrow involvement in 50%. More than 80% of these patients present constitutional symptoms such as unexplained fever, night sweats, or significant weight loss. The overall survival of HIV related Hodgkin lymphoma prior to the introduction of HAART

was around 18 months. This high mortality was associated to an increased vulnerability of infections after systemic chemotherapy and the short disease free interval often associated with this cancer. The introduction of HAART has improved the survival of patients with HIV related Hodgkin lymphoma, decreasing the incidence of opportunistic infections, and allowing greater tolerance to the antineoplastic drugs.

2.2.1.3 Therapy

The therapy of Hodgkin lymphoma depends of the stage of disease at initial presentation. The therapy of this lymphoma is multidisciplinary in nature with external beam radiation therapy, chemotherapy or a combination of both. Surgical interventions have a limited role. Radiation therapy or chemotherapy is an effective treatment for stage I and II of the Hodgkin lymphoma. For more advanced stages, the use of combination chemotherapy with the ABVD regimen (adriamycin, bleomycin, vinblastine and dacarbazine) along with involved field radiation in selected patients is recommended. A rate of 80% of complete remission is associated with this regimen.

2.2.1.4 Epidemiology

Hodgkin's lymphoma accounts for less than 1% of all the tumors in the US and is more common in men than in women. There are two incidence peaks between the ages of 15 to 34 and in those over the age of 55 years. Hereditary factors, infection with Epstein-Barr virus, and T-lymphocyte immune dysfunction, are associated with this type of cancer. The risk for Hodgkin's lymphoma is significantly higher in the HIV/AIDS population with a standardized incidence rates between 5.6 and 16.2 in relation to the general population (Grulich et al., 2007). This type of lymphoma has a more aggressive debut in HIV infected persons, than in the general population. When evaluating the effect of antiretroviral therapies in the incidence of Hodgkin's lymphoma a great majority of the studies reported a significant increment of this type of cancer in the HIV population after the availability of HAART (Bedimo et al., 2004). Standardized incidence rates of Hodgkin's lymphoma that in the pre HAART era was around 2.0 increased beyond 6.0 in the HAART era (Simard et al, 2010; Engels et al., 2008).

2.2.1.5 Prevention

There are not specific measures to prevent this type of lymphoma.

2.2.2 Lung cancer

Lung cancer is one of the most frequent tumors seen in the general population and is the leading cause of cancer related mortality in the United States. Around 90% of the genesis of this neoplasm is directly associated to the use of tobacco. Passive smokers have a small but significant risk of developing lung cancer when compared to non-smoking population (Miller, 2004). Other risk factors for lung cancer include a genetic predisposition, exposure to environmental toxins, the presence of chronic pulmonary infections, and the presence of an immunosuppressive state. This later risk factor has been confirmed in the organ transplanted populations of patients, which require prolonged use of immunosuppressant therapy (Grulich et al., 2007). The incidence of lung cancer is increased in HIV infected individuals and is often diagnosed in younger age individuals with a history of smoking. The implementation of HAART has not resulted in a significant change in the lung cancer incidence in these patients (Bonnet & Chene, 2008).

2.2.2.1 Pathophysiology

The majority of malignant tumors of the lung originate from the bronchial epithelium. These bronchogenic carcinomas are histologically divided into small cell lung cancers and non-small cell lung cancers. The non-small cell lung cancers are subdivided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma. The adenocarcinoma is the most frequent histological subtype found in HIV infected patients. The presence of small cell lung cancers tends to be less common in HIV infected persons. The management of small cell lung cancers is generally chemotherapy and for early stages of non-small cell lung cancers, the use of surgery or radiotherapy is usually employed. The process of malignant transformation towards lung cancer is associated to a multistep accumulation of genetic mutations, which regulate growth, and apoptosis of the respiratory epithelium. Premalignant lesions including squamous dysplasia and atypical alveolar hyperplasia have been associated with some chromosomal mutations including chromosomes 3p, 2p, and 9p. Bronchogenic carcinomas have been related to alterations in chromosomes 3p, 5q, 9p, 11p, 13q and 17P. The majority of the genetic alterations in these tumors involve deletions of tumor suppressor genes that are essential for the proliferation of tumor cells. Other than genetic mutations, an increase in cellular proliferation may be the result of autocrine growth through factors that include neuropeptide growth factors, insulin like growth factors, transforming growth factor alpha, stem cell growth factor, and heregulins. The precise mechanisms behind the increased incidence of HIV associated lung cancer remains unknown. Immunological damage induced by the virus, pulmonary epithelium damage induced by recurrent infections, the use of tobacco and other drugs are synergistic factors which could contribute to the development of this cancer in the HIV population.

2.2.2.2 Clinical manifestation and diagnosis

Lung cancer is usually asymptomatic when it is detected in its early stages. It is not unusual to have an abnormal routine chest radiograph as the initial test, which leads to the diagnosis. In late stages the presence of pulmonary related symptoms is common. Common symptoms and findings in these patients include cough, changes in frequency and intensity of a chronic cough, hemoptysis, airways obstruction, chest pain, disnea, postobstructive pneumonia, fever and pleural effusion. Symptoms related to direct organ invasion to the heart, great vessels of the upper mediastinum, brain, bone, adrenal glands and liver may be present (Miller, 2004). In metastatic cancer, cervical and supraclavicular lymphadenopathy may be present. HIV associated lung cancer is usually diagnosed in the late stages and as a consequence is associated to a worse prognosis (James, 2006). A diagnosis of lung cancer can be made by examination of sputum cytology or histological evaluation of tissue biopsy. Positron- emission tomography scanning or contrast nodule enhancement CT is occasionally used as a non-invasive alternative to discriminate between a malignant and a non-malignant pulmonary lesion. This technique is associated to a high number of false negative and false positive results.

2.2.2.3 Therapy

Surgery is the most appropriate treatment in non-small cell lung cancer for patients that have potentially resectable disease. It is imperative that patients in whom a pulmonary resection is being considered, the baseline pulmonary function tests are adequate to tolerate the resection and that the general medical condition is optimal to minimize surgical

complications. Immunological status is not a very important prognostic variable to preclude surgical cure for these patients. Radiation therapy is also an effective treatment for the non-small cell lung cancer, especially when combined with chemotherapy. In advanced stages of the disease, palliative chemotherapy in the form of cisplatin, carboplatin, paclitaxel, mitomycin, vinca alkaloids, gemcitabine, vinorelbine, ifosfamide and etoside may be used. The therapeutic interventions available for HIV positive patients are similar to their HIV negative counterparts.

2.2.2.4 Epidemiology

Lung cancer is one of the most frequent tumors in the US and is the leading cause of cancer related mortality. In 2007, the incidence in the United States was of 65.5 per 100,000. Lung cancer is the most frequent non- AIDS defining tumor in the HIV infected patient. The standardized incidence ratio (SIR) of this tumor is higher in the HIV infected population, as compared to the general population (Simard et al., 2010; Engels et al., 2008; Bonnet et al., 2008; Patel et al., 2008). The impact of HAART in modifying the incidence of the HIV associated lung cancer is minimal. Engel et al. has reported that the SIR for the lung cancer before and after HAART therapy remains 2.6 in their study cohort (Engels et al., 2006).

2.2.2.5 Prevention

The predominant intervention, which will reduce the incidence and prevalence of lung cancer in the HIV infected population, is the avoidance or reduction in tobacco exposition. It is highly recommended that non-smokers remain free of tobacco and that smokers reduce or cease tobacco use. This recommendation continues to be relevant even in the group in with a diagnosis of lung cancer has been established. In addition HIV infected persons need remain compliant with their HIV therapy in order to reduce the likelihood of recurrent pneumonia and other respiratory complications associated to HIV.

2.2.3 Hepatocelullar carcinoma

Hepatocellular carcinoma is the most common primary liver cancer, with an estimated incidence of 500,000 worldwide cases per year. It is more common in men and more frequently seen between the ages of 50 and 60 years old. Hepatocellular carcinoma is the third leading cause of cancer mortality worldwide. The incidence rates of this carcinoma in United States have historically been lower as compared to other tumors; nevertheless it has doubled in the past decades. In addition the trends of mortality associated to this tumor have increased at a faster rate than most other tumors of the body. Hepatocellular carcinoma often arises in the setting of a damaged liver, as seen in liver cirrhosis. As a consequence the risk factors for hepatic cirrhosis are also risk factors for this cancer. The most common external agents responsible for hepatic cirrhosis include prolonged abuse of alcohol, and chronic infection with the Hepatitis virus type B (HBV) and C (HCV) virus. The coexistence of HIV and HCV infection has been associated to a synergistic damage to the liver leading to a higher incidence of this liver cancer. The incidence of Hepatocellular carcinoma in HIV infected persons has increased with the introduction of HAART. With the growing armamentarium of anti retroviral interventions available for these patients, the survival and quality of life have markedly improved. This survival improvement has permitted re-exposition or continued expositions to drugs, alcohol, tobacco and viral agents, which will compound the extent of liver tissue damage in this high-risk population.

2.2.3.1 Pathophysiology

Hepatocellular carcinoma is an epithelial tumor that arises from the malignant transformation of the hepatocyte. In the majority of patients the tumor originates in the background of a cirrhotic liver suggesting the need of a damaged liver for the malignant transformation to occur. As a consequence all conditions, which lead to hepatic cirrhosis, increase the risk of this carcinoma. The conditions, which are considered risky factors for hepatic cirrhosis, include chronic HBV or HCV infections, chronic alcohol abuse, hemochromatosis, sialohepatitis, certain congenital hepatic disorders, and exposure to hepatotoxic agents. There are exceptional cases in which Hepatocellular carcinoma develops in the absence of liver damage. The exact mechanism for the genesis of this malignancy is uncertain in many of the scenarios described. In patients with chronic HBV infection, the integration of the HBV DNA into the hepatocyte genome produces a significant disturbance in the host tumor suppressor genes and an activation of oncogenes. This leads to a disruption in the cell's cycle, inhibition of the DNA repair mechanisms, and inhibition of hepatocyte apoptosis. These mechanisms contribute to the malignant transformation and tumor proliferation. In chronic HCV infection, immune mediated inflammation is present which results in inhibition of hepatocyte apoptosis. It has been postulated that the co-existence of HBV, HCV and HIV infection produces a significant increment in the risk in developing Hepatocellular carcinoma. These co-infections have also been associated with a reduction in the therapeutic efficacy for HBV and HCV, resulting in continued active co-infection with an augmentation in the incidence and the progression of this neoplasm (Fallon et al., 2006; McDonald et al., 2008).

2.2.3.2 Clinical manifestation and diagnosis

Hepatocelullar carcinoma usually presents with pain in the right upper quadrant of the abdomen, jaundice and hepatomegaly. Constitutional symptoms may include, fever, early satiety, lost of weight and anorexia. Occasionally some patients may present with hepatic function decompensation causing ascites, lower extremity edema, esophageal varices bleeding, acute portal hypertension, and encephalopathy. Laboratory findings related to liver failure may be present including elevated levels of alkaline phosphatase, total bilirubin, ALT or AST. The presences of an elevated α-Fetoprotein or des-gamma carboxyprothrombin are markers for the presence of the liver carcimoma and may be used as measures of tumor growth. Ultra sound (US), three-phase tomography (CT) or magnetic resonance imaging (MRI) is the imaging techniques that suggest the presence of this neoplasm. Histological evaluation of the hepatic mass is often used to confirm the diagnosis. Current guidelines suggest that in the presence of an elevated level of α-Fetorprotein and the presence of a hepatic mass in the context of a cirrhotic liver, a confirmatory biopsy is not necessary. Tissue confirmation is recommended for cases without elevated level of α-Fetorprotein or if the diagnosis remains uncertain (Fallon et al., 2006; McDonald et al., 2008).

2.2.3.3 Therapy

The prognosis of the Hepatocelullar carcinoma is variable and it largely depends whether complete surgical resection of the tumor is possible. Effective surgical interventions are compromised when the primary tumor is large, if there is vascular involvement, if the tumor infiltrates both hepatic lobes, and if there is evidence of metastatic disease. In addition, poor residual hepatic function may prevent hepatic resection. It is estimated that

less than 15% of the patients with this cancer are surgical candidates and of these 60% have a tumor recurrence. Additional therapeutic interventions, which may be appropriate, include liver transplantation, hepatic chemoembolization, intratumoral injection of ethanol, and radiofrequency ablation. Hepatic transplantation is performed in patients with Hepatocelullar carcinoma without metastasis, which fulfills the Milan criteria. Systemic therapy with one of the tyrosine kinase receptor inhibitors such as sorafenid or sunitinib may be used. These therapies are not considered curative in nature but will increase survival (Fallon et al., 2006; McDonald et al., 2008).

2.2.3.4 Epidemiology

Hepatocelullar carcinoma is the fourth more common malignant tumor in men and the sixth most common in females in the United States. It is the third leading cause of cancer mortality worldwide. The incidence of Hepatocelullar carcinoma in HIV infected patients is higher than in the general population in great measure related to the common transmission related practices shared between HIV with HBV and HCV. Co-infected patients have been reported to present with more advanced Hepatocelullar carcinoma, and have a higher mortality as compared with patients who are HIV negative. The introduction of HAART has improved the life expectancy among HIV positive individuals but has allowed a greater risk for exposure to additional agents with oncogenic potential. In the HIV/AIDS Cancer Match Study of Simard and collaborators an increment in incidence of Hepatocelullar carcinoma of 90% (RR, 1.9: 95% CI, 0.9%-3.92%) was seen when comparing the pre HAART with the post HAART era (Simard et al., 2010). Other studies have confirmed this evolving increasing trend in the incidence and prevalence of this malignancy across time in different populations (Engels et al., 2008; Mayor et al., 2008b). Furthermore, the standardized incidence ratio (SIR) of Hepatocelullar carcinoma is significantly higher in the HIV infected patient as compared to the general population (Simard et al., 2010).

2.2.3.5 Prevention

The pathogenesis of Hepatocelullar carcinoma is intimately associated to alcohol abuse and chronic infection with HBV and HCV. Primary, secondary and tertiary preventive measures that reduce the risk for exposure to these agents or viruses will directly and indirectly reduce the incidence of this cancer. This is particularly true in the higher risk groups such as those with HIV infection. It has been shown that patients with HIV infection have high-risk practices that predispose them to co-infection with hepatitis A (HAV), HBV, and HCV. In addition alcohol abuse continues to be common practice in these patients. HAV infection carries a predominant fecal-oral viral transmission route that involucrate more commonly men who have sex with men and injecting drug users; HBV infection is predominantly transmitted by percutaneous or mucous contact with infected blood or body fluids including semen and saliva. HIV associated risk groups such as men who have sex with men, high risk heterosexual contact, or injecting drug use are the predominant group with this risk factor. Lastly, HCV infection is transmitted principally by percutaneous contact with infected blood, and this is a relevant issue in HIV patients who are injecting drug use (Samet, 2007) or who received transfusions of unscreened blood. Most patients with acute HBV or HCV infection are asymptomatic and early diagnosis rarely occurs. Approximately 4 % of the HBV mono-infected persons and 20% co-infected with HIV will develop chronic liver disease. Over 80% of HCV infected individuals will eventually develop chronic hepatic disease. In the majority of patients with either infection, the process will remain

asymptomatic and undetected many years prior to the onset of liver damage and the development of cancer. All patients infected with HIV should undergo screening testing for HAV, HBV and HCV. In patients who are positive for the HCV serology and in those with unexplained liver disease determination of HCV virus load is suggested. Repeated testing after 4 months of follow up may be required in some cases if the infection was recently adquired. If high risk behaviors persist after an initial negative screening test, repeat testing on an annual basis is recommended. There is no HCV vaccine available. In patients where HBV infection is suspected, determination for the presence of the multiple viral components and antibodies in the serum is recommended. If the surface antigen (HBsAg) and the surface antibody (HBsAb) are negative, then vaccination against the HBV is suggested. This is particularly relevant for the HIV infected individual since the risk for HBV is high in this group. In individuals with detectable HBsAg, detectable HBsAb, or with elevated serum liver enzymes levels, the determination of the HBV viral load needs to be done. Chronic inactive viral infection is determined when the antibodies are positive and the viral load is negative. Both HCV and HBV require opportune therapy in order to minimize the extent of liver damage. HCV chronic infection is treated principally by the combination of peg interferon alpha and Ribavirin. Chronic HBV infection is treated with antiviral agents such as Lamivudine (3TC), Ettricitabine (FTC), Adefovir or Tenofovir. HIV co-infected persons on ART need to be monitored with liver function tests, since concomitant ART could cause liver damage and be responsible for metabolic disorders when used in combination with other medications.

Counseling and educational interventions directed to reduce the risk behavior associated to HBV, HCV and HIV transmission play an important role in Hepatocelullar carcinoma prevention (Center for Disease Control, 2001). One example of an intervention used in our cohort was a multimedia educational intervention, which was validated in Hispanic HIV injecting drug users in Puerto Rico (Mayor el al., 2010). This intervention motivated the participant to abolish their risky behaviors practices when injecting drugs. The Health Belief Model and Social Cognitive Theory were used as theoretical framework to modify the decision making process that led to the avoidance, or reduction of the risk factors relevant for acquiring new HCV infection (Mayor et al., 2008a). We are planning to extend this intervention to patients who are at an early stage of drug addiction in order to capture a larger cohort of patients who have not been infected with HBV or HCV. Counseling and educational interventions regarding alcohol use and abuse is an important approach particularly in the HIV infected person who has a high prevalence of both drug and alcohol use and abuse.

2.2.4 Squamous cell cancer of the anus

Squamous cell carcinoma of the anus is a tumor that originates from the epidermal cells of the hair bearing perianal skin. This tumor may develop outside and beyond the anal verge. The tumor is responsible for 3% of the malignancies of the lower gastrointestinal tract. It is intimately associated to infections with one of the carcinogenic types of HPV. The majority of patients with this tumor had anal intercourse as HIV risk factors, especially in the MSM group (Davis, 2008; Doweiko, 2007a; National Institute of Health, 2011).

2.2.4.1 Pathophysiology

Quite similar in pathogenesis to uterine cervix neoplasias, HPV infection has an important role in the genesis of the anal dysplasia or anal intraepithelial neoplasia (AIN) and its

progression to squamous cell cancer. HPV is the most common sexually transmitted infection in the United Sates. The incidence of HPV infection is high and there is evidence of an increasing prevalence of infection in the HIV infected group of patients. HIV associated risk factor of MSM is associated to a high prevalence of anal HPV infection and at higher risk of developing anal cancer. The degree of anal dysplasia is inversely correlated with $CD4^+$ T lymphocyte count, suggesting an important role of the immune system in controlling the impact of HPV infection. With improvement in survival associated to HAART, the latency period for HPV infection has also increased, incrementing the risk of malignant transformation of the dysplastic tissue. Anal squamous cell cancer has a more aggressive presentation and clinical course in HIV infected persons when compared to HIV negative individuals. Other risk factors for the development of anal dysplasia include, heavy cigarette smoking, anal intercourse, and a greater number of lifetime sexual partners. These factors have all been associated to the increasing incidence of the anal cancer in men and in women across the world (Daling et al., 2004).

2.2.4.2 Clinical manifestations and diagnosis

Dysplasia of the squamous epithelium of the anus is a silent condition that becomes symptomatic as it evolves to the malignant stage. Anal carcinoma can induce changes in the intestinal habits, rectal bleeding, rectal itching, rectal irritation or the presence of lumps in the anal area. Low back pain and vaginal symptoms could be also part of the symptoms associated to these processes. In advanced stages the malignant process could ulcerate and infiltrate the anal sphincter muscle, incrementing the magnitude of the symptoms. A disruption of the integrity of the anal mucosa seen in these tumors may predispose to the development of infections in this area. The presence of anal dysplasia and invasive carcinoma require pathologic confirmation. The anal Pap smear is a screening test to evaluate cytologic changes in the anal epithelium in high-risk persons. High-resolution anoscopy (HRA) should be considered if the anal Pap smear shows atypical cytology and should be performed in patients who have low or high grade squamous intraepithelial lesions. Visible lesions should be biopsied to determine the magnitude of the histological changes and to rule out invasive cancer.

2.2.4.3 Therapy

Localized dysplasia requires clinical follow-up with anoscopy and colposcopic biopsy every 4 to 6 months. Lesions can be removed with photocoagulation. Frank carcinoma should be managed with surgical excision or a combination of chemotherapy with concomitant radiotherapy. Chemotherapy with 5-fluorouracil, mitomycin-C, platinum and other analogues has been used with success, particularly for early stage tumors. This modality will preserve anal sphincter function in the majority of patients. More advanced tumors will require an abdomino/perineal tumor resection with the placement of a permanent colostomy.

2.2.4.4 Epidemiology

Prior to the HIV epidemic, the presence of carcinoma of the anus was seen in the older patient, particularly women. With the onset of HIV infection in the community, anal carcinoma is detected in younger patients, and very often associated to HPV infection. Anogenital dysplasia and anal carcinoma are more frequently associated with HPV types 16, 18, 31, 33 and 35. Similar to other tumors influenced by external agents such as viruses, the incidence of anal carcinoma has increased significantly in the HAART era (Simard et al.,

2010; Engels et al., 2008; Long et al., 2008). Simard and coauthors in their United States HIV/AIDS Cancer Matched Study reported a 190% increment in the incidence of anal carcinoma (RR, 2.9: 95% CI, 2.1%-4.0%) in the HAART era when compared to pre HAART era. HAART associated increments in the survival of HIV infected patients will also prolong the HPV carcinogenic effects over the anal epithelium leading to an increased incidence of malignant transformation.

2.2.4.5 Prevention

Although formal guidelines recommending anal Pap smear screening have not been adopted, it is clear that anal cytologic screening for HIV-infected men and women at risk of HPV infection or with anogenital warts is warranted. Follow up exams are mandatory for patients with anal dysplasia, or history of anal cancer. Risk reduction education and intervention in sexual and smoking behaviors could have an indirect effect in the prevention of the anal cancer.

2.2.5 Oral cavity/pharynx cancer

The malignant processes of the cavities of the head and neck have different histological types. In this discussion we are reviewing the data associated to squamous cell carcinoma of the oropharyngeal tract. Other important histologies cancers of the oral cavity and pharynx, such as lymphomas, sarcomas, thyroid tumors and benign tumors are not addressed in this section. The squamous cell carcinomas, which originate in the oral cavity, oropharynx, hypopharynx, and larynx are strongly associated to the use of tobacco. The tobacco may be inhaled in several forms such as cigarettes or cigars, or it may be smokeless such as chewing tobacco or snuff. Tumors localized in the oropharynx may also be vinculated to infection with HPV (Posner, 2004). As anticipated the incidence of oropharyngeal cancer is higher in the HIV infected patient as compared to the general population and the incidence of this tumor is higher in the post HAART era.

2.2.5.1 Pathophysiology

Tobacco use in any form, alcohol consumption, HPV infection, a weakened immune system, micronutrient deficiencies, and poor oral hygiene have all been implicated in the pathogenesis of head and neck neoplasms (Kreimer et al.,2004; Marur et al., 2010; Posner, 2004, National Institute of Health, 2005). Smoking produces a direct exposure of the oral and pharynx mucosa to nicotine and other carcinogenic components of the tobacco, which increase the risk of squamous cell proliferation. Frequent and heavy consumption of alcohol produces local and systemic carcinogenic effect over the mucosa. It is well established the synergism associated between the use of alcohol and tobacco abuse and the risk of head and neck tumors. Infection with HPV types 16 has also been implicated in oropharyngeal tumors. The exact mechanism of HPV associated tumor transformation is unclear. It is postulated that HPV induces the inactivation of tumor suppressor proteins or genes, which promote cell immortality and dedifferentiation. HPV infection is very common and widespread in HIV infected patients. Damage of the HIV individuals' immune integrity may enhance the tissue susceptibility induced by HPV.

2.2.5.2 Clinical manifestations and diagnosis

The clinical manifestation are varied and related to the location and stage of the tumor. Lumps, masses, ulcers may be present in the oral cavity. Problems with swallowing,

bleeding or pain may be some of the symptoms. There may be restrictions in the movement of the tongue, or difficulty swallowing certain products. Other manifestations my include, loose tooth, pain in the different bone structures of the face, difficulties with visual acuity, hoarseness, and lymph node enlargement. A diagnosis should be suspected on the basis of the clinical manifestations, physical examination of the head and neck region, endoscopy, computer tomography (CT) scan, magnetic resonance imaging (MRI), positron-emission tomography (PET). Histological confirmation with a needle aspiration and biopsy or excisional biopsy needs to be done. Complete staging of the tumor should follow a histological diagnosis (Posner, 2004).

2.2.5.3 Therapy

The management of these cancers is varied and may include surgery, radiotherapy, chemotherapy, neoadjuvant-chemotherapy, chemo-radiotherapy, and combination-modality interventions. Nutritional support to prevent significant weight loss is important. Associated morbidities such as lung, heart or liver dysfunction need to be identified in order to modify the cancer therapy to be instituted. Speech rehabilitation is occasionally required. Lifelong follow-up is suggested.

2.2.5.4 Epidemiology

Head and neck cancers account for 3 to 5% of all the tumors diagnosed in the United States. It is the sixth most common cancer worldwide. About 40,000 new cases are detected annually. The majority (95%) are squamous cell carcinomas with the oropharynx representing the most common anatomic site (Posner, 2004). These cancers are three times more common in men with a peak incidence over the age of 50 years of age. Approximately 13,000 deaths are attributable each year to these cancers. The patient with HIV infection is at a higher risk for oropharyngeal cancer with a SIR between 2.1 and 5.6 (Grulich et al., 2007; Patel et al., 2008). As with the other HPV related cancers, the impact of HAART in the natural history of these tumors remains unclear. Engels and co-authors have reported a decline in the rates of HIV associated oropharyngeal cancer with the introduction of HAART showing a reduction of the standardized incidence ratio (SIR) from 2.5 to 1.5. Nevertheless the risk of HIV associated head and neck cancer is higher as compared to the general population (Simard et al., 2010; Engels et al., 2008).

2.2.5.5 Prevention

There is no approved test for the early detection of oral cavity/pharynx cancers. Consequently the prevention of these tumors rests on improving the risky behavior patterns of patients. Smoking and alcohol abuse avoidance and cessation are the most important prevention measure for this type of cancer. Up today there is not an effective prevention protocol for HPV in relation to oropharynx cancer. Having a faithful relation with one person, limiting the number of sex partners, having a partner who did not have o had few sex partners, could limit the probability of HPV infection, but not eliminate it.

3. Conclusion

The use of HAART for patients with HIV infection has led to a partial restoration of the immune system prolonging the survival of these patients. The success of this therapy has dramatically altered the natural history and clinical course of infection. HIV/AIDS has become a chronic disease with the co-existence of co-morbid conditions, which have an

important effect on the health of these patients. An increased likelihood of exposure to cancer promoters such as oncogenic viruses, increments in the exposure to tobacco and alcohol and continued risky practices have had a major role in the increased risk of developing malignant conditions in these patients. The incidence of most of the AIDS defining malignancies have decreased in large part due to immune restoration present in many patients. However, the incidence of other tumors such as uterine cervical cancers, Hodgkin's lymphoma, certain non-Hodgkins lymphomas, HPV related cancers, lung cancer, and liver cancer have all seen an increase in the HAART era. The synergistic effects of tobacco use, alcohol use, dietary elements and viral co-infections are having an effect in the malignant transformation of tissues in the HIV infected patient. Consequently, an appropriate and opportune management of the HIV infection needs to be supplemented with cancer preventive strategies in this high-risk group of patients. Implementation of recommended cancer screening techniques, educational intervention, and relevant vaccination in the HIV infected populations should decreased the morbidity and mortality rate of HIV associated malignancies. Furthermore, adequate and opportune cancer prevention efforts would be cost effective in the management of this high risk population. Researches into the barriers present, which are obstacles to the implementation of these important prevention techniques, are very relevant and require further evaluation.

4. Acknowledgement

This publication was made possible by the RCMI-NIH Grant number G12RR03035 from the National Center for Research Resources and the NIH Grant number U45RR026139. We would like to thank Christine Miranda for her help in the chapter preparation.

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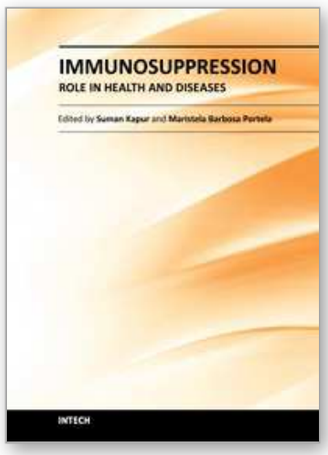
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Immunosuppression - Role in Health and Diseases
Edited by Dr. Suman Kapur

ISBN 978-953-51-0152-9
Hard cover, 470 pages
Publisher InTech
Published online 24, February, 2012
Published in print edition February, 2012

A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Angel Mayor, Yelitza Ruiz, Diana Fernández and Robert Hunter-Mellado (2012). HIV/AIDS Associated Malignant Disorders: Role of Highly Active Antiretroviral Therapy, Immunosuppression - Role in Health and Diseases, Dr. Suman Kapur (Ed.), ISBN: 978-953-51-0152-9, InTech, Available from: http://www.intechopen.com/books/immunosuppression-role-in-health-and-diseases/neoplasm-in-hiv-aids-adult-population-before-and-after-highly-active-antiretroviral-therapy

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