Management of malignancy in HIV infection

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The prevalence of HIV-related malignant disease is increasing, probably due to more effective management of opportunistic infection. The most frequent tumours are Kaposi's sarcoma, systemic non-Hodgkin's lymphoma and primary central nervous system lymphoma. Management of these conditions must take into account host indicators of immunosuppression and prognostic outcome in order to minimise treatment associated complications.

Introduction

One of the most important complications of the immunosuppression that results from infection with human immunodeficiency virus (HIV), is the development of malignant tumours. Although there has been improved survival of patients with the acquired immunodeficiency syndrome (AIDS), resulting from better prophylaxis and treatment of opportunistic infection, AIDS-related malignancy remains a major clinical problem. More than 40% of these patients are diagnosed as having a malignant disease at some point (Reynolds et al., 1993).

Types of cancer in AIDS

It is well established that the three major neoplasms associated with HIV infection are Kaposi’s sarcoma (KS), primary CNS lymphoma (PCNSL) and non-Hodgkin’s lymphoma (NHL). In January 1993 the US Centers for the Disease Control (US-CDC) added invasive cervical cancer to the list of AIDS defining conditions, not because of conclusive evidence that HIV predisposed to cervical cancer but because HIV infected women have a higher rate of cervical dysplasia.

Other malignancies which may be associated with AIDS include Hodgkin’s disease (HD) and squamous cell carcinoma (SCC) of the anus. Whether the incidence of HD has increased remains controversial but there is little doubt that in immunocompromised individuals, particularly those who are seropositive and have a history of intravenous drug abuse, HD displays more aggressive clinical behaviour than in the general population (Reynolds et al., 1993; Rubio, 1994). Current estimates of anal cancer have suggested that it is becoming increasingly common, particularly among

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individuals with HIV infection (Frisch, Melbye & Moller, 1993). The reason for this rise is unclear but may reflect changes in sexual habits and increased exposure to human papilloma virus (HPV), which has been strongly implicated in the pathogenesis of anal SCC (Beckmann et al., 1989). A history of homosexual activity appears to be a particular risk factor, presumably through receptive anal intercourse.

Reports of AIDS patients with other solid tumours have been sparse but have included tumours of the brain and bronchus, non-melanomatous skin cancer, cancer of the nose and middle ear; they have been anecdotal and the numbers remain too small to conclusively link them to HIV infection (Levine, 1993).

This review will focus predominantly on the management of KS, PCNSL and NHL as these are currently the most prevalent malignant tumours in patients with HIV infection.

**Kaposi's sarcoma**

This condition occurs in various forms and before the association with HIV was established, the classical form of KS in elderly Jewish and Mediterranean males and the African endemic variant were the most well known. With the advent of iatrogenic immunosuppression, particularly following allograft transplantation, a further type has been identified. Although the incidence of KS presenting as an AIDS-defining diagnosis has steadily declined from an initial 40%, KS still occurs in approximately 20 to 30% of homosexual men with AIDS (Hoover et al., 1993). This is twenty times more common than in HIV infected haemophiliacs which suggests that additional factors are involved in its pathogenesis (Beral et al., 1990).

KS is a rare, multicentric, multiorgan neoplasm; the individual lesions are proliferations of aberrant vascular structures, lined by abnormal endothelial cells and extravasated erythrocytes with a mononuclear cell infiltrate. Its malignant potential is conferred by the spindle cell which is a tumour cell of mesenchymal origin and lies between the vascular structures (Zhang et al., 1994). The extent and rate of progression vary considerably among patients and it has been postulated that KS is a reactive tumour and not a true malignancy (Chang et al., 1994; Griffiths, 1996). Studies have suggested that growth factors and cytokines from HIV infected cells interact with an infectious cofactor to result in the pathogenic lesions of KS. To date, many agents have been implicated, but most recently herpesvirus-like DNA sequences which were previously unidentified, have been isolated from KS lesions in patients with AIDS. This represents a new human herpesvirus which has been given the descriptive name of KSHV (Moore & Chang, 1995). Regulatory factors include: oncostatin M, interleukin 6, tumour necrosis factor and platelet-derived, fibroblast, vascular growth factors (Mitsuyasu, 1995). The HIV transactivating gene (tat) and its gene product (Tat) are retroviral factors which may initiate the process of transformation and KS cell growth. An autocrine/paracrine stimulation of angiogenesis has been postulated in the pathogenesis of these lesions (Barillari et al., 1992).

**Clinical manifestations**

Initial presentations of AIDS-KS range from small, innocuous looking macules in inconspicuous locations to eruptions of symptomatic cutaneous, oral and visceral confluent areas, which may be prominent and troublesome. Lesions are of variable size
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and shape but are generally non-pruritic and painless, although they can cause lymphatic obstruction. Their colour ranges from pink and brown to deep purple and they have a predilection for the territory drained by the superior vena cava, although lesions can occur anywhere. One clinical variant initially affects both feet and travels centripetally similar to the classical form. The distribution is curiously symmetrical although no explanation is available for this phenomenon. KS can occur at any time in the course of HIV disease, often occurring very early with a preserved CD4 count, although exacerbations have been linked to opportunistic infections.

Kaposi’s sarcoma presents several clinical problems which can be debilitating and occasionally fatal. The visible lesions carry a social stigma which is often the precipitant for seeking help. Dermal and lymphatic infiltration may cause oedema in the periorbital area, genitals, or extremities and may predispose to ulceration and cellulitis. Pedal involvement may give rise to difficulty in walking and palatal or gingival infiltration can result in orodental symptoms.

Visceral involvement can be rapidly fatal if untreated and although it is usual for it to reflect progression of mucocutaneous KS, cases can present with little or no skin involvement. Although KS has been reported to occur at virtually any site, the two viscera most commonly affected are the lung and the gut.

Asymptomatic gastrointestinal (GI) KS is seen in a proportion of patients and investigations may be prompted by unexplained recurrent anaemia, symptoms of gastric outlet obstruction or enteropathy in small bowel involvement. GI KS has a typical raised red appearance, which may be confirmed on endoscopic biopsy. However because of its submucosal location angiography may be required to identify actively bleeding lesions.

Palatal KS is a strong indicator of disease in the respiratory system (Moss et al., 1989) and pulmonary KS often presents with symptoms including dyspnoea with or without fever and frequent haemoptysis. It is rarely an incidental finding although may be discovered during investigations to exclude an infectious pathology which may coexist. The transfer factor coefficient (KCO) is a sensitive index and a fall in this value would arouse suspicion of lung involvement: serial measurements are used to assess disease progression (Miller et al., 1992).

Chest radiography typically demonstrates diffuse reticulonodular infiltrates, mediastinal involvement and sometimes pleural effusions (Meduri & Stein, 1992). Definitive diagnosis is usually by bronchoscopic appearance; endobronchial or transbronchial biopsy is no longer thought necessary unless lesions are atypical. However, for parenchymal lesions not seen at bronchoscopy imaging with CT, or spiral CT, is useful (Wolff, Kuhlman & Fishman, 1993).

Treatment options for Kaposi's sarcoma

Management of Kaposi’s lesions is dependant on the extent of involvement and the level of immunosuppression most usefully reflected by the CD4 count. In many cases the development of KS is the first AIDS defining diagnosis and comes as an abrupt shock. Medical help is usually sought when camouflage or make up can no longer disguise the lesions. Treatment can be local or systemic and is summarised in Table I (Denton, Miller & Spittle, 1995):
Local treatment

Excision. This may be appropriate for small lesions although patients should be warned that recurrence may occur in the scar, and cryotherapy for small isolated lesions may also be effective.

Radiotherapy. Cutaneous KS can be treated locally with radiotherapy producing marked flattening, lightening and reduction in the size of individual lesions (Spittle, 1989). Irradiation is unlikely to make established lesions disappear completely but can improve the appearance considerably and prevent further growth. As older lesions bleed into the skin they deposit haemosiderin which will tattoo the area so that, although radiotherapy will reduce oedema and the size of lesions, a pigmented area will remain. Hence, the earlier new lesions are treated the better the cosmetic result. Virtually all skin locations are amenable to radiotherapy including periorbital areas where a lead eyeshield may be used to protect the lens. Hair will be lost over irradiated areas, which may be of relevance on the face. Radiotherapy is also a useful modality for treating palmar and plantar lesions which are particularly troublesome in terms of pain and oedema. Infiltrated lymph nodes causing lymphatic obstruction can be relieved with this form of treatment and palatal and gingival lesions also respond well to radiotherapy. However mucositis, possibly related to glutathione deficiency (Vallis, 1991), is a recognised complication which can be uncomfortable and occur at very low radiation doses, but it is short lived, and usually considered worthwhile in view of the excellent response in mucocutaneous disease.

Although radiotherapy is effective with few side effects, it is time consuming in terms of radiographer and machine allocations. For this reason treatment sessions have to be limited to five to six lesions at a time. A dose of 8 Gray at 100 Kv in a single fraction

<table>
<thead>
<tr>
<th>Table I. Treatment options for Kaposi's sarcoma (Denton et al., 1995)</th>
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<tbody>
<tr>
<td><strong>Local</strong></td>
</tr>
<tr>
<td>excision</td>
</tr>
<tr>
<td>radiotherapy</td>
</tr>
<tr>
<td>intrallesional injection</td>
</tr>
<tr>
<td>photodynamic therapy</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
</tr>
<tr>
<td>biological response modifiers</td>
</tr>
<tr>
<td>if CD4 &gt; 200/µL for zidovudine and α-interferon 3-10 MU thrice weekly</td>
</tr>
<tr>
<td>if CD4 &lt; 200/µL consider chemotherapy</td>
</tr>
<tr>
<td>administration of chemotherapy (3 weekly cycles)</td>
</tr>
<tr>
<td>(a) BV</td>
</tr>
<tr>
<td>bleomycin 30 units in 250 mL normal saline over 30 min</td>
</tr>
<tr>
<td>vincristine 1.4 mg/m² (max 2 mg) bolus</td>
</tr>
<tr>
<td>(b) ABV</td>
</tr>
<tr>
<td>doxorubicin 10-20 mg/m² bolus</td>
</tr>
<tr>
<td>bleomycin 10 units/m² infusion</td>
</tr>
<tr>
<td>vincristine 1.4 mg/m² (max 2 mg) bolus</td>
</tr>
<tr>
<td>(c) continuous B</td>
</tr>
<tr>
<td>bleomycin 20 mg/m² in 1 L normal saline over 18 h for 3 days</td>
</tr>
<tr>
<td>(d) L dox</td>
</tr>
<tr>
<td>liposomal doxorubicin 20 mg/m² in 250 mL 5%</td>
</tr>
<tr>
<td>dextrose over 30 min</td>
</tr>
<tr>
<td>(e) L dauno</td>
</tr>
<tr>
<td>liposomal daunorubicin 40 mg/m² in 250 mL 5%</td>
</tr>
<tr>
<td>dextrose over 30 min</td>
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</table>
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is a standard dose for lesions on non-sensitive skin (Spittle, 1987). In facial and plantar areas, or retreatments, fractionating the dose may produce a better cosmetic result. Palatal lesions are conventionally treated with a total dose of 15 Gray with simulated parallel opposed fields in ten fractions at 5 Mv photons. The low dose per fraction is given to reduce the severity of the mucositis.

Radiotherapy has less of a role in the treatment of visceral KS although early intervention is of particular value in the treatment of laryngeal or epiglottic lesions causing obstructive symptoms. Localised radiotherapy can also be used to control haemoptysis from lobar disease employing a total dose of 15 Gray in divided fractions (Meyer, 1993).

**Intralesional injections.** For lesions that are considered either inaccessible or resistant to irradiation, or which have demonstrated excessive mucositis from previous treatments, intralesional chemotherapy may be of value. Vinblastine, often with a local anaesthetic, produces optimal responses after only one or two treatments at weekly intervals (Moyle, Youle & Barton, 1993).

**Photodynamic therapy.** This is an innovative treatment, principally for cutaneous tumours, which involves use of a skin sensitisier which is activated by laser treatment of individual KS lesions. The porphyrin based agent is differentially retained in the tumour and subsequent activation results in tumour destruction with little effect on the normal surrounding tissue. At present this remains an experimental form of therapy, but in the future it may have a wider application (Bernstein, Wilson & Mang, 1994).

**Systemic treatment.** The natural history of AIDS related KS is very variable but inevitably the lesions progress, often after long trouble free periods. Progression occurs in the form of periodic exacerbations or eruptions which often correlate with opportunistic infections or falls in the CD4 count, and not infrequently visceral KS can be a new manifestation or represent progression of cutaneous involvement, although one can occur independently of the other. At this stage new lesions are developing faster than they can be irradiated, so that systemic treatment becomes necessary; either using immunotherapy with biological response modifiers such as interferon; or chemotherapy depending on host factors.

**Interferon.** In the subgroup of patients who present with advanced KS but have a well preserved immune system with a CD4 count in excess of 200/μl, the use of alpha-interferon can be employed. Patients must be well motivated to tolerate interferon which is administered by subcutaneous (sc) injection three times a week, as the influenza-like side effects can be extremely unpleasant. Interferon is given in three month courses to allow patients to recover from symptoms and assess response. The dose of interferon used varies but starts at 3 MU sc three times a week. If this is tolerated then the dose can be progressively increased (Krown et al., 1992). Conventionally, interferon is thought to be most effective if given in conjunction with an antiviral agent such as zidovudine because, although recombinant α-interferon has been shown to inhibit tumour angiogenesis (Ho et al., 1985), the combination of α-interferon and zidovudine inhibits HIV replication in vitro (Hartshorn et al., 1987). Marker lesions are identified and serially monitored to assess response. In effect, the patient then receives a combined antineoplastic and antiviral regimen which can be successful in causing lesions to regress and halts further progression of disease (Krown et al., 1990). Interferon has considerable myelosuppressive and nephrotoxic properties and regular monitoring of haema-
tological and biochemical profiles should be performed with prophylaxis against opportunistic infection.

Chemotherapy. Once the CD4 count falls below 200/μl, a state of profound immunodeficiency is reached when progression of untreated KS can be associated with considerable morbidity and mortality. At this stage chemotherapy is required in order to palliate both cutaneous and visceral involvement. The principle of therapy is to arrest tumour progression. Most current chemotherapy regimens, though effective, are myelosuppressive and therefore prophylaxis against opportunistic infection is important. As this is a palliative treatment in the context of two coexisting incurable conditions, the main aim is to control symptoms and improve quality of life with minimal side effects. The need for haematological support with granulocyte colony stimulating factor (G-CSF) may well arise if prolonged myelosuppression causes delay between cycles.

The standard first line chemotherapy regimen currently in use for advanced KS incorporates bleomycin and vincristine (BV). This tends to be well tolerated with few side-effects; although alopecia is minimal, patients should be warned about potential hair thinning. Nausea is generally mild although some patients suffer constitutional symptoms shortly after administration. Recognised complications of long term bleomycin include accelerated pulmonary fibrosis in HIV infected individuals; this is dose related and should be carefully monitored with serial pulmonary function tests. There have also been isolated reports that bleomycin can induce a Raynaud’s phenomenon which occasionally leads to digital gangrene (von Gunten, Roth & Von Roenn, 1993). It is well established that vincristine can cause peripheral neuropathy and if this occurs then vinblastine can be substituted.

Gompels et al. reported that 57% of 46 patients with KS who were treated with BV attained partial response and a further 35% demonstrated stable disease (Gompels et al., 1992). Combinations using Adriamycin, bleomycin and vincristine (ABV) are also commonly employed in the treatment of KS and, although slightly more effective, produce greater toxicity (Ireland-Gill et al., 1992). The use of a three day infusion course of bleomycin has recently been reported (Remmick et al., 1994).

As stated above Adriamycin is noted to be effective in the treatment of KS but is associated with significant toxicity. However, the newer liposomal anthracycline derivatives have fewer side-effects and high intrallesional accumulation than the conventionally administered form of this drug. This agent is well tolerated and effective, with a 90% partial response rate (Simpson, Miller & Spittle, 1993), although early reports suggest that it may be associated with a higher rate of myelosuppressive complications (Harrison et al., 1995) and hepatotoxicity with liver failure has been reported (Hengge et al., 1993). Liposomal daunorubicin and liposomal doxorubicin are currently available only on a compassionate use or trial basis.

All these regimens may give effective tumour control but unfortunately relapse is inevitable. Our current policy is to use BV as a first line agent to achieve a satisfactory response and upon relapse or progression, liposomal anthracyclines are then effective as second line agents. It should be appreciated that treatment of this condition is problematic because it represents an advanced stage of an aggressive disease occurring in a profoundly immunosuppressed host.
Non-Hodgkin's lymphoma

NHL is now a well established complication of HIV disease but it was not until 1985 that the US-CDC included NHL as an AIDS-defining diagnosis. NHL can present as a systemic illness or as a PCNSL which is limited to the cranial-spinal axis.

Aetiology and pathogenesis

The association between lymphoma and immunodeficiency is well recognised and occurs in all HIV infected groups. Potential pathogenetic mechanisms include disturbed immunosurveillance against Epstein-Barr virus (EBV)-infected cells, allowing clonal expansion of B cell populations which may precipitate tumour (Shibata et al., 1993). However the role of EBV remains controversial as although its genomic proteins are consistently detectable in PCNSL they can only be demonstrated in 50% of AIDS-associated systemic NHL (Shibata et al., 1993). Chronic immune stimulation of B cells by antigens, viruses and mitogens is also thought to produce a highly proliferative environment that may predispose the cell genome to oncogenic mutations (Subar et al., 1988; Ballerini et al., 1993) and cytokine networks may produce a combination of growth factors that may support the expansion of an emerging tumour clone (McGrath et al., 1993).

Systemic NHL

The incidence of NHL in AIDS has increased to 3%, which is 60 times greater than that found in the general population, but it is suspected that the true frequency may well be in the region of 10–20% as late diagnoses tend to be under-reported (Beral et al., 1991). In addition, the incidence of NHL increases with the length of survival and HIV-infected patients who survive for up to 3 years with antiviral therapies are more likely to develop lymphoma (Pluda et al., 1990).

The majority of HIV-infected patients with NHL have the high, or intermediate grade, B cell variety. Reported studies indicate that Burkitt’s and Burkitt’s-like (small non-cleaved) comprise 35%, whereas immunoblastic (large cell) comprise 30% and diffuse large cell (large non-cleaved) 25% (Ioachim et al., 1991).

The pattern of clinical features of NHL in HIV differs from that in immunocompetent individuals, with a greater frequency of B symptoms and more widespread disease at initial presentation (often stage III/IV at diagnosis). In addition, extensive extranodal involvement is the hallmark of this condition with the gastrointestinal tract, CNS and bone marrow commonly being affected. Overall, there is a worse prognosis stage-for-stage than in non-HIV patients because the risk of dying from opportunistic infections is as great as the risk of dying from lymphoma. Median survival is approximately 6 months (Ziegler et al., 1984).

Diagnosis and staging

Histological confirmation of the diagnosis is essential as many AIDS-related illnesses (e.g. *Mycobacterium avium intracellulare* infection) can mimic NHL. Once the diagnosis has been established, staging investigations including CT scanning, CSF cytology, and bone marrow assessment are necessary to define the extent of disease. The Ann Arbor Staging classification is commonly used as described in Table II (Carbone, 1971). Determining the level of host immunosuppression is equally important in planning
Table II. Ann Arbor Staging for non-Hodgkin's lymphoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region, or a single extra-lymphatic organ or site (IE).</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions on the same side of the diaphragm, or localized involvement of extra-lymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIIE).</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm, which may also be accompanied by localized involvement of extra-lymphatic organs or sites (IIIE), or by involvement of the spleen (IIIIS) or by involvement of both (IIIIES).</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues, with or without associated lymph node enlargement.</td>
</tr>
</tbody>
</table>

Treatment of systemic NHL

Development of effective treatment strategies for NHL in immunocompetent individuals has been characterized by progressive dose intensification and has generally

Table III. EORTC guidelines for treatment of systemic NHL

<table>
<thead>
<tr>
<th>Stratification by host factors</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 100/μL</td>
<td>Low risk</td>
</tr>
<tr>
<td>KPS &lt; 70</td>
<td>Induction with three cycles ACVB and adjuvant involved field radiotherapy in localised extra abdominal disease (stage I–IE)</td>
</tr>
<tr>
<td>A previous AIDS defining condition</td>
<td>Induction with four cycles of CHOP and adjuvant radiotherapy as above</td>
</tr>
</tbody>
</table>

Protocol

Low risk

Induction with three cycles ACVB and adjuvant involved field radiotherapy in localised extra abdominal disease (stage I–IE)

Induction with four cycles of CHOP and adjuvant radiotherapy as above

*ACVB

Cyclophosphamide 1200 mg/m²
Adriamycin 75 mg/m²
Vindesine 2 mg/m²
Bleomycin 10 mg
Prednisolone 40 mg/m²
G-CSF d6–14
Repeat on days 15 and 30 (cycles)

*CHOP

Cyclophosphamide 750 mg/m²
Adriamycin 50 mg/m²
Vincristine 1.4 mg/m²
Prednisolone 40 mg/m²
G-CSF d6–21
Repeat on d22, 43 and 64 (4 cycles)
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Medium risk
(a) Induction four cycles of standard CHOP and radiotherapy as before
   Induction four cycles of low dose CHOP and radiotherapy as before

(b) LD CHOP
   Cyclophosphamide 400 mg/m²  d1
   Adriamycin 25 mg/m²  d1
   Vincristine 1.4 mg/m²  d1
   Prednisolone 40 mg/m²  d1–5
   G-CSF d6–21
   Repeat cycle on 22, 43 and 64 (4 cycles)

High risk
Induction four cycles of LD CHOP and radiotherapy as before
Induction with four cycles of vincristine and prednisolone and radiotherapy
as above. Two weekly cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>2 mg</td>
<td>d1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>50 mg/m²</td>
<td>d1–5</td>
</tr>
<tr>
<td>G-CSF</td>
<td></td>
<td>d6–14</td>
</tr>
<tr>
<td></td>
<td>Repeat</td>
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CNS involvement
PCNSL
   Whole brain irradiation 36 Gy in 18 fractions
   Systemic treatment after CNS complete response as for high risk inclusion group.

Systemic NHL
   Whole brain irradiation 36Gy in 18 fractions
   Systemic NHL with meningeal disease does not affect the risk group
   2 weekly intrathecal methotrexate for nine courses till CSF clear

CNS prophylaxis
   intrathecal methotrexate at staging lumbar puncture
   zidovudine 500 mg daily
   alpha interferon 4.5 MU sc
   three times a week if complete response/PR achieved after induction

Maintenance
   zidovudine 500 mg daily
   alpha interferon 4.5 MU sc
   three times a week if complete response/PR achieved after induction


"d1, day one
NHL, non-Hodgkin's lymphoma; PCNSL, primary CNS lymphoma; KPS, Karnofsky performance states.

resulted in improved survival rates. However, this principle does not extrapolate to HIV-related lymphoma. In the last 10 years treatment of this condition has been revolutionised by the use of low dose regimens, the availability of haemopoietic colony stimulating growth factors, the improved treatment and prophylaxis of opportunistic infections and, finally, the stratification of patients into different prognostic categories.

At present chemotherapy with the CHOP regimen is the standard approach producing a complete response rate of between 10–50% with 15% surviving over 12 months (Roithmann et al., 1991). Other regimens have included that of using a modified form of M-BACOD with CNS prophylaxis and zidovudine maintenance therapy (Levine et al., 1991); the published results included a complete response rate 50% and median survival of 6.5 months. Gisselbrecht et al. (1993) employed an intensive regimen in good prognosis patients (ACVB/LNH 84) producing complete response rates of 63%
and a median survival of 9 months. Similarly, Taillan et al. (1993) used good prognosis patients and another intensive regimen MACOP-B with a 58% complete response rate and median survival of 16 months.

Currently, the European Organisation for Research and Treatment of Cancer (EORTC) AIDS Tumour Group are conducting a trial comparing intensive and low dose chemotherapy regimens in the three stratification groups with the use of G-CSF, prophylaxis against opportunistic infection and, of course, informed consent being mandatory before inclusion into the study (Table III). The results of this large multicentre study should be instructive in determining optimal management for this difficult condition.

**Primary CNS lymphoma**

This is a separate entity from systemic NHL and occurs in 2–4% of HIV infected individuals (Goldstein et al., 1991). It is usually a late manifestation of AIDS, occurring in end stage disease with extremely low CD4 counts. By the time the diagnosis is confirmed, individuals are often in poor physical shape with refractory opportunistic infections, B symptoms and a low performance status. The clinical presentation is varied, ranging from subtle personality changes and cognitive impairment to confusion, disorientation, focal neurological deficit or seizures.

**Diagnosis**

Radiographically, unifocal or multifocal lesions may be seen on CT or MRI. The appearance of ring enhancing lesions correlates with central tumour necrosis and is generally indistinguishable from toxoplasmosis. Many clinicians prescribe an empirical trial of anti-toxoplasmosis therapy before proceeding to tissue biopsy. Because of the rapid growth of PCNSL a prompt diagnosis followed by tumour directed treatment is important, but unfortunately this remains a condition which is under diagnosed and often not discovered until autopsy.

**Treatment of PCNSL**

In immunocompetent individuals conventional treatment with radiotherapy ± chemotherapy produces a median survival of 10–18 months (Henry et al., 1994). In AIDS patients with untreated PCNSL, death is likely within 1–1.5 months, whereas the institution of prompt therapy can prolong survival up to 5 months (Rosenblum et al., 1988). Although this is only a modest survival increase even patients with poor functional status have responded dramatically to radiation therapy with neurological improvement and better quality of life. Most patients treated with whole brain irradiation and steroids die of opportunistic infection and not of progressive lymphoma. A variety of regimens for whole brain irradiation have been used, administering a total radiation dose of 30–40 Gy in 10–20 fractions, with obvious practical advantages for the shorter regimens.

In immunocompetent patients with PCNSL the use of concurrent chemotherapy has been shown to prolong survival. Several studies have investigated whether this finding extrapolates to seropositive patients receiving combined modality treatment. Forsyth, Yahalom & De Angelis (1994) used pre-radiotherapy chemotherapy with systemic
methotrexate, thiotepa and procarbazine, supplemented with intrathecal methotrexate. The overall response to treatment for the 10 patients was 3.5 months. Chamberlain (1994) treated four patients with good prognostic features with bimodal therapy using whole brain irradiation and hydroxyurea, followed by procarbazine, lomustine and vincristine (PCV). Although median survival with this form of treatment was 13.5 months, such therapy is only feasible in early disease so that the majority of patients with PCNSL are excluded and the most appropriate management is by radiotherapy alone.

Conclusion

With the improved survival of HIV patients, we are likely to see an increased incidence of the AIDS related malignancies and it is to be hoped that new improved therapies will emerge as more is revealed about the aetiology and pathogenesis of these conditions.

References


