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Intrathoracic Kaposi's sarcoma in patients with AIDS

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In early 1981 the acquired immunodeficiency syndrome (AIDS) was initially recognised from the outbreak of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia among young, previously healthy homosexual men.[1 2] The incidence of Kaposi's sarcoma as an inaugurating event has decreased regularly since the mid 1980s from between 35–40% to less than 15% of all cases of AIDS presently reported in Europe and the USA[1 3 4]; Kaposi's sarcoma, however, still remains the most frequent cause of pulmonary localisation of AIDS associated malignancies, and the prognosis of Kaposi's sarcoma is related in part to visceral involvement, particularly the lung.[1 2 5] Although our knowledge of this disease remains incomplete, several recent studies have considerably advanced our understanding of the pathogenesis, diagnosis and, to a lesser extent, the treatment of Kaposi's sarcoma, particularly in cases of visceral involvement.[1–4 6] The purpose of this review is threefold: firstly, to summarise recent advances concerning the pathogenesis of Kaposi's sarcoma; secondly, to review briefly the pathological and clinical features of the disease; and finally, to describe current approaches to its diagnosis and treatment. Although all forms are discussed, this review will concentrate on intrathoracic Kaposi's sarcoma. There are a number of recent reviews available which emphasise other aspects of the disease.[3 4 6]

Pathogenesis of Kaposi's sarcoma: an unresolved debate

The use of new technology in investigating the cellular and molecular changes has resulted in better understanding of the pathogenesis of Kaposi's sarcoma, but numerous questions remain unanswered.

CELL OF ORIGIN

The original cell which gives rise to the "spindle cells" of Kaposi's sarcoma lesions has long been a point of controversy and different cell types have, in turn, been suspected. Recent data, however, indicate that the original cell could well be a multipotential cell of mesenchymal derivation.[3 4 6] This hypothesis is based on phenotypical and cytochemical studies performed on spindle cells obtained from long term culture of AIDS-associated Kaposi's sarcoma tissue.

AETIOLOGICAL FACTORS

The aetiology of Kaposi's sarcoma has not been precisely established, even if the most widely accepted view is a multifactorial one. Genetic, endocrinological, and environmental factors, as well as infectious agents, have been suspected in the development of Kaposi's sarcoma. Although the major histocompatibility antigens, HLA-DR5 and HLA-DR2, were reported with increased frequency both in classical Kaposi's sarcoma and in AIDS-associated Kaposi's sarcoma at the beginning of the AIDS epidemic, these data were not confirmed in HLA typing in subsequent later series of AIDS-associated Kaposi's sarcoma.[6 7] The human immunodeficiency virus was the first infectious agent proposed as an aetiological factor in the Kaposi's sarcoma epidemic. The HIV genome has not yet been detected in Kaposi's sarcoma lesions, but this does not rule out a possible indirect role for HIV; it has recently been shown, for example, that mice transfected by the HIV*tat* gene developed clinical and histological Kaposi's sarcoma-like tumours. In this model the HIV genome is present on epidermal cells but absent in dermal tumours, indicating that HIV could act in an indirect way to cause the proliferation of the endothelial, lymphatic, or multipotential cells found in Kaposi's sarcoma lesions.[8 9] Another possible infectious origin is suggested by a number of epidemiological studies which have led to the theory of a possible sexually transmitted co-agent.[3 4 6] None of the suspected causative agents (CMV, EBV, HPV-16, HTLV-I, HBV, *Mycoplasma incognito*) has yet been proved to be involved. Several other data also argue against this hypothesis or limit its scope: firstly, no one causative agent has been regularly isolated in Kaposi's sarcoma tissue; secondly, this theory of sexual transmission does not explain the male predominance in African patients with AIDS-associated Kaposi's sarcoma in whom HIV has been transmitted through heterosexual contact, or the development of Kaposi's sarcoma in non-AIDS immunocompromised hosts.

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Finally, some investigators have recently proposed a role for a different subtype of HIV or a defective form of HIV because of the presence of antibodies against gp41 and *nef* in the serum of an HIV seronegative patient with Kaposi's sarcoma.[6]

IMMUNE IMBALANCE AND THE HISTOGENESIS OF KAPOSI'S SARCOMA

It has generally been accepted that immune deficiency was a prerequisite for the development of Kaposi's sarcoma, but at the present time it seems more likely that Kaposi's sarcoma in AIDS results from an immune imbalance rather than a true immune deficiency. Studies in classical and endemic Kaposi's sarcoma show no detectable immune deficiency.[3 4] Similarly, a small number of HIV seropositive patients develop Kaposi's sarcoma without clinical or biological data, indicative of immune deficiency.[10] It has recently been suggested that Kaposi's sarcoma may develop in a subject with a particular genetic background who is exposed to numerous infectious agents and environmental factors which, at a given point, trigger the immune and inflammatory response. Through the effects of mediators such as interleukins 1 and 6, fibroblast growth factor, and oncostatin M[11–13] and/or viral proteins (*tat*-protein), the immune activation may initiate the proliferation of mesenchymal cells observed in Kaposi's sarcoma lesions.[8 9] As a result of the effects of their extracellular products, these activated AIDS-associated Kaposi's sarcoma cells may maintain their own proliferation by an autocrine and paracrine pathway leading to the proliferation of endothelial cells, smooth muscle cells, and fibroblasts which histologically characterise Kaposi's sarcoma.[14]

Clinical and radiological features of intrathoracic Kaposi's sarcoma

In Europe and the USA epidemic Kaposi's sarcoma occurs in patients of all ages, is mainly found in HIV-infected homosexual or bisexual men, and is observed in less than 10% of patients in other groups at risk for HIV infection.[3 4 6] In Africa the predominance of Kaposi's sarcoma in men is less pronounced than in Europe and the USA.[4 6] Epidemic Kaposi's sarcoma mainly involves the skin, particularly the lower limbs. The lesions vary in colour from red to purple and in appearance from macular, papular, or nodular lesions to plaques. These lesions, frequently localised at the onset of Kaposi's sarcoma, usually progress in a multifocal and widespread distribution with possible later mucosal and visceral involvement. Virtually all organs may be involved, but lymph nodes, the gastrointestinal tract, and the lungs are the commonest sites.[15–17]

FREQUENCY

Although there has been a steady decrease in the proportion of patients with Kaposi's sarcoma among those infected with HIV in recent years, it is still the foremost cause of lung tumours in patients with AIDS[12] and the third and fourth cause of all pulmonary disease in HIV-infected Africans and Europeans respectively.[1 2 18] The frequency of intrathoracic Kaposi's sarcoma has been appreciated in various situations. In HIV-infected patients, whatever the risk factor, Kaposi's sarcoma was at the origin of 8–18% of lung disorders[2 5 19–22] and from 10–45% of pleural effusions.[23] In patients with cutaneous Kaposi's sarcoma and respiratory symptoms it was identified as the cause of respiratory disease in 18–40% of cases.[15 16 18 22 24] In patients with cutaneous Kaposi's sarcoma but no respiratory symptoms it was present in 6–20% of cases,[15 25 26] while in those with cutaneous lesions it was the cause of virtually all bilateral pleural effusions.[27] Finally, in patients with cutaneous Kaposi's sarcoma intrathoracic Kaposi's sarcoma was found at necropsy in 38–75% of cases.[12] Almost all intrathoracic structures may be involved – that is, lung parenchyma, airways, and pleura and, to a lesser extent, the lymph nodes, pericardium, and heart.[12] Macroscopic examination of the lung at necropsy reveals bright red or violaceous haemorrhagic nodules which may coalesce into larger masses or cause septal angiomatous infiltration; the pleural and the intrathoracic lymph nodes are involved in more than 50% of cases.[12] Microscopic findings at necropsy show that the lung lesions have a predominantly peribronchial and perivascular distribution and, in some places, invade the bronchial and vascular walls.[12]

CLINICAL MANIFESTATIONS

In patients with cutaneous Kaposi's sarcoma the discrepancy between the low frequency of respiratory symptoms due to Kaposi's sarcoma and the high frequency of respiratory Kaposi's sarcoma found at necropsy indicates that intrathoracic Kaposi's sarcoma is insidious in most cases. Except in Africa[18] patients are homosexual or bisexual men in 95% of cases and have had progressive, previously treated, cutaneous lesions in more than 50% of cases.[15 16 26 28] However, simultaneous cutaneous Kaposi's sarcoma may be absent in 5–23% of patients with symptomatic pulmonary Kaposi's sarcoma.[16 28 29] Other visceral localisation is not unusual and gastrointestinal tract involvement has been observed in at least 27% of cases from a homogeneous series of patients with pulmonary Kaposi's sarcoma.[28] Clinical and/or biological expression of immune deficiency is common. At least one opportunistic infection has occurred in 35–79% of patients before the diagnosis of their pulmonary Kaposi's sarcoma.[15 17 24 25 28] Mean CD4 cell counts have been 77, 96, and 170/µl in three recent series.[24 28 30] However, pulmonary Kaposi's sarcoma has been reported in patients with more than 400 CD4 cells/µl.[24 28] Progressive dyspnoea is observed in 83–100% of cases[15 17 18 24 25 28]; mean PaO_2 was 8·0, 8·0, 9·0 and 10·2 kPa at presentation in four recently published series.[15 18 24 28] Furthermore, acute respiratory failure requiring mechanical ventilation has occurred in patients with no

pulmonary or cardiovascular disease other than Kaposi's sarcoma.[16 31] Non-productive cough is present in 67–100% of cases and is associated with mild haemoptysis in about one third.[15 17 18 22 24 25 28 29] Lower thoracic pain attributed to pleural effusion is reported in 17–47% of patients.[15 17 24 25 28] High fever ($\geqslant 38 \cdot 5°C$) on presentation is found in 30–53% of patients with pulmonary Kaposi's sarcoma[15–17 24 28]; in most of these it is related to concomitant pulmonary or extrapulmonary bacterial and/or opportunistic infection. However, aggressive pulmonary Kaposi's sarcoma itself, or in association with multicentric Castleman's disease, has also been reported as the cause of such fever.[28 32 33] Physical examination of the thorax is usually normal or indicates non-specific signs such as crackles, wheeze, or stridor in patients with Kaposi's sarcoma of the upper respiratory tract.[12]

CHEST RADIOGRAPHY AND COMPUTED TOMOGRAPHY

Although chest radiographs of patients with intrathoracic Kaposi's sarcoma may be normal in 5–20% of cases,[15 26 34–38] they commonly show diffuse parenchymal abnormalities in two major patterns which correlate well with pathological findings. The first is a predominance of perihilar linear densities that follow septal lines and are observed in about 40% of cases; the second is a predominance of a single nodular opacity or of multiple nodular opacities with no preferential distribution which may sometimes coalesce and are also seen in about 40% of cases.[15 26 34–38] The association of both abnormalities found in nearly 70% of patients is highly suggestive of pulmonary Kaposi's sarcoma. Other parenchymal abnormalities such as segmental or lobar, alveolar or interstitial infiltrates and atelectasis are less common findings on radiography. The frequency of pleural and intrathoracic lymph node involvement on the radiograph has varied widely. Pleural effusions have been observed in 7–50% of chest radiographs.[15 26 34–38] When present they are usually large, bilateral, and associated with parenchymal lesions[15–17 25 27 38]; these characteristics are highly suggestive of Kaposi's sarcoma.[27 34 39] Intrathoracic lymph nodes visible on radiography have been reported in 8–46% of cases but their Kaposi's sarcoma origin has seldom been verified by histological examination.[15 19 26 27 35 38 39]

Few studies have been published about the computed tomographic (CT) examination of patients with proven or highly probable intrathoracic Kaposi's sarcoma and no associated opportunistic infection. The respective frequencies of pulmonary nodules, peribronchovascular thickening, pleural effusions, and tumour masses has varied from 31–100%, 35–87%, 55–70%, and 15–56%, respectively, in recent series of patients evaluated by computed tomographic scanning.[34 37 39 40] In the largest (unpublished) series evaluating CT scanning in 61 patients with intrathoracic Kaposi's sarcoma the association of two or more of these abnormalities was found in 75% of cases. In the same series mediastinal lymph nodes were visible in 43% of cases but were enlarged in less than one third. Other abnormalities such as septal lines and pericardial effusion are still less frequent; ground glass opacities are very unusual and, if present, are associated with alveolar haemorrhage.

FIBREOPTIC BRONCHOSCOPY

There are two main reasons why bronchoscopy is the gold standard for the diagnosis of intrathoracic Kaposi's sarcoma in cases with visible endobronchial lesions: (1) bronchial biopsy samples of Kaposi's sarcoma lesions have a poor diagnostic yield and cannot be repeated indefinitely[12]; and (2) in most cases the macroscopic appearance of endobronchial lesions is highly suggestive of Kaposi's sarcoma and their presence has been found to be predictive of parenchymal Kaposi's sarcoma in at least one necroscopic study.[17] Consequently, in patients with known histologically proven Kaposi's sarcoma cutaneous lesions, suggestive endobronchial lesions are considered to be sufficient for diagnosis.[12 41] Endobronchial Kaposi's sarcoma lesions typically consist of single or multiple, red or purple, flat or raised, non-stenotic lesions that tend to predominate in the trachea and at segmental junctions in the main bronchi.[12] Less frequently macroscopic lesions are distal and stenotic, although complete obstruction by intraluminal tumour is very uncommon.[12] Endobronchial lesions have been found in 4–25% of patients with cutaneous Kaposi's sarcoma and respiratory symptoms, whether they are related to intrathoracic Kaposi's sarcoma or not.[15 24 25 42] They were present in more than 70% (35–95%) of patients receiving chemotherapy for symptomatic intrathoracic Kaposi's sarcoma.[15 24 25 28 42] Although generally safe, bronchial or transbronchial biopsy samples have a poor diagnostic yield (less than 30%) but have only been evaluated in small series of patients (5–27 patients).[2] Since an associated infection was reported in 17–27% of patients evaluated for symptomatic intrathoracic Kaposi's sarcoma, a further role for bronchoscopy in these patients is its ability to demonstrate the absence of any such pulmonary infection before starting chemotherapy.[2 15 18 22 25 28 29] In this context, the frequency of bacterial colonisation or infection due to *Staphylococcus aureus* and *Pseudomonas aeruginosa* should be stressed.[18] Finally, some studies of bronchoalveolar lavage in patients with pulmonary Kaposi's sarcoma without pulmonary infection have shown a high frequency of alveolar haemorrhage[31]; other series have failed to confirm this finding.[29 43]

PULMONARY FUNCTION TESTS

The abnormalities of pulmonary function tests observed in patients with pulmonary Kaposi's sarcoma are usually non-specific and consist of a reduction in the forced expiratory volume in one second/forced vital capacity and a low diffusing capacity (TLCO); although less frequent, a decrease in vital capacity has also been

reported.[17 18 22 29 44] The severity of the airways obstruction has been correlated to the widespread finding of radiological abnormalities and endobronchial Kaposi's sarcoma lesions.[22 29] Finally, it has also been suggested that a normal TLCO and an improvement in the alveolararterial oxygen gradient during exercise were more likely to be found in patients with pulmonary Kaposi's sarcoma than in those with opportunistic pneumonia.[2 44]

ISOTOPE TESTS

Unlike pulmonary infections or lymphoid processes in HIV-infected patients, pulmonary Kaposi's sarcoma does not fix gallium so, in an AIDS patient with or without cutaneous Kaposi's sarcoma, interstitial and/or nodular changes on the chest radiograph that do not label with gallium strongly suggest pulmonary Kaposi's sarcoma. On the other hand, the presence of focal gallium uptake in lungs or mediastinal lymph nodes in patients with Kaposi's sarcoma is highly suggestive of concomitant infection and/or lymphoma.[45–47] In addition, Kaposi's sarcoma, but not infectious lesions, has been shown to fix thallium,[48] other radionuclides such as technetium pertechnetate-99 and pooled human immunoglobulin labelled with indium-111 have also been studied.[45 49] The clinical interest of these tests, however, requires further investigation.[45]

MAGNETIC RESONANCE IMAGING

In a recent study, spin echo T1 enhancement after gadolinium associated with a marked reduction of the second echo of the spin-echo T2 in the pathological areas were observed in patients with pulmonary Kaposi's sarcoma but not in patients with *Pneumocystis carinii* pneumonia.[50] The angiomatous and fibrous components of Kaposi's sarcoma would account for this finding.

Diagnostic approaches to intrathoracic Kaposi's sarcoma (figure)

Whatever their suggestive diagnostic value, no clinical or radiological data allow the clinician to make a firm diagnosis of intrathoracic Kaposi's sarcoma. In most cases fibreoptic bronchoscopy showing suggestive lesions suffices for this diagnosis. In the absence of such lesions thoracoscopy, mediastinoscopy, or thoracotomy are needed, depending on the radiological appearances of the intrathoracic involvement.

DIAGNOSTIC APPROACH IN ASYMPTOMATIC PATIENTS

In patients with known cutaneous Kaposi's sarcoma but without pulmonary symptoms, systematic chest radiography may reveal abnormalities. From the therapeutic point of view the requirement is not to diagnose Kaposi's sarcoma but to identify infection. In cases where non-invasive investigations such as CT scans, gallium scans, pulmonary function tests, and plasma levels of lactate dehydrogenase (LDH) are all in agreement with a diagnosis of Kaposi's sarcoma, fibreoptic bronchoscopy must be the next step. Either endobronchial Kaposi's sarcoma lesions are seen and the diagnosis is complete, or further radiological and endoscopic examinations must be repeated regularly unless cytotoxic treatment is given for respiratory symptoms. The appearance of endobronchial Kaposi's sarcoma lesions will confirm retrospectively the diagnosis in most cases. When results from non-invasive investigations are conflicting, fibreoptic bronchoscopy with bronchoalveolar lavage is necessary. In cases
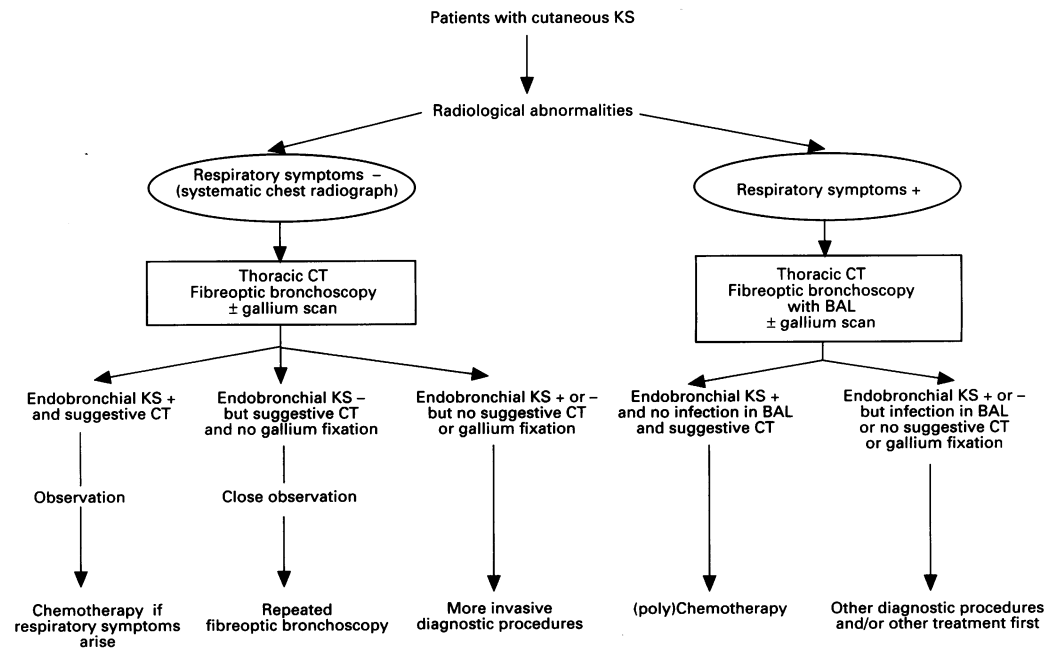
Algorithm for clinical approach to HIV-infected patients suspected of having intrathoracic Kaposi's sarcoma.

where this does not find pathogens or Kaposi's sarcoma other invasive procedures may be undertaken.

DIAGNOSTIC APPROACH IN SYMPTOMATIC PATIENTS

In most cases clinical data, particularly extensive cutaneous Kaposi's sarcoma, and CT data, particularly a combination of multiple nodules, peribronchovascular thickening and bilateral pleural effusions, are highly suggestive of bronchopulmonary Kaposi's sarcoma. In these patients fibreoptic bronchoscopy will reveal obvious endobronchial lesions and bronchoalveolar lavage would exclude the possibility of associated infection. This is enough to justify starting cytotoxic chemotherapy. In cases with a negative result on bronchoscopy the macroscopic Kaposi's sarcoma lesions necessary to start chemotherapy must be sought by thoracoscopy or thoracotomy.

There are three particular situations which need additional investigation even when endobronchial Kaposi's sarcoma lesions are visible.

Patients with high fever (≥38·5°C)

The fever may be caused by Kaposi's sarcoma or by an infection. Bronchoalveolar lavage and protected bronchial brushing are justified, particularly in the presence of ground glass opacities on CT scanning[39] and/or high gallium uptake[45] and/or an increase in plasma levels of LDH.[12]

Patients with enlarged mediastinal lymphadenopathy

In this situation mediastinoscopy is required, particularly in cases where the CT scan is suggestive of a necrotic process[39] and/or where there is a high gallium uptake, in order to diagnose other possible causes such as tuberculosis, cryptococcosis, histoplasmosis, or lymphoma.[28]

Patients with isolated pleural effusions

Kaposi's sarcoma is the cause in half the homosexual patients. The other causes include tuberculosis, bacterial infection or, more rarely, opportunistic infection (cryptococcosis, pneumocystosis, leishmaniasis) or tumour (carcinoma, lymphoma).[23 27] In a recent series of 37 cases of pleural effusion with an identified cause an analysis of the diagnostic value of clinical and/or radiological data was made in an attempt to differentiate Kaposi's sarcoma-related pleural effusions from those of infectious origin.[27] Clinically the presence of cutaneous Kaposi's sarcoma, no fever, and the progressive onset of symptoms had a positive predictive value for Kaposi's sarcoma-related pleural effusion of 80%, 80%, and 83%, respectively, while their absence had a negative predictive value of more than 92%. Radiologically the presence of bilateral effusions and the association of lung opacities had a positive predictive value of 95% and 90%, respectively, whilst their absence had a negative predictive value nearing 100%.[27] Macroscopically, blood-stained or chylous pleural effusion is suggestive of Kaposi's sarcoma.[15 16 25 27] In contrast, cells and tissue obtained by pleural fluid aspiration and biopsy are no help in establishing a diagnosis of Kaposi's sarcoma.[2 15 16 25 27] The final diagnostic strategy differs in two sets of circumstances. In the first, clinical and radiological data are suggestive and Kaposi's sarcoma endobronchial lesions are seen: thoracoscopy is unnecessary to confirm the origin of the effusion. In the second, clinical and radiological data are conflicting and/or no Kaposi's sarcoma endobronchial lesions are seen: visualisation of pleural or parenchymatous Kaposi's sarcoma lesions by thoracoscopy or thoracotomy is required for diagnosis.

Treatment of intrathoracic Kaposi's sarcoma

Indications for treatment are based on the following findings: (1) dyspnoea due to progressive parenchymal disease, large pleural effusions, or airways obstruction by tumour is the major symptom of intrathoracic Kaposi's sarcoma which can affect the quality of life[12]; (2) death usually results from the extension of Kaposi's sarcoma itself or from associated infection[24 28 42]; (3) survival of untreated symptomatic patients is usually less than four months[16 17 26] although asymptomatic patients may survive for up to several years[12]; (4) improvement in symptoms, the quality of life, and survival have all recently been reported in symptomatic patients treated by multidrug chemotherapy[15 16 24 28 30 36 42 51 52] but half these patients died of drug-induced complications.[15 24 28 30 36 42 51 52] Because of the risks and limitations of treatment it should be reserved for symptomatic patients, the objective being more to improve short term comfort than to increase long term survival. Modalities for treatment include prophylaxis and immune response modifiers, as well as chemotherapy, radiotherapy, and best supportive care.[12]

PROPHYLAXIS, ANTIRETROVIRAL AGENTS AND IMMUNE RESPONSE MODIFIERS

Since patients with intrathoracic Kaposi's sarcoma usually have less than 200 CD4 cells/μl and/or prior opportunistic infections, they require combined prophylaxis and antiretroviral therapy.[53] Since the efficacy of and tolerance to trimethoprim-sulphamethoxazole (TMP-SMZ) (400–80 mg daily) has been demonstrated in groups of patients with Kaposi's sarcoma, it should be given as the first line prophylactic drug against *Pneumocystis carinii* pneumonia.[54] In addition, TMP-SMZ has a protective effect against toxoplasmosis and certain bacterial infections.[54 55] If TMP-SMZ is contraindicated, dapsone should be preferred to aerosolised pentamidine because of the unforeseeable bioavailability of the latter in patients with bronchopulmonary Kaposi's sar-

Results obtained with monochemotherapy or polychemotherapy in the treatment of patients
with intrathoracic Kaposi's sarcoma

Treatment Drug[dose] interval	No. of patients*	Response (%)	Survival (months)
A[40]B[10]Vb[6] every month[15]	19 (19)	NR	6
A[10–20]B[10]V[1,4] or BV or A[20] every two weeks[24]	20 (20)	60	8
A[40]B[15]V[1,4] every three weeks[28]	30 (30)	40	6
A[40]B[10]Vb[6] every month[35]	19 (NR)	74	NR
A[20]Vb[4]B[15] at day 1, Act[1]V[1,4] Dac[375] at day 8, B[15] at day 15, every month[51]	18 (4)	93	NR
A[10]B[10]V[1,4] every two weeks[42]	21 (7)	90	8
A[20]B[10]V[1,4] every two weeks[42]	12 (2)	58	8
A[20]B[10]V[2] every two weeks[30]	24 (8)	88	9
A[20] every two weeks[30]	29 (7)	48	4

* Numbers in parentheses are numbers of patients with intrathoracic Kaposi's sarcoma; NR = not reported.
A = adriamycin, B = bleomycin, V = vincristine, Vb = vinblastine, Act = actinomycin D, Dac = dacarbazine. For each drug the dose per course expressed in mg/m^2 is indicated in square brackets.

coma.[54–56] Zidovudine (AZT) by itself retains its antiretroviral activity in patients with cutaneous Kaposi's sarcoma but has no effect on the lesions.[57] A combination of AZT, vincristine, and bleomycin has been reported to be well tolerated and partly effective.[58] Alpha-interferon (α-INF) has been successful in patients with cutaneous Kaposi's sarcoma and moderate immune deficiency.[6] It is not, however, appropriate for individuals with symptomatic intrathoracic Kaposi's sarcoma because (1) it loses its efficacy and is less well tolerated with the progression of immunodeficiency; (2) the time to clinical response with α-INF is long (6–8 weeks) making it inappropriate for patients with respiratory symptoms; and (3) there is no proof of the efficacy of α-INF in patients with visceral Kaposi's sarcoma. The hope of enhancing the effect of α-INF has led to studies combining it with antiretroviral and/ or cytotoxic drugs. In these studies no increase in efficacy has been shown, but toxicity was increased.[6 59 60]

CHEMOTHERAPY
Many reports have been published in this field but they differ greatly according to the presence or absence of visceral involvement, the regimens used (monochemotherapy or polychemotherapy), and the results expressed in terms of response and/or survival.[15 16 24 28 30 36 42 51 52 61] The results from the series including patients with intrathoracic Kaposi's sarcoma are summarised in the table. Even if the progress of such patients is not always specifically noted, analysis of the series leads to the following conclusions. (1) There is a discrepancy between the effectiveness on respiratory symptoms and radiographic opacities.[24 28 30 36 42] A major improvement in respiratory symptoms as early as the first course of chemotherapy is often observed[15 16 24 28 30 36 42 51 52] which was associated with a large rise in PaO$_2$ in one series.[28] In contrast, a partial radiological response occurs in 48–93% of patients but complete response is observed in 0–38%.[24 28 30 36 42] (2) Beneficial effects persist for a mean period of 2–4 weeks but do not usually exceed two months.[24 28 30 36 42] Moreover, average survival after the first course of chemo-

therapy is 6–9 months even though survival of more than two years has been reported.[15 16 24 28 30 36 42 51 52] (3) There are prognostic factors for poor survival. Multivariate analysis of results from at least three series indicates that haemoglobin values <10 g/dl, leucopenia <1500/μl, CD4 count <100 μl, and the presence of opportunistic infection before chemotherapy are all predictors of rapid evolution to death.[24 28 30 42] In some series certain factors such as the presence of bilateral effusions, Karnofsky index of <70%, the absence of response on radiography, and the absence of cutaneous Kaposi's sarcoma in patients without previous chemotherapy allowed prediction of a shorter survival.[24 28 30 42] Finally, in one series previous treatment of cutaneous Kaposi's sarcoma by α-INF and/or monochemotherapy, the degree of hypoxaemia, the platelet count before chemotherapy, and the degree of improvement of PaO$_2$ after the first course of chemotherapy were not statistically related to survival.[28] These factors were not evaluated in other series. (4) All patients experience some side effects. Fever and shivering related to intravenous bleomycin occurs in some patients but may be countered by paracetamol. Peripheral neuropathy and cardiomyopathy are observed in patients receiving vincristine and adriamycin, respectively, but rarely to the point where treatment must be interrupted.[24 28 30 42] In contrast, the episodes of severe leucopenia with frequent bacterial infection, which occurs in 50% of patients, usually necessitate longer breaks between courses of chemotherapy. Moreover, the fact that most patients die either from bacterial infection and/or acute respiratory failure due to progression of pulmonary Kaposi's sarcoma suggests an indirect but major contribution of leucopenia to these fatal outcomes.[15 16 24 28 30 36 42 51 52]

RADIATION THERAPY
Radiation therapy has been used as palliative treatment in a small number of patients with intrathoracic Kaposi's sarcoma.[62–65] Various total doses (5–35 Gy) have been used and indications have varied widely (severe haemoptysis, high fever, tracheal or bronchial obstruction, respiratory symptoms refractory to chemotherapy, and/or inability of the patient to tolerate the myelosuppressive effects of chemotherapy).[62–65] Improvement of symptoms and only minor complications, such as transient loss of appetite or malaise, are usually observed in patients who complete therapy. When precisely reported, survival was short (1–8 months).[62–65] In one recent study in which whole lung irradiation fields of 10–15 Gy were used six of 25 patients died before completing treatment while 16 reported subjective improvement and three did not. The average survival in this study was 12·1 weeks.[65]

ASSOCIATED THERAPY
Various associated therapies (oxygen, antipyretics, analgesics, antibiotics, and enteral or parenteral nutrition) may be required to

improve symptoms in these patients. The role of steroids is still nuclear. On the one hand, in vitro studies suggest that they may increase the progression of Kaposi's sarcoma[2] but favourable outcomes have been observed in patients with acute respiratory failure from pulmonary Kaposi's sarcoma even under controlled ventilation.[28 31] Moreover, in these patients steroids given with the first course of chemotherapy did not increase infections or reduce survival as in patients receiving steroids for acute respiratory failure due to *Pneumocystis carinii* pneumonia.[28] In Kaposi's sarcoma effusion treatment is usually limited to repeated thoracocenteses[1 2] because of the lack of efficacy of chemotherapy and the inability of chest tube thoracostomy, with or without instillation of bleomycin or tetracycline, to prevent recurrence.

THERAPEUTIC STRATEGIES FOR THE FUTURE

The results currently achieved in intrathoracic Kaposi's sarcoma are disappointing. Progress may be hoped for in three different areas: (1) improved staging should be sought. Classically, staging of bronchopulmonary lung cancer is based on extension of the tumour. This is inappropriate for Kaposi's sarcoma because other factors such as immunodeficiency and non-tumour manifestations of AIDS also play a part in the choice and limits of treatment and in the outcome for the patient.[1 2] At the present time the most appropriate classification we have is the TIS classification (T: tumor extension; I: immune system; S: systemic illness abnormalities), even though it was not specifically designed for intrathoracic Kaposi's sarcoma[41]; (2) the intervals between courses of chemotherapy could be better adhered to if the induced neutropenia could be limited by use of less toxic drugs (liposomal daunorubicin)[66 67] and concomitant administration of haematological growth factors.[68 69] New trials are under way to evaluate their activity with particular attention being paid to the detection of any in vivo stimulation of HIV replication[68 69]; and (3) improved therapeutic approaches could result from a better understanding of the physiopathological mechanisms of Kaposi's sarcoma and investigators are currently looking at manipulations of various growth factors as well as their antibodies, soluble receptors, and angiogenesis inhibitors.[6]

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