

#### STUDY DESIGN

1. Contact Bay Area oncologists for malignant lymphomas in young men 1980-1983 and obtain clinical data.
2. Review Bay Area Cancer Registry for non-Hodgkins lymphoma in single men age 20-50 over two time periods: 1975-78 and 1979-82.
3. Review clinical features of 29 men with undifferentiated lymphoma treated at the National Cancer Institute 1974-1980.

# UNDIFFERENTIATED LYMPHOMA

## IN BAY AREA

|               | <u>1975-78</u> | <u>1979-82</u> |
|---------------|----------------|----------------|
| Burkitt's     | 2              | 9              |
| Non-Burkitt's | 5              | 19             |
| Total         | 7              | 28             |

# LYMPHOMA PATIENT CHARACTERISTICS

|                    | <u>Bay Area</u> | <u>NCI (Control)</u> |
|--------------------|-----------------|----------------------|
| Number (Gay)       | 16 (15)         | 29 (0)               |
| Median Age (range) | 35 (24-55)      | 23 (17-35)           |

# HISTOLOGIC CLASSIFICATION

|                                | <u>Bay Area Cases</u> |
|--------------------------------|-----------------------|
| Undifferentiated-non-Burkitt's | 9                     |
| Undifferentiated-Burkitt's     | 3                     |
| Diffuse histiocytic            | 3                     |
| "Reticulosis"                  | 1                     |

# MAJOR PRODROMAL MANIFESTATIONS

|                             | <u>Bay Area</u> | <u>NCI (Control)</u> |
|-----------------------------|-----------------|----------------------|
| Generalized lymphadenopathy | 9               | 0                    |
| Opportunistic infection     | 3               | 0                    |
| Kaposi's Sarcoma            | 3               | 0                    |
| None                        | 1               |                      |

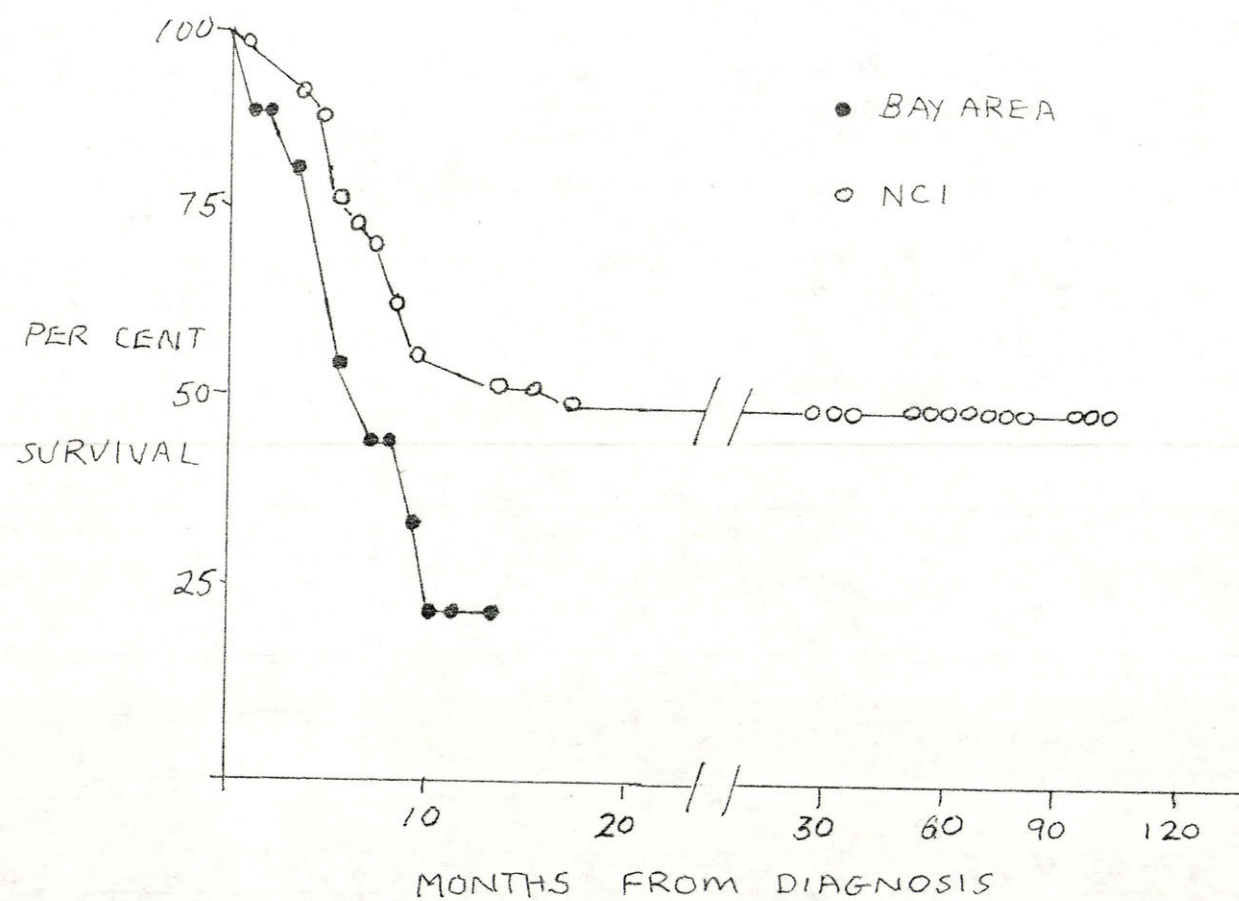
CLINICAL STAGE

| Stage:   | <u>Bay Area</u> | <u>NCI (Control)</u> |
|----------|-----------------|----------------------|
| A, B, AR | 1               | 5                    |
| C        | 2               | 8                    |
| D        | 13 (81%)        | 16 (55%)             |

# RESPONSE TO TREATMENT

|                | <u>Bay Area</u> | <u>NCI (Control)</u> |
|----------------|-----------------|----------------------|
| Complete       | 12 (86%)        | 24 (83%)             |
| Partial        | 2               | 5                    |
| (No treatment) | 2               |                      |

# SURVIVAL OF YOUNG MEN WITH LYMPHOMA



Mr. Chairman, Ladies and Gentlemen:

First slide please (Slide 1)

~~Acquired immunodeficiency syndrome~~ (AIDS) has been defined by the Centers <sup>for</sup> Disease Control (~~CDC~~) as the occurrence of Kaposi's Sarcoma or severe opportunistic infection in a previously healthy individual ~~under 60 years of age~~ who does not have other medical <sup>reasons for</sup> ~~illnesses known to cause~~ immunosuppression. Although cerebral lymphoma is included in the case definitions, generalized non-Hodgkin's lymphomas are excluded in the belief that the lymphoma itself could be a cause of immune suppression. Despite this exclusion, an apparent excess of undifferentiated <sup>of</sup> (immunoblastic) lymphomas are reported among the AIDS risk groups, particularly in homosexual men. Common to these cases are preexisting lymphadenopathy, concomitant opportunistic infections or Kaposi's Sarcoma, and an extremely poor prognosis. The poor outlook of patients with AIDS-associated lymphoma is reminiscent of lymphomas that develop in immunosuppressed renal allograft recipients and in patients with inherited immunodeficiencies. On the other hand, the natural history of patients with de novo malignant lymphoma of similar histology is considerably more favorable, ~~with an estimated 50-60% cure rate~~. In the latter patients, complicating infections are generally bacterial due to treatment-induced leukopenia.

Next Slide Please (Slide 2)

In order to quantitate these impressions we contacted Bay Area oncologists to <sup>to obtain clinical characteristics on cases of</sup> ~~characterize~~ malignant lymphomas in young men between 1980 and 1983, <sup>diagnosed</sup> ~~and the clinical~~ <sup>to</sup> ~~data were analysed~~. Second, we reviewed the Bay Area Cancer Registry for cases of undifferentiated non-Hodgkin's lymphoma in single men aged 20-50 over two four-year time periods, 1975-1978, and 1979-1982. Finally, we reviewed clinical features of 29 men with undifferentiated lymphoma treated at the National Cancer Institute between 1974 and 1980. This latter group served as historical controls.

whom were homosexual. All were diagnosed between 1980 and 1983. Data from the Bay Area Cancer Registry indicates a four-fold rise in undifferentiated lymphoma since 1979, and increase accounted for in large part by an excess in singlemen.

Our series contains one and possibly two "de novo" cases of lymphoma that might be expected to occur during this time period from the large single male population at risk. Both patients are relatively long survivors of chemotherapy (10+ and 13+ months) and are unencumbered with opportunistic infections or Kaposi's sarcoma. The remaining 14 patients, all homosexual, suffered from widespread aggressive lymphoma complicated by multiple opportunistic infections, and/or Kaposi's sarcoma. While three remain alive, all have other diagnostic criteria for AIDS and their prognosis is extremely poor.

A comparison of this group of cases with the natural history of undifferentiated malignant lymphoma derived from the seven-year experience at NCI disclosed four major differences. First, all 15 homosexual men had "prodromal" manifestations of <sup>while</sup> ~~generalized lymphadenopathy, Kaposi's sarcoma or opportunistic infections, or both.~~ Such disorders were absent in all of the male patients at NCI. Second, the majority of Bay Area men had ~~Stage D~~ (widespread) lymphoma on presentation. Third, while responding well to initial chemotherapy, the Bay Area patients (with two exceptions) relapsed and suffered infectious complications uncharacteristic of treated malignant lymphoma. Finally the actuarial survival of only 22% was significantly worse than the NCI controls.

Because of these differences and the high frequency of AIDS-associated conditions in the Bay Area homosexual men, we argue that malignant lymphoma that occurs in members of AIDS risk groups should be a diagnostic criterion for AIDS. The notion ~~propounded by the CDC~~ that immunodeficiency predisposing to AIDS-like conditions is a consequence of the lymphoma is not tenable for several reasons. First, with the exception of rare cases of Hodgkin's disease or HTLV-associated T-cell malignancy, severe AIDS-like opportunistic infections prior to therapy are not seen in patients with undifferentiated malignant

generalized lymphadenopathy, before development of lymphoma. Three patients had severe opportunistic infections and three had Kaposi's Sarcoma. Pneumocystis carinii pneumonia was diagnosed in five patients prior to the onset of malignant lymphoma. The only patient lacking prodromal manifestations was the non-homosexual man. None of the control patients had prodromal signs or symptoms associated with AIDS.

The next slide (Slide 7)

shows the clinical stage compared to the control group. All but three patients (81%) presented with Stage D tumors as compared to 55% controls presenting with Stage D.

The next slide (Slide 8)

shows that response rates among 14 Bay Area patients treated with chemotherapy (86%) was similar to NCI controls (83%). However, all but two <sup>of our patients</sup> have relapsed, ~~one of whom (No. 12) is the only non-homosexual patient.~~ <sup>The one is a man</sup> All partial responders and untreated patients have died. <sup>Remains in remission.</sup>

Next Slide (Slide 9)

Survival in the Bay Area cases is shown in this slide. Actvarial analysis shows a survival of 22% as compared to 48% in controls. Nine Bay Area patients died of progressive drug-resistant tumors and eleven suffered from opportunistic infections. No control patients developed severe opportunistic infections such as Pneumocystis carinii pneumonia or other conditions associated with AIDS. Rather, control patients succumbed to progressive tumor and bacterial or fungal sepsis related to aggressive cytotoxic therapy. Oncologists caring for Bay Area men with lymphoma remarked on the profound and prolonged leukopenia that these patients experienced following chemotherapy or antibiotics.

Slide off and lights please

We describe 16 men with malignant lymphoma from the San Francisco Bay Area, 15 of

Next Slide Please (Slide 3)

*single men 20-5*  
The Bay Area Cancer Registry records a total of ~~six~~<sup>7</sup> undifferentiated lymphomas ~~(one~~<sup>+two</sup> Burkitt's, five non-Burkitt's) in the period 1975-78, and ~~24~~<sup>28</sup> ~~(five~~<sup>9</sup> Burkitt's and 19 non-Burkitt's) in the period 1979-82. This four-fold rise represents a significant increase since the overall reporting of non-Hodgkin's lymphomas over these periods has remained constant.

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Through personal contact with Bay Area oncologists, clinical details of 16 cases of undifferentiated lymphoma in single men aged 20-~~60~~<sup>50</sup> diagnosed between 1979 and 1983 were available for review. Fifteen of these men were homosexual. Twnety-nine controls from the NCI were reviewed. The median age and range are shown on the slide.

Next Slide Please (Slide 5)

The initial diagnoses of these patients are shown in this slide. Twelve patients had undifferentiated lymphoma, nine were non-Burkitt's and three were Burkitt's type. There were three cases of diffuse histiocytic lymphoma. One patient had a midline reticulosis that was felt to be malignant.

*these cases*  
In two cases, the diagnosis of lymphoma was made at autopsy: one patient presented with progressive neuropathy and multiple opportunistic infections and disseminated immunoblastic lymphoma involving the central nervous system, spinal cord, bone marrow and abdominal viscera was found at autopsy. A second patient had long-standing Kaposi's sarcoma and intestinal cryptosporidiosis, and an asymptomatic cerebral immunoblastic lymphoma was discovered at autopsy.

Next Slide Please (Slide 6)

Prodromal manifestations associated with AIDS are shown in this slide. Nine patients had

lymphoma. Second, the infectious complications that do arise among lymphoma patients are usually bacterial, or terminally, disseminated viral or fungal conditions following profoundly immunosuppressive chemotherapy. Pneumocystis carinii pneumonia or Kaposi's sarcoma did not occur in a single case in the NCI series. Finally, the poor prognosis in the present series cannot be attributed to inadequate therapy. All patients were treated by Board-certified medical oncologists with <sup>as</sup> aggressive current state-of-the-art protocols.

*omit* ~~Rather, the poor prognosis is more likely a result of the disease stage, the unusual susceptibility of the patients to life-threatening opportunistic infections, to diminished bone marrow tolerance to chemotherapy, and (theoretically) to a profound and continued state of immunodeficiency despite tumor regression.~~

Although Kaposi's sarcoma <sup>still</sup> appeared to be the dominant neoplasm associated with AIDS, there are increasing reports of malignant lymphoma among AIDS victims. The clinical outcome of these patients, like the majority of our cases, is atypically <sup>poor</sup> dismal. ~~Moreover, these cases are not restricted to homosexual men, but are found among other AIDS risk groups and intravenous drug abusers with AIDS.~~ The increased incidence of malignant lymphoma in AIDS is entirely reminiscent of lymphomas that occur in other immunosuppressed <sup>states.</sup> common etiopathogenesis.

*A current speculation concept*  
~~The present thinking on the origin of lymphomas is that they result from a monoclonal outgrowth from a proliferating pool of immunocytes. The immune system, charged with the responsibility to recognize and eliminate non-self antigens must be able to undergo controlled proliferation in response to new or remembered antigens. There are many cellular and tumoral controls that regulate this response, both genetic and acquired, but aberrations abound in this complex system. Thus, any stimulated cell can proliferate indefinitely if the controls are removed.~~ Fortunately, malignant lymphomas are still "rare" and their development requires at least two additional genetic "accidents" for malignant transformation to occur. Patients with AIDS suffer from severe immune dysregulation of unknown cause, the early manifestations of which are intense B cell proliferation. The

Epstein Barr virus undoubtedly plays a role since several lymphomas in AIDS patients are positive for EBV genomes. Thus an etiologic model might be constructed in which dysregulated B cells, stimulated by EBV and unresponsive to normal T cell controls, proliferate; by chance, because of a larger population at risk, genetic accidents such as Chromosomal translocations will occur, and a monoclonal lymphoma will result. Whatever the pathogenesis, AIDS provides an important model for study of viral oncogenesis and clinicians must be alert to the development of lymphomas in this population.

In summary, we conclude that:

1. There is a significant increase in the incidence of undifferentiated lymphoma among homosexual men in the San Francisco Bay Area.
2. Clinical features of these cases include prodromal manifestations (generalized lymphadenopathy, Kaposi's sarcoma, and opportunistic infections) that are associated with AIDS.
3. The mortality of AIDS-associated lymphoma is 80%, compared to 50% in controls.
4. There is no clinical evidence that the lymphoma itself predisposes to immunodeficiency and the development of AIDS-associated conditions.
5. Malignant lymphoma that occur in AIDS risk groups should be a diagnostic criterion for AIDS.



### CONCLUSIONS

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5. Malignant lymphoma that occurs in AIDS risk groups should be a diagnostic criterion for AIDS.