THE EPIDEMIOLOGICAL STUDY OF ADULT LEUKAEMIA IN THE NORTH WEST

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INTRODUCTION

Leukaemia in adults is of unknown cause except in that minority of cases (about 5%) where it follows treatment with cytotoxic drugs or radiation. Certain very rare forms are now known to be caused by a retrovirus but such cases are hardly ever seen in this country. The treatment of acute leukaemia in adults is unsatisfactory. Before any specific treatment was available, the median survival was about 6 weeks. At present in this region it is about 10 months. A minority of younger patients do very well and are probably cured by intensive treatment which may include marrow transplantation, but for most the outlook remains black. More than half of all cases occur in those aged >65 and while remissions may be obtained in this group, the chances of survival for more than a year are small.

In general, environmental factors are thought to play a major part in the cause of most common cancers. Much of the evidence for this comes from observations of variation in incidence between different populations with immigrants tending to acquire the cancer pattern of their new locality as they adopt a different lifestyle. It is reasonable to wonder whether leukaemia incidence might be influenced by environmental factors and many people have suggested that this might be so. Problems abound with the study of any uncommon disease particularly one which is rapidly fatal but epidemiology – the study of diseases in populations – is the only means by which such suggestions can be examined.

This article describes the epidemiological work being carried out in Lancaster on adult leukaemia and presents a few of the findings from the study.

INITIAL OBSERVATIONS

In the 1970s, two papers appeared drawing attention to unusual numbers of leukaemia cases in Northwest Lancashire [1,2]. One was anecdotal insofar as it consisted of observations from a single general practice but described an excess of cases over what might be expected from consideration of the known incidence and the list size. The second paper sought by examining death certificates to establish whether there was an excess of cases of leukaemia in this area (Fylde) and concluded that indeed there was. Inherent in these two papers are all the difficulties of leukaemia epidemiology: the small case numbers, the inaccuracy of death certificate data, the problems of retrospective analysis without predefining the population, and the use of data from the 'interest generating observation' in hypothesis testing.

The idea of setting up a registry for leukaemia stemmed partly from the need to avoid these problems in examining ideas about leukaemia and partly from a wish to accumulate data on unselected cases from a large population. Such a data base reveals the natural history of the disease and the influence of treatment in a way that has not been available before: almost all series consist of patients selected by virtue of being referred to specialist centres or surviving long enough for treatment. The Lancaster study includes all adults diagnosed in the entire region since mid-1982.

OBJECTIVES

The main aim of the study is to accumulate data which is accurate and complete. The hypothesis that there is a coastal excess of leukaemia has been tested in various ways using the data and some of the results are summarised later.

The broader aim of accumulating a sufficiently large and complete data collection to examine the natural history of the disease remains. At present, more than 800 consecutive cases are stored and a major analysis is about to begin.

METHODS

A form designed in 1982 is still in use for case registration although minor modifications have been made over the years. Demographic data is of prime importance and so, as well as identification and location, the patient's occupation, religion, marital status and previous address(es) are noted. It is impossible to predict exactly what information will turn out to be important at the beginning so the attempt was made to collect as much as was reasonably easily available. One notable and serious omission has been the patient's smoking history: at least one American study has indicated an increased risk of leukaemia in smokers.

Information on exposure to chemicals and radiation, both occupational and therapeutic is collected together with a small amount of medical data mainly concerned with the presenting blood count and the exact diagnosis.

Leukaemia is only diagnosed by haematologists and so in theory, if every haematologist in the region could be persuaded to register each case at diagnosis then the collection would be complete and accurate. Whilst co-operation has in fact been excellent, occasional cases must be forgotten or missed. Ascertainment is however as good as it possibly can be and certainly very much better than that available through mortality figures. Annual reports circulated to colleagues have kept interest at a reasonably high level and the fact that follow up forms are circulated every 3 months for each patient helps to keep colleagues aware of the study.

A computer is at the heart of the study. It holds all the data, handles the correspondence and can manipulate what is now a very large file with great speed and flexibility. The programme is RBase version V and runs on an Olivetti M24 IBM-compatible PC.

SOME FINDINGS - COASTAL EXCESS

The demonstration of an excess of cases has to involve some estimate of the number expected. Because there is no comparable national data source, the approach has been to calculate Standard Incidence Ratios (SIR) using the actual data for any given year. The total number of cases occurring in the region in a year can be analysed according to age. This gives the observed age distribution in, for example, 10 year groupings. The Office of Population and Census Studies supplies up-to-date population figures for the region and by combining the age distribution of cases with the age distribution of the population of the region, the age incidence of the disease can be calculated. This is important because there is a marked positive correlation with age and many coastal districts are retirement areas with an elderly population. Having worked out the age incidence of the disease, the age structure of each district's population can be considered and for each 10 year grouping, the number of cases which would be expected given an even distribution can be calculated and hence the total number of cases the district might have expected in that year can be worked out. By comparing this figure with the observed number, the SIR can be calculated. SIRs of >130 have been taken as significant.

Whilst this is possible for Health Districts, analysis at a finer level, eg electoral wards, needs a different approach as the age structure of the population is not known at this level.

Some results are shown in the table - high SIRs for Blackpool and Lancaster are a regular feature of the annual analysis and only sporadic elsewhere. The complex analysis of coastal v non-costal electroral wards shows a similar pattern for the year of analysis (1987). It is noteworthy that a larger study by the Leukaemia Research Fund, a national body, has drawn similar conclusions from other parts of the country.

ACUTE LEUKAEMIA

Health District	1983	1984	1985	1986
Lancaster	2.58	3.08	1.58	2.09
Blackpool	1.05	2.46	1.20	1.43
Preston	0.71	0.35	1.18	1.03
Blackburn	0.54	0.33	0.86	0.65
Burnley	0.61	0.95	1.33	1.30
West Lancs.	0.48	0	0	0
Chorley	1.05	0.52	1.09	0.8
Bolton	0.36	0.18	0.91	0.4
Bury	0.81	1.30	0.93	0.8
Manchester	0.82	0.69	0.85	0.96
Oldham	1.09	0.21	1.09	1.05
Rochdale	0	0.66	1.37	0.7
Salford	1.85	0.71	0.46	1.22
Stockport	0.64	0.16	0.41	0.96
Tameside	0.39	0.73	1.31	1.13
Trafford	1.25	0.82	0.53	0.47
Wigan	1.11	1.38	1.92	0.95

- TIME CLUSTER

One unexpected result of the sequential data capture was to reveal an extraordinary cluster of acute leukaemia (mainly acute myeloid leukaemia). This grouping was in time alone and showed no spatial aggregation[3]. Seventeen cases were diagnosed in the region in January 1985 where 5 or 6 might have been expected (fig 1). This phenomenon has not recurred and is unexplained. It has naturally been the subject of much speculation for whilst it might occur by chance, calculations suggest that this should only be once every 300 years.

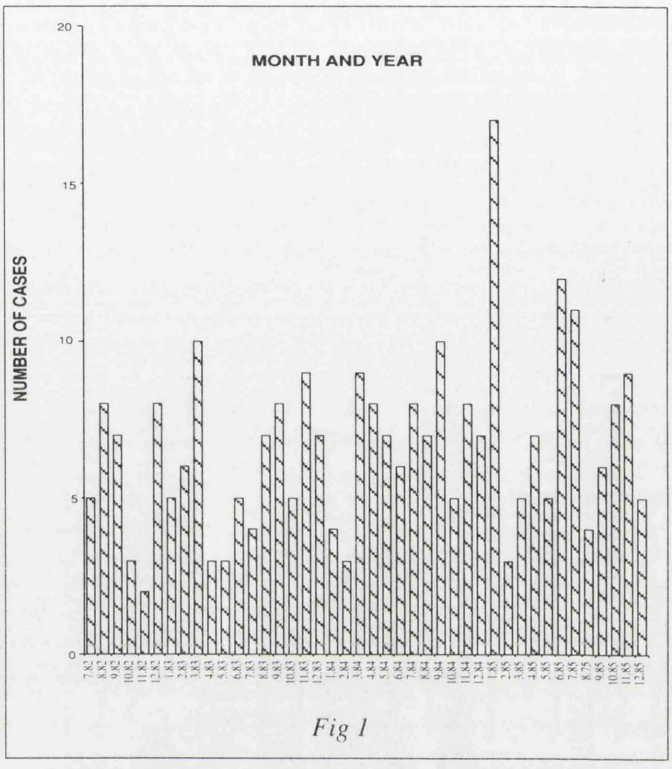


Fig 1

- AGE INCIDENCE

The major effect of age has become apparent from a study of the data. Over half of all cases occur in those over the age of 65 (fig 2) and not only does this have profound implications for the epidemiological studies mentioned

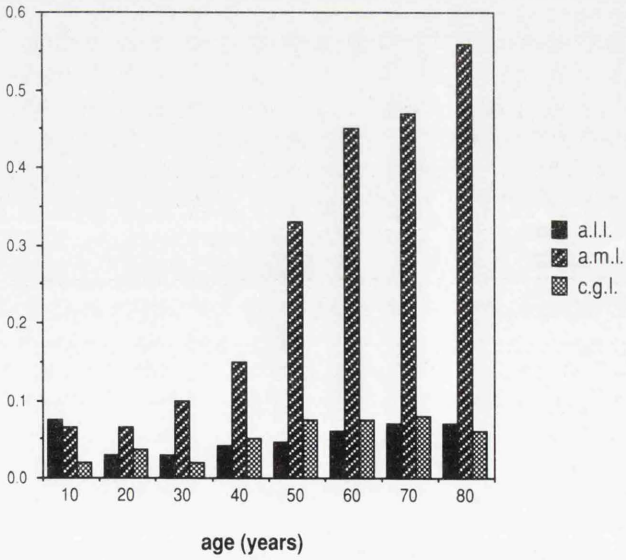


Fig 2

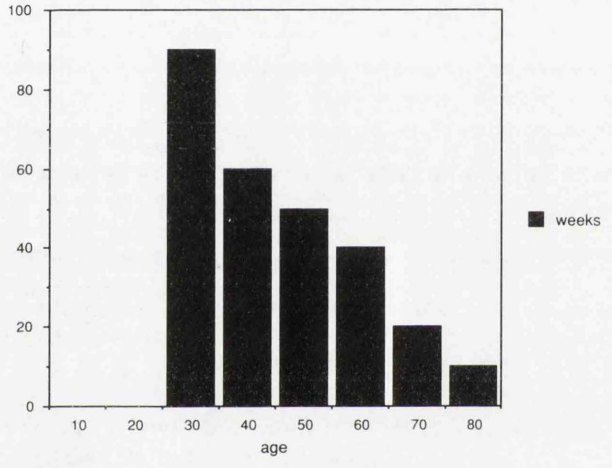
above, it also is of great importance in any assessment of treatment and support for these patients. It must be telling us something about the cause of the disease.

- SURVIVAL FIGURES

Analysis of the survival of a cohort of patients, some of whom are still alive, is complex and requires the use of specialised techniques. A simple approach is to consider median survival as more than half of the patients in the study have died (fig. 3). This however does not bring out the tail of long survivors as would a formal survival curve. Some representative groups are shown in the figure. (fig 4)

- SECONDARY CASES

Every year, approximately 5% of all leukaemia occurs in those previously given radiation or chemotherapy for malignant (or occasionally benign) disease. Analysis shows that lymphomas of all kinds are the commonest antecedent conditions[4].



MEDIAN SURVIVAL FROM DIAGNOSIS AML n=639

Fig 3

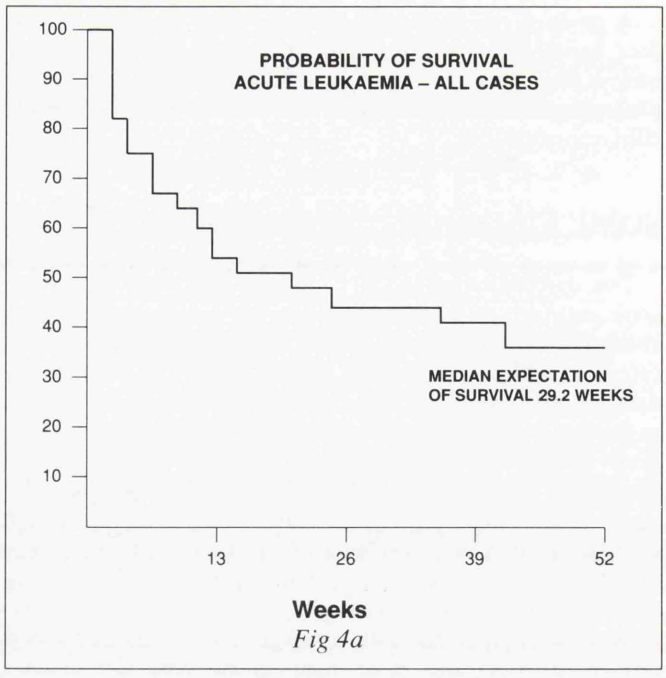


Fig 4a

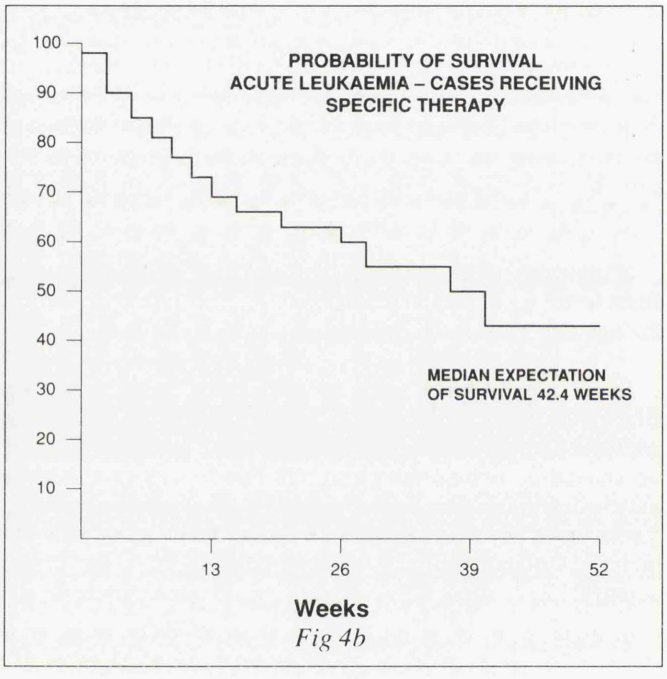


Fig 4b

CONCLUSIONS

This work has demonstrated the practicability of constructing a regional register for a specified malignant condition. It has proved possible at minimal cost to accumulate and maintain high quality data on a large population in a District General Hospital. Analysis has been aided by collaboration with the University. The data set is of increasing value as it gets larger both for the study of the natural history of the disease and for testing hypotheses raised in response to both professional and lay anxieties concerning possible causes of this dreadful disease.

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