ECONOMIC ASPECTS OF NON-HODGKIN'S LYMPHOMA

NHL

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CONTENTS

1 INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is not a single disease entity but covers a complex group of different types of malignancy. They differ in the cells affected, their course and the structures they form in the lymph glands. The unifying feature of the lymphomas as a whole is that they are all cancerous growths of lymphocytes. These are cells of the immune system which are produced from bone marrow and are located within the lymph glands. Lymphocytes are designed to fight infection by either directly producing or helping to produce antibodies.

The primary aim of this booklet is to examine the economic issues in the current and future treatment and care of NHL, and to provide a first estimate for the UK of the costs of this treatment and care. These estimates (section 7) are based on the two main NHL clinical types that make up approximately 75% of all lymphomas: these are known as diffuse large B-cell lymphomas, and follicular lymphomas. The treatment of these two types is distinct and the clinical outcomes are well defined.

There are several reasons why NHL is important for epidemiological and economic analysis. Firstly, in many countries there has been a rapid increase in incidence rates in recent years. In the UK, there were more than 5,000 people with NHL in 1994, but this was projected to increase. In Europe and North America the greatest incidence rates of NHL are in the over 65's, which is partly due to the increased number of elderly in the population, but also because the age specific incidence rates of NHL are increasing through time. Section 2 of this booklet presents descriptive epidemiological data for NHL internationally and for the UK.

Secondly, although several risk factors for NHL have been proffered and some links established (for example, the existence of infectious agents such as HIV, and genetic susceptibility), there is still much uncertainty surrounding all the potential causes of the disease. This makes the designing of effective screening or prevention programmes difficult. Section 3 reviews what is known about the risk factors for NHL.

Thirdly, advances in therapy mean that NHL is potentially curable with chemotherapy. However, outcome depends on the type of tumour, with a cure rate of 40-70% for diffuse large B cell lymphomas (depending on the extent or bulk of tumour and patient age), whereas the cure rate for follicular lymphomas is very low. Patients with follicular lymphoma have a median survival of eight to ten years. For all patients who are not cured or who cannot tolerate chemotherapy, survival after an NHL diagnosis is variable depending on whether the

tumour is fast or slow growing. For such patients palliative care can be provided, the quality of which has greatly improved in recent years through the services of hospices and specialists such as MacMillan nurses in the UK. In section 4 we describe the clinical differences between fast and slow growing NHL tumours, the conventional treatment and care options for each, and the role of new interventions such as autologous bone marrow transplantation (ABMT).

With high and increasing numbers of NHL, uncertainty about its causes, costly existing and new methods of treatment and palliative care, and high mortality and morbidity, the potential economic and health burden of NHL is significant. Health care purchasers in the UK directly face the costs of treatment and care, and with budget limits need to set priorities for resource allocation. In a broader sense the whole of society is affected by the economic and health burden of cancers such as NHL.

The economic analysis of NHL can take a number of forms. Firstly, it is useful to quantify the cost of disease, so that the actual and future potential size of the economic burden can be assessed. This includes the direct costs of the treatment and care of NHL patients, and could include the indirect costs of the loss of social and economic productivity due to illness and premature death from NHL.

Secondly, economic evaluations of the cost effectiveness or cost-benefit of treatment and care interventions for NHL can provide information to aid priority setting in the use of health care resources for NHL or, more generally, cancer services. Section 5 outlines the recognised techniques of economic analysis, and their objectives. In section 6 the limited published evidence for the cost effectiveness of two new developments in the treatment of NHL are reviewed: autologous bone marrow transplantation, and a growth factor G-CSF for the prevention of chemotherapy-induced febrile neutropenia (which is a fever associated with a reduction of infection-fighting white blood cells).

As section 6 illustrates, there have been no economic analyses of NHL treatment and care conducted for the UK. A critique of studies conducted in other countries is presented in this section. In section 7 an initial direct cost assessment for the health care costs of NHL is presented: this covers cost per patient and total incidence cost (i.e. cost of all new cases each year) for England and Wales. Using decision analysis software, treatment/outcome trees were constructed to map the expected treatment, clinical outcome and resource use pathways for different categories of NHL patient. This enabled the production of 'ballpark' estimates of the costs of treating NHL. It does not represent a direct substitute for costing exercises using actual patient-based resource use data, nor for full economic evaluations of the cost effectiveness of alternative treatments and care options. However, the treatment/outcome tree approach represents a relatively low research

cost method of direct cost estimation which is useful for indicating the general economic burden of the disease. This approach could be developed to undertake a much more rigorous cost assessment if desired. More importantly, as alternative treatment courses can be identified in the tree, it offers the basis for analysis of the cost effectiveness of alternative treatment options.

NHL represents a growing problem in the UK and internationally. A fourfold growth in numbers could be expected over the next 20 to 30 years, with a possibly even greater increase in costs if new developments in cancer treatment and care, such as ABMT or new chemotherapy regimens, become common practice. In conclusion, section 8 discusses key economic and epidemiological issues in NHL, and outlines a possible research agenda for future economic evaluations in the field.

2 DESCRIPTIVE EPIDEMIOLOGY

2.1 The sub-types of non-Hodgkin's lymphoma

There is now good evidence that NHL itself comprises several distinct biological subtypes which derive either from different types of white cells or by separate cancer causing mechanisms. It is known that epidemiological differences exist between the broad clinical disease types as determined by one scheme of classification, known as the Kiel 'high' and 'low' grade subtypes (McKinney et al., 1990). Most of the available epidemiology, however, groups NHL together as one disease.

2.2 Age and sex distribution and geographical variation

NHL is a disease of all ages but incidence rates do increase with age. At each age group there are more males affected than females. The numbers of new cases occurring each year by age and sex are similar throughout Europe, North America and Australasia but in parts of Asia, Africa and South America the conditions are rarer and present in different age or sex patterns. This is shown in Table 2.1 which gives the numbers of new cases occurring annually as a rate, which allows inter-country comparisons. In Israel and elsewhere in the Middle East the disease is relatively common. Amongst the 'European type' of disease there are variations in the absolute rate from country to country.

Based on sample international data, a typical distribution of age-specific incidence rates (number per 100,000 population on a log scale for graphical convenience) for males and females is shown in Figure 2.1. When carefully examined the rates also vary within each country. In the UK the incidence is greater in southern England than northern England. Within-country variation also occurs (Barnes et al., 1987b). The condition, however, does not appear to be diagnosed seasonally nor form unusual close case aggregations or clusters. The reason for these variations in rates is not known.

2.3 Trends in new case numbers with time

The most important descriptive feature of NHL is the apparent increase in annual numbers of cases diagnosed. This was noted some years ago (Barnes et al., 1987a) but was thought initially to be due to improvements in diagnosis. Similar trends, however, have been shown to occur throughout those countries with the 'European type' disease and at such rates that cannot be ascribed to diagnostic artefacts.

Table 2.1 **Age-specific incidence rates of NHL: international comparisons (number of new cases per year per 100,000 population)**

Males

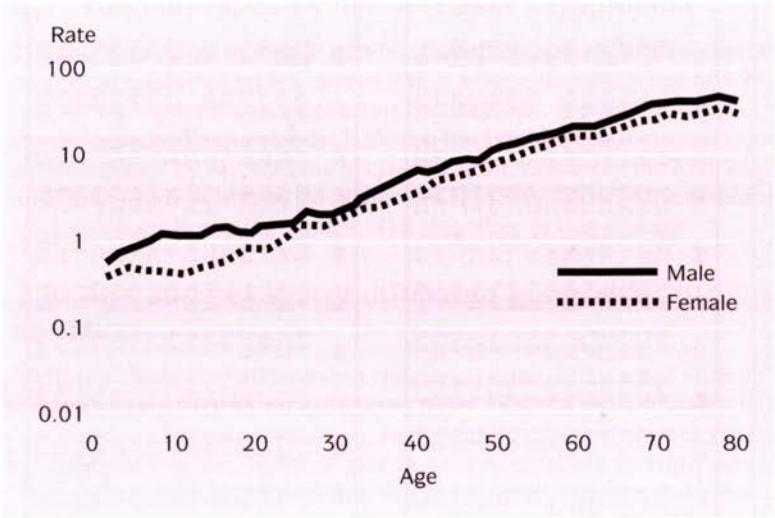
Age	0–	1–	5–	10–	15–	20–	25–	30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85+	Overall rate
Colombia	2.6		2.4	0.8	2.7	0.8	1.0	3.6	4.3	2.4	4.2	7.5	12.2	18.9	27.1	18.2	19.5	1.8	22.7	3.7
USA (Connecticut – White)	1.0		1.2	1.8	2.0	1.7	2.7	3.9	3.4	9.3	11.4	19.2	32.8	36.0	48.5	53.9	80.5	83.8	65.7	13.4
USA (Connecticut – Black)	0.0		0.0	0.0	0.0	0.0	0.0	2.5	0.0	7.4	4.3	23.4	26.7	21.9	30.6	49.1	56.3	0.0	89.3	4.9
Hong Kong	2.0		1.8	1.6	2.1	2.1	2.8	4.7	6.1	7.4	9.3	12.7	12.7	20.4	21.3	30.4	29.4	27.0	6.5	5.9
India (Bombay)	0.9		1.1	1.4	1.2	1.1	1.0	1.2	2.1	1.7	3.3	5.7	6.8	8.3	11.2	9.0	18.9	86.7		2.0
Israel (all Jews)	0.6	2.0	2.7	2.4	1.9	2.6	3.1	4.3	6.2	10.0	13.3	15.9	21.9	28.1	43.8	54.5	60.8	80.8	71.1	10.6
Israel (Jews – Africa/Asia)	0.0	42.1	0.0	0.0	3.2	3.6	6.0	2.8	6.2	8.5	8.0	12.9	19.4	28.6	21.0	34.9		38.4		10.9
Japan (Miyagi)	1.6	0.8	0.3	1.0	0.9	1.9	0.9	1.1	1.6	3.3	6.4	4.9	13.0	11.2	15.9	37.4	16.2	19.1	8.7	4.3
Singapore (Chinese	1.4	10.6	1.2	1.4	1.4	1.3	1.2	4.0	2.3	4.0	4.0	5.5	13.9	22.4	20.0	22.1	30.6	50.5	38.4	3.9
Singapore (Malayan)	0.0	0.0	0.0	0.0	0.8	0.9	1.3	1.8	0.0	2.7	12.3	8.6	10.3	15.0	43.7	28.3	0.0	0.0	165.3	3.1
Denmark	1.1		2.0	1.3	1.6	1.4	1.7	3.1	5.4	4.7	8.9	10.4	15.8	24.1	23.9	42.3	44.7	49.7	41.7	9.2
Hungary (Vas)	0.0		0.0	0.0	0.0	0.0	3.2	1.8	6.6	0.0	2.5	0.0	9.3	7.8	3.2	11.7	12.6	12.9	0.0	2.9
Spain (Zaragossa)	0.0	0.0	7.9	1.2	2.3	1.9	0.7	2.1	5.8	5.2	2.8	10.8	7.0	14.5	24.4	10.7	13.0	5.2	15.6	6.1
UK (Birmingham)	0.0	1.4	1.8	0.8	0.9	1.5	1.7	2.0	2.9	5.0	6.2	8.6	15.6	18.7	20.8	25.7	38.0	34.5	20.1	6.9

Females

Age	0–	1–	5–	10–	15–	20–	25–	30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85+	Overall rate
Colombia	1.2		0.3	0.8	0.2	0.9	0.4	1.0	0.6	1.4	7.0	4.4	7.5	10.7	25.3	14.4	20.6	22.8	35.8	2.1
USA (Connecticut – White)	0.7		0.2	0.2	1.1	1.9	0.8	2.1	3.9	6.3	7.5	12.4	21.6	29.5	38.5	37.7	54.4	62.9	56.6	12.2
USA (Connecticut – Black)	0.0		0.0	1.6	1.5	0.0	7.7	4.2	2.5	0.0	7.2	8.0	9.2	11.8	29.5	32.4	46.6	0.0	38.6	4.7
Hong Kong	1.1		0.9	1.2	1.4	2.0	3.7	2.7	6.3	4.6	7.0	10.0	12.1	15.6	13.0	19.5	18.2	20.3	21.5	5.0
India (Bombay)	0.3		0.3	0.2	0.2	0.4	0.5	0.8	0.8	1.6	2.5	4.4	5.2	5.7	8.7	8.1	6.8	28.4		1.1
Israel (all Jews)	0.0	1.4	1.0	0.5	1.5	1.6	1.7	4.6	3.7	5.0	7.3	9.4	16.0	27.2	34.4	45.4	50.7	67.5	37.0	8.3
Israel (all Jews – Africa/Asia)	0.0	0.0	0.0	0.0	0.0	0.0	1.2	3.2	1.7	5.2	7.6	5.8	16.6	19.6	20.5	43.4		37.1		8.5
Japan (Miyagi)	3.3	0.0	0.6	0.3	0.6	0.0	0.9	0.3	2.7	3.1	2.0	2.2	6.6	6.2	7.1	10.3	17.6	11.3	4.0	2.5
Singapore (Chinese)	1.6	1.1	0.4	0.4	0.4	1.0	1.0	1.3	2.7	1.6	4.0	5.2	8.8	10.4	12.6	17.7	4.2	8.6	0.0	2.5
Singapore (Malaysian)	7.1	0.0	1.2	0.0	0.8	0.0	0.0	0.0	0.0	12.4	0.0	6.7	18.8	6.8	10.5	16.4	0.0	0.0	0.0	2.1
Denmark	1.1		0.2	0.4	0.8	0.4	0.9	1.7	4.3	3.4	4.8	7.8	11.5	14.1	20.0	25.9	33.6	36.8	28.1	7.3
Hungary (Vas)	0.0		0.0	0.0	2.4	0.0	1.7	2.0	0.0	0.0	0.0	2.1	2.0	22.7	15.8	8.5	0.0	22.0	0.0	3.3
Spain (Zaragossa)	0.0	2.7	1.8	0.0	0.0	0.7	0.0	0.7	0.0	1.8	0.0	2.2	2.1	1.6	7.4	10.1	5.0	3.3	3.3	1.8
UK (Birmingham)	0.8	0.2	0.0	0.4	0.4	0.5	1.2	1.7	1.6	2.2	3.9	6.1	7.7	12.4	15.4	17.3	21.1	21.1	27.8	5.2
Australia (NSW)	1.1		0.3	0.4	0.4	1.0	1.4	2.5	3.3	4.9	8.4	14.0	19.3	22.8	33.3	41.0	51.8	43.8	31.7	8.8

Source: Muir C, Mack T, Powell J, Whelan S. *Cancer incidence in five continents.* Volume V. IARC, 1987.

Figure 2.1 **Age-specific incidence rates for all types of non-Hodgkin's lymphoma in people aged 0-79, expressed as new cases per 100,000 population per year**



Source: Data taken from the specialist register of leukaemia/lymphona (1984-93) held at the Leukaemia Research Fund Centre in Leeds.

There are convincing reports of an increasing trend with time in NHL in adults (Cartwright et al., 1994) with evidence to suggest that this dates from the 1940s to 1960s (Devesa SS, Fears T, 1992; Cartwright, 1992). One recent review (Hartge et al., 1994), has indicated that in certain areas there is both an artificial decline due to changes in diagnostic practices and an additional 'natural' decline in incidence in adult Hodgkin's disease (HD) cases. HD is a closely related condition which could be misdiagnosed occasionally as NHL. The extent to which the rise in NHL may be a diagnostic artefact arising from transfer to NHL from HD and other malignancies is debatable, however. When the incidence of all lymphomas is examined (e.g. in Australia), there is still an upward trend with time (McCredie et al., 1992). Hartge et al. (1994) conclude that a 3.4% per year rise in NHL incidence is beyond diagnostic bias. The fact that in Yorkshire (UK) the trend is about 5% per year (McNally et al., 1997) at all ages over about 30 years, also argues against a diagnostic artefact. An earlier study (Barnes et al., 1987a), using nodal material only, indicated a real increase in incidence between reviewed material from the 1960's and the late 1970's, again arguing against an explanation based on diag-

Table 2.2 **Projected UK case numbers for NHL 1994-2024**

	Rate/100,000 population					*Population projections (millions)*				*Predicted NHL case numbers*			
Ages	**1984-93**	**1994**	**2004**	**2014**	**2024**	**1994**	**2004**	**2014**	**2024**	**1994**	**2004**	**2014**	**2024**
0-4	0.54	0.54	0.54	0.54	0.54	3.75	3.38	3.27	3.23	20	18	18	17
5-9	0.82	0.82	0.82	0.82	0.82	3.70	3.53	3.27	3.29	30	29	27	27
10-14	0.72	0.72	0.72	0.72	0.72	3.52	3.78	3.40	3.27	34	39	37	34
15-19	1.03	1.03	1.03	1.03	1.03	3.30	3.75	3.57	3.27	34	39	37	34
20-24	1.20	1.20	1.20	1.20	1.20	4.00	3.64	3.86	3.39	48	44	46	41
25-29	1.82	1.82	1.82	1.82	1.82	4.58	3.42	3.85	3.56	83	62	70	65
30-34	2.58	2.68	3.97	5.88	8.70	4.54	4.07	3.68	3.85	122	162	216	335
35-39	3.99	4.15	6.14	9.09	13.46	3.92	4.61	3.43	3.83	163	283	312	515
40-44	6.13	6.38	9.44	13.97	20.68	3.71	4.55	4.06	3.65	237	429	567	755
45-49	8.12	8.44	12.50	18.50	27.39	3.95	3.90	4.58	3.39	334	488	847	929
50-54	12.01	12.49	18.49	27.37	40.51	3.15	3.65	4.47	3.99	393	675	1223	1616
55-59	16.64	17.31	25.62	37.92	56.13	2.92	3.80	3.77	4.43	505	973	1430	2487
60-64	20.01	20.81	30.80	45.60	67.50	2.74	2.94	3.43	4.24	570	906	1564	2862
65-69	27.67	28.78	42.60	63.05	93.33	2.60	2.58	3.43	3.44	748	1099	2163	3211
70-74	33.98	35.34	52.31	77.43	114.62	2.50	2.22	2.46	2.93	883	1161	1905	3358
75-79	36.98	38.46	56.93	84.27	124.74	1.61	1.83	1.92	2.63	619	1042	1618	3281
80-84	36.79	38.26	56.64	83.84	124.10	1.27	1.41	1.34	1.58	486	799	1123	1961
85-89	33.63	34.98	51.77	76.63	113.44	0.69	0.65	0.29	0.91	241	337	222	1032
90+	25.55	26.57	39.33	58.22	86.18	0.30	0.43	0.48	0.54	80	169	279	465
Overall rate	14.22	14.78	21.72	32.00	47.21								
TOTAL						56.75	58.14	58.56	59.42	5623	8741	13692	23014

Note: For all age-groups over 30, a 4% per annum increase in rates is assumed.

nostic fashion. It is not known which, if any, subgroups of NHL are on the increase, although some have been suggested (Weisenberger, 1994).

In recent years there has been an annual increase in NHL cases of 3-5% for different countries and age groups. Based on this evidence, a reasonably conservative estimate of a 4% annual increase for the UK population over the age of 30 will lead to a dramatic increase in incidence in future years. This is partly because of the increased number of elderly people and the fact that the greatest rates of NHL occur in the over 65's. Table 2.2 gives estimates of annual newly diagnosed case numbers for the UK based on population projections and an annual increase in the incidence rate of NHL of 4% for age groups over 30. Thus, case numbers in the UK in 1994 of roughly 5,000 will rise to be over 23,000 by 2024. By that time case numbers will be similar to current annual numbers of breast, bowel, lung and skin cancer. Thus within the next 30 years NHL could, depending on trends in other cancers, become one of the most common cancers.

3 ANALYTICAL EPIDEMIOLOGY

3.1 Major risk factors

Focusing specifically on the 'European type" of disease, i.e. that forming in white populations throughout the world, the risk factors for the lymphomas present certain anomalies. Unlike the majority of cancers there is no obvious or strong link, for example, with cigarette smoking or ionising irradiation. There are, however, a few well acknowledged strong risk factors.

(a) Infectious agents

Viruses: The AIDS virus, the Epstein Barr virus (EBV, known to cause glandular fever) and the human t-cell lymphotropic virus (HTLV), are all known to have links with NHL. The AIDS virus causes profound immunosuppression, which leads to a marked increase in NHL in carriers of the virus (Serraino et al., 1992; Clark et al., 1988). HIV is known to be on the increase but NHL occurs in only about 3% of all HIV positive individuals. EBV may have a role in NHL causation but it is still obscure how this occurs (de The, 1976). This virus is not increasing in its infectivity. The HTLV is rare and confined to the Caribbean and parts of Japan, and again is not increasing.
Bacteria: Infections by an organism found in the stomach wall known as *Helicobacter pylori* are associated with a rare and specific lymphoma of the gastric mucosa (Wetherspoon et al., 1991).

(b) Immunosuppressive therapy and related chronic diseases

A major risk for NHL can result from specific chronic conditions associated with a significantly damaged immune system, such as certain chronic renal diseases. People who have had severe and prolonged immunosuppression therapy – usually as a result of successful organ transplantation – also have a risk (Kinlen 1985, 1992). The increase in organ transplantation is ongoing and the risk of secondary lymphomas (NHL and HD) is quite high. Nevertheless, there is no close link between the rise in incidence of NHL and the increase in these procedures (Filipovitch et al., 1992) in that the NHL increase predates the time from which transplantation has become common.

(c) Genetic susceptibility

A number of families with lymphomas in blood relatives have been described, suggesting an inherited susceptibility. A link appears to exist between certain rare inherited conditions known as homozygote

recessive (in which there exist in a person two copies of a rare gene with abnormal DNA repair) and lymphoma. There is also the possibility that those with only one copy of such a rare gene might also display an increased risk of NHL. However, there is no evidence yet available to suggest that there has been an increase in the numbers genetically susceptible in the population.

3.2 Minor risk factors

A variety of studies have thrown up other possible risk factors. Aspects of diet, especially a link with total fat consumption, have been suggested (Franceschi et al., 1989; Weisenburger, 1994). A recent study implied that high nitrate levels from drinking water might be associated with the risk of NHL (Ward et al., 1996).

More speculatively, but with some biological support, metal joint replacement may confer a risk as fragments of metal can be shown to cause reactions in both lymph glands and bone marrow (Case et al., 1994). Various case reports also link this with lymphogenesis (Dodson and Putz, 1982). The epidemiological studies addressing this issue are conflicting, however, with some showing an association (Gillespie et al., 1988; Visuri et al., 1991) and one none (Nyren et al., 1995).

There have been a large number of studies suggesting a link between occupations associated with agriculture and the lymphomas. (Cartwright and McNally, 1994). Overall, there appears to be a weak link between lymphoma and herbicide use in farmers and applicator contractors but not in herbicide manufacturers (Saracci, 1991). Similarly some Vietnam war veterans, some of whom were exposed to Agent Green, Agent Orange and other defoliants, have an excess of lymphomas, but this is the case only among the navy veterans (Namboodiri and Harris, 1991). Workers in the petrochemical industry have been shown to have some excesses of lymphomas (Ott et al., 1987). Exposure to asbestos has also been reported as associated with lymphoma and myeloma (Bengtsson et al., 1982; Ross et al., 1982; Linet et al., 1987; Calavrezos et al., 1988; Schwartz et al., 1988; Pasqualette et al., 1991).

None of these weaker risk factors, nor the stronger factors listed in the previous sub-section, can explain the rise in incidence seen over the last 30-40 years. The HIV epidemic, the increase in number of transplanted people and the increase in joint replacement will all, possibly, make a contribution to the increase in incidence (more probably in the future than at present) but cannot account for the magnitude and duration of increase overall. Hence there is a need for new insights into the cause of the increase, with an eye on possible preventative measures.

3.3 Speculative risk factors

Cartwright et al. (1994) and Adami et al. (1995) have suggested that increased exposure to sunlight not only explains the increase in non-melanomatic skin cancer but also the parallel increase in NHL. This would also account for excess NHL in farmers and applicators (but not manufacturers) who also have more skin cancer due to exposure to sunlight. Recently available data for the UK during the period 1981-86 show a significant excess of NHL in female farmers when adjustments for age and social class are made. There is a non-significant, slight excess for male farmers (Roman E, personal communication, 1996). In addition, the idea that sunlight can profoundly influence the human immune system through cell damage, has much experimental support.

Other common factors increasing in the population over the last 50 years which have the potential to alter our immune system include the widespread use of antibiotics and the ever increasing quantities of airborne pollutants. These pollutants derive largely from internal combustion engines and are known, in some people, to cause acute allergic responses. They are quite likely to have chronic effects on the immune system.

A wide range of very common exposures could be responsible for the occurrence and increase of the lymphomas, such as those noted above. In addition, an extension of a biological hypothesis regarding childhood acute lymphoblastic leukaemia (ALL) (Greaves, 1993) has also been put forward. This is the suggestion that a particular pattern of infections and immunity in early life resulting from lack of contact with other persons could predispose to NHL in adulthood.

4 SYMPTOMS, DIAGNOSIS AND TREATMENT STRATEGIES

The common feature of all lymphomas (Hodgkin's and non-Hodgkin's) is that they are cancers of the lymphocytes, which are immune system cells that patrol the body and respond to invader substances (bacteria or viruses) by adapting themselves to repel the invader. The general symptoms, diagnosis and treatment options are similar, although cure rates may differ. However, differences in patient case-mix (e.g. in terms of age/sex) lead to differences in overall cancer patient management strategies being adopted for different lymphomas. The rest of this section refers to NHLs, but because the only real difference from Hodgkin's disease is in terms of histology much of the text also applies to this lymphoma.

The normal function of the lymphocytes is to fight infection by the direct production, or help in the production, of antibodies. These cells are manufactured in the body's bone marrow and located in the lymph glands (or lymph nodes). The normal function of lymphocytes is carefully regulated and when these cells become cancerous this function is disrupted, the lymph glands are affected, resulting in the signs and symptoms of lymphoma. These symptoms include tiredness, inappropriate fevers or sweats and weight loss. The lymph glands, mainly those in the neck, armpits and groin will become swollen. The glands can swell up quickly, which is associated with 'aggressive', rapidly growing tumours or more slowly, which is associated with 'indolent', more slowly growing tumours. Aggressive and indolent tumours, respectively, correspond to the epidemiological classification of high/intermediate grade and low grade NHLs (see section 2.1).

It is important to diagnose NHL rapidly and accurately in order to determine the best treatment and counselling strategy for the patient. Diagnosis is best achieved by cutting out a lymph gland swelling and examining it under a microscope (biopsy). This normally requires a small operation, usually performed as a hospital day case, but sometimes with an overnight stay. The majority of lymph gland swellings will be due to conditions other than NHL: most are due to bacterial or viral infections. Therefore, to avoid misdiagnosis and inappropriate treatment pathological expertise is essential. A pathology service should incorporate a number of features including a dedicated and skilled pathologist, with access to a full range of monoclonal antibodies and molecular techniques which are essential to the provision of a firm diagnosis. For efficient use of resources, this specialist service is likely to be best provided at a regional level.

The treatment of NHL depends on whether the tumour is fast or slow growing. If fast growing (aggressive) tumours are left untreated they are likely to rapidly result in death, whereas the slow growing (indolent) tumours do not require such urgent treatment and patients frequently have long periods in which they can carry out usual activities even in the absence of treatment. Paradoxically, conventional chemotherapy treatment can cure up to 60-70% of patients with rapidly growing tumours but almost never cures patients with slow growing tumours for whom the aim is to relieve symptoms. It is for this reason that different types of treatment are appropriate for these two clinical types of tumour.

Aggressive NHL. Diffuse B cell lymphomas are typically aggressive tumours. These are usually treated with injections of several types of intensive chemotherapy given at three weekly intervals for a total of six cycles (one course). Several courses may be given. A frequently used combination chemotherapy regimen is CHOP (cyclophosphamide, doxorubicin, vinicristine, prednisone). During most of this time the patient remains an outpatient, but requires close monitoring in case an infection due to febrile neutropenia (low white blood cell count with fever) develops as a side effect of the treatment. If an infection does develop, the patient requires intravenous antibiotics as this may be rapidly fatal in the absence of treatment. During chemotherapy, the patients lose all their hair, but the problem of nausea (emesis) has been reduced by the advent of effective, but expensive, modern antiemetics such as ondanestron.

Indolent NHL. Follicular lymphomas are typically indolent tumours. Other types include chronic lymphocyte leukaemia (CLL) and mantle cell lymphoma. These are usually treated with mild but effective chemotherapy, such as chlorambucil, which aims to reduce the size of the lymph glands and reduce symptoms. This treatment is usually through tablets taken for six days every four weeks for six to eight months. They are not usually associated with emesis, have only minimal effects on the hair and do not suppress the blood counts, such that life threatening infections are less of a problem than with intensive chemotherapy injections. However, more intensive chemotherapy (e.g. CHOP) possibly administered on an inpatient basis may be used in the 60% of patients who relapse after first line chemotherapy.

In order to help define the type of treatment required, in addition to a biopsy, the extent of the tumour in the body is determined by a process known as staging. This involves a CT scan to look at lymph gland swellings which cannot be felt by the doctor during a clinical examination. This is a specialised service which is best operated by a radiologist with an expertise in this area. An example of how staging may effect treatment is that if only a single lymph gland swelling is present

then some patients can be treated with radiotherapy alone. The CT scan can also be useful to monitor the effects of treatment. After two or three cycles of chemotherapy, the scan is repeated to determine the swellings are decreasing in size. If the swelling is still detectable this is known as a no or partial response to chemotherapy (or partial remission). At the end of treatment a scan will be used to confirm the complete removal of the swelling, where there is no evidence of residual lymphoma. If this is the case a complete response or remission (CR) to treatment has been achieved.

With aggressive NHLs more than 80% of patients achieve a response to chemotherapy, although this does not always result in a cure and long term survival. The cure rate depends on the histology of the tumour, and the extent of the tumour in the patient and ranges from 40-70%. If the patient relapses and the lymphoma returns after treatment, there is still the potential for cure with more intensive chemotherapy. This tends to be more toxic and more expensive, but does produce a substantial number of cures. It is at this point that autologous bone marrow transplantation (ABMT) is considered in patients with chemotherapy responsive tumours. If the patient has achieved CR through conventional chemotherapy, ABMT may be used to consolidate this. The aim of the approach is to achieve a cure from the cancer or long term treatment-free survival, and is used in younger patients (under 65 years or an even lower age limit) who can tolerate the treatment. Once there are no signs of cancerous lymphocytes, highly intensive chemotherapy is used to remove even the least cancerous cell. In the absence of a transfusion of the patient's bone marrow, the blood cells would not return. The process is also called bone marrow rescue as the bone marrow infused rescues the patient from the effects of the intensive chemotherapy. ABMT should be provided within a specialist unit with adequate infrastructure and nursing support to ensure that the appropriate level of patient care and support is provided.

There is some uncertainty about the efficacy of these treatments, although the few small clinical trials (Johnson et al., 1998) that have been conducted suggest 10-20% improvement in cure or survival rate for patients receiving ABMT following high dose chemotherapy compared to the use of a standard course of less intensive and less toxic chemotherapy only (the 20% figure has been used in the cost assessment in section 7).

For indolent tumours, cures are rarely if ever achieved. Patients with this type of NHL tend to be older (over 65 years) and the aim of treatment is to maintain the patient symptom-free in a complete or partial remission. Half the patients survive in this state with minimal treatment for between eight and ten years, and often die of other causes not related to their lymphoma. For younger patients, even

though survival periods are reasonably long, current treatments are aimed at increasing the duration of survival and hopefully to produce true cures. It is for these younger cases that bone marrow transplantation is an option, with the aim of increasing treatment-free survival time.

Certain types of lymphoma, for example hairy cell leukaemia, have specific treatments which have been shown to be particularly appropriate. These, however, are rare tumours which, although individually expensive to treat, do not have significant economic or epidemiological implications and so are not addressed in this review.

NHL treatment is focused on the use of various chemotherapy regimens following diagnosis. Chemotherapy and ABMT are often used but are costly interventions. Currently, much clinical research is being undertaken to assess the impacts of alternative intensive chemotherapy regimens and bone marrow transplantation on cure rate and duration of remission. It has also been found that cell growth factors which act on the blood cells may lessen the toxicity and side effects endured by the patient. In particular, a glycoprotein hormone called G-CSF (recombinant granulocyte colony stimulating factor) is a relatively new development that can be used prophylactically to reduce duration of chemotherapy-induced febrile neutropenia, thereby reducing hospital inpatient stay and use of antibiotics (see review by Goa and Bryson, 1994 and review in section 6.3 of this booklet). G-CSF may not produce savings to the health care system if the decreased toxicity of intensive chemotherapy means more patients with lymphoma are able to tolerate such treatment. Therefore, the main benefit of G-CSF for NHL patients may be in terms of health related quality of life, which has not to date been evaluated.

An area of development which is showing promise and may in the relatively near future reduce or avoid the need for intensive chemotherapy for NHL, is the use of therapeutic antibodies which specifically target the lymphoma. Another development that is also showing promising results in the laboratory is the use of 'antisense' treatment. These small DNA molecules can specifically target the lymphoma and may be used to improve the effectiveness of standard chemotherapy. These developments are likely to add to direct cost pressures of treating NHL, but if they increase the chance of cancer cure then the patient quality of life gains and resource use savings that would be generated could make such interventions highly cost-effective.

Palliative care offers a potential care option in particular for elderly patients with aggressive tumours who cannot tolerate intensive chemotherapy. This consists mainly of home care services and pain relief provided by a range of specialists in terminal care, but can also involve admission to hospices. The range of specialist care adds to the

costs of treatment and care, but provides quality of life benefits for terminally ill patients. A limiting factor for total NHL costs is the survival time of the patient. However, the main burden for those who die quickly is not on health care resources, but the loss of lives and life years to the individual, their family and society.

In the next section, estimates of the lifetime costs (i.e. from diagnosis to death or end of treatment) of different groups of NHL patients are provided. These costs should be set in the context of the wider mortality and morbidity burden of the disease.

5 THE ECONOMIC ASSESSMENT OF DISEASE

5.1 Types of analysis

There are two main approaches that have been used for the economic analysis of diseases:

Analysis of the economic burden of disease. A cost-of-illness (COI) evaluation is employed to measure the direct costs of a disease (e.g. hospital treatment and care, primary care, social care, costs incurred by patients and family) and the indirect costs associated with lost economic and (sometimes) social productivity resulting from premature mortality and morbidity associated with a disease.

Analysis of efficiency in the use of resources for the treatment and care, cure or prevention of a disease. This involves the use of one of the main recognised forms of economic evaluation for measuring efficiency in the allocation and use of resources: cost analysis, cost-benefit analysis, cost utility analysis, cost effectiveness analysis and cost-minimisation analysis. Table 5.1 summarises the main features of each type of economic analysis.

Our cost estimates of NHL reported in section 7 of this booklet represent a direct cost assessment, which can be located in the box in the top left-hand corner of Table 5.1. In this table a distinction is made between cost evaluations and full economics evaluations. The main difference between these is that in full economic evaluations the clinical and/or health outcomes of treatment interventions are related to the costs and cost consequences of each intervention. In a COI study only the economic burden of disease, measured in monetary terms, is determined and the health outcomes of interventions are not assessed (Rice et al., 1985; Hodgson, 1984). Such studies can be useful for illustrating the economic importance of diseases, aid health care resource and budget planning, especially if the separate components of direct costs are identified, and used as a basis for developing scenarios of the future cost burden of disease (Drummond 1992, Ament and Evers, 1993). However, the lack of measurement of the effectiveness of health care interventions in a COI study has led to them being severely criticised by many economists (Shiell et al., 1989; Drummond, 1992; Davey and Leeder, 1992).

As COI studies do not include any assessment of the health or other benefits of interventions they cannot be used to determine if an increase or decrease in resources allocated to the treatment, care or prevention of a disease would substantially alter individual patient and population health outcomes. One danger in presenting COI

Table 5.1 **The types of economic analysis**

Cost evaluations	
Cost of Illness Study (COI)	***Cost Analysis (CA)***
Direct and indirect costs of disease/condition measured in £'s/$'s etc.	Costs and cost consequences of treatment interventions measured in £'s/$'s etc.
The direct costs of treatment and care (and sometimes indirect costs of lost productivity) associated with a disease/ condition are assessed.	The direct (and sometimes indirect) costs/ cost consequences associated with treatment interventions compared to an alternative are assessed.
Full economic evaluations	
Cost Minimisation Analysis (CMA)	***Cost Effectiveness Analysis (CEA)***
Costs/cost consequences of treatment interventions measured in £'s/$'s etc.	Costs/cost consequences of treatment interventions measured in £'s/$'s etc.
Outcomes measured in natural units e.g. life years gained, reduction in cholesterol level.	Outcomes measured in natural units e.g. life years gained, reduction in cholesterol level.
Effectiveness of alternative treatment interventions are the same. Programmes assessed by comparing costs/cost consequences.	Treatment interventions assessed by comparing differences in costs per unit of outcome.
Cost Utility Analysis (CUA)	***Cost Benefit Analysis (CBA)***
Costs/cost consequences of treatment interventions measured in £'s/$'s etc.	Costs/cost consequences of treatment interventions measured in £'s/$'s etc
Outcomes measured using health utility scales such as quality adjusted life years (QALYs).	Health and related benefits valued in £'s/$'s etc.
Treatment interventions assessed by comparing difference in costs per QALY gained.	Treatment interventions assessed by comparing net benefit, or benefit to cost ratio.

results is that they may mislead decision makers in giving resource allocation priority to diseases with the highest economic cost, rather than to the interventions that can reduce the health burden of disease by the greatest amount for a given cost.

Criticisms have also been levelled against the measurement of indirect costs in COI studies using the human capital approach, which unrealistically assumes the loss of work productivity due to death or

ill-health is permanent. Recently, it has been advocated that only 'frictional' indirect costs associated with the time it takes to replace a member of the workforce should be measured in COI studies and economic evaluations, although this poses additional measurement difficulties (Koopmanschap MA, Van Ineveld, 1992). A further argument against indirect cost assessments is that they add nothing to assessments of life years lost or morbidity data.

Given the controversy and measurement problems with indirect costs, it is maybe preferable in COI evaluations to focus efforts on direct cost assessment, where a breakdown of expected costs of treatment and care for a disease can help planning of current and future resource needs. The cost per case and total cost of a disease can be evaluated using a prevalence or incidence approach. The prevalence approach measures all the costs associated with a disease at one point in time, usually covering a year, whilst the incidence approach measures costs associated with a disease from diagnosis to death, end of treatment or cure (Hartunian et al., 1980). The two approaches produce the same total cost and cost per case if the natural history of the disease is less than one year, or for chronic diseases such as rheumatoid arthritis or diabetes. The prevalence approach will enable treatment and care costs in any one year to be determined, which could assist annual budget planning. However, for acute diseases such as most cancers the incidence approach is useful for identifying high cost aspects of treatment and care over the course of a disease, and assessing the avoidable costs from preventing new cases of the disease.

5.2 Economic evaluations

Even if COI studies, primarily direct cost studies, have some merits, they are not considered by health economists as important as full economic evaluations, especially as research resources are also scarce. Economic evaluations can help decision makers set priorities for resource allocation. Each economic evaluation technique outlined in Table 5.1 can be used for a different resource allocation purpose. A cost analysis is only a partial economic evaluation, as direct measurement of intervention effectiveness on patient outcomes is not typically undertaken (only the resource savings that potentially could be made). However, cost analyses may include an assumption regarding the relationship between resource utilisation and patient outcomes.

Cost minimisation or cost effectiveness analysis could be used to identify which intervention for the treatment, care or prevention of a disease produces a specific patient outcome at least cost (known as technical efficiency in the use of resources).

Cost utility analysis (CUA) could also be used for this purpose, but is primarily intended for comparing different health care programmes

across diseases, in the pursuit of maximum population health gain (usually measured in quality adjusted life years – QALYs) for the available resources (known as productive efficiency). Cost per QALY gained estimates of new treatment interventions versus standard treatments can be generated to compare, with caution, against cost utility estimates for other health care programmes (Mason et al., 1993). This aids decision makers judgement over their relative value, but does not allow precise specification of which intervention is the most worthwhile investment.

Cost benefit analysis (CBA), by using monetary values for both costs and benefits, can be used to directly assess the value of investments or disinvestments in specific interventions, in absolute terms or relative to other interventions. Health benefits are valued using a method whereby patients (or members of the public) are asked to express the maximum amount they would be willing to pay for the benefit expected from a treatment intervention (Gafni, 1991). Alternatively, indirect benefits of the expected gains in productivity from the impact the intervention has on preventing premature mortality or morbidity could be valued. For this the same caveats as outlined for measurement of indirect costs apply.

Economic evaluations are particularly valuable for diseases for which there exist treatments which have a high cost per case, or where there are high numbers of cases producing a high total cost. They are also important when there is uncertainty over the efficacy, effectiveness and efficiency of existing or new treatments. These situations exist in oncology (Bonsel et al., 1993). For example, high dose chemotherapy with autologous bone marrow transplantation is a relatively new treatment strategy. Because of its high cost per case and uncertain effectiveness, the allocation of resources to this procedure as a standard therapy would benefit from evaluation of its incremental (i.e. additional) costs and effects relative to the incumbent course of action.

Assessments of the costs and cost consequences of interventions are best performed within an economic evaluation (Hodgson, 1994), but direct cost assessments do at least provide data to identify aspects of treatment and care for a disease which are high cost and hence merit further investigation of cost effectiveness.

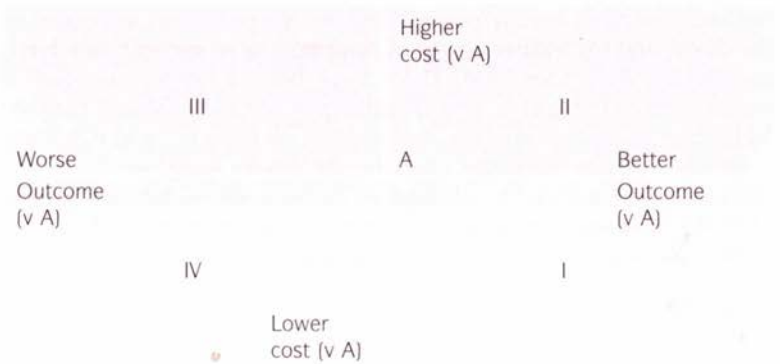
5.3 Interpreting relative cost effectiveness

A graphic representation of cost effectiveness is useful for interpreting the results of economic evaluations of health care interventions (Laupacis et al., 1992; Black, 1990). Figure 5.1 shows costs and cost consequences on the vertical axis and clinical/health outcomes on the horizontal axis. Using this the cost effectiveness of a new therapy can

be assessed relative to the costs and outcomes associated with an existing treatment for a disease, which is represented by point A. Figure 5.1 has four segments for interpreting relative cost effectiveness of a new treatment, such as high dose chemotherapy. A new treatment located in segment I can be considered cost-effective relative to the alternative A. If it falls into segment III it cannot be considered to be cost-effective relative to A. Segments II and IV represent areas of potential relative cost effectiveness. It may be difficult to justify a treatment in segment IV which produce economic benefits (i.e. reduced net costs), but has poorer clinical or health outcomes than the current treatment. A treatment intervention in segment II requires careful consideration by the decision maker (e.g. the clinician, hospital manager or health care purchaser) as to whether the extra benefits are worth the extra costs of achieving them. This is likely to depend on the type of outcomes measured and budget constraints faced. The costs and outcomes can be narrowly defined or, preferably, be comprehensive. In the latter case all the relevant costs and cost consequences of a new technology for cancer treatment would be included and health outcomes (e.g. survival, quality of life, QALYs) would be measured.

Figure 5.1 is useful for interpreting the results of full economic evaluations (but not cost studies), as is illustrated in the section 6 review of economic studies of treatments for NHL patients.

Figure 5.1 **Interpreting relative cost effectiveness**



Source: Modified from Laupacis et al. (1992)

6 ECONOMIC ANALYSES OF NON-HODGKIN'S LYMPHOMA

6.1 Literature search

Economic analyses that have been conducted in the field of oncology have primarily been directed at a few important cancers, such as breast cancer, colorectal cancer, lung cancer and leukaemia (Gravelle et al., 1982; Whynes et al., 1993; Smith et al., 1993;). This focus is due to a combination of the large numbers involved, the high potential direct cost per case and health burden, and the potential for implementing screening and prevention programmes. For some cancers, such as leukaemia, there is a particularly emotive element related to childhood cancer that might be influencing evaluation priorities.

In general, however, analysis of the cost effectiveness of cancer programmes is difficult due to problems in designing clinical trials with sufficient sample size, representivity and duration of follow-up to measure economic and quality of life outcomes. Maynard (1993) has stated a need for more evaluations of cancer screening, primary prevention, treatment and terminal care. Most economic evaluations in the field of oncology have assessed the cost effectiveness of alternative screening interventions rather than treatment and care (Bonsel et al., 1993).

We conducted a literature search using MEDLINE and linked searches for cost analyses and full economic evaluations (published in English and covering industrially developed countries only) of interventions for NHL for the period 1982-96. No published estimates of the direct and/or indirect costs of lymphomas in general, nor NHL specifically, were identified. There have been a limited number of evaluations of the cost or cost effectiveness of treatment and care for NHL, and these are critically reviewed in sections 6.2 and 6.3. They cover the use of two relatively new treatments for lymphomas. Firstly, high dose therapy with autologous bone marrow transplantation (ABMT) is being increasingly adopted in the treatment of NHL for those who can tolerate it. Secondly, the hemopoietic growth factor, G-CSF, is targeted at reducing infections associated with aggressive chemotherapy. These interventions are interesting for economic analysis as they are perceived as potentially high cost interventions, with uncertain efficacy and effectiveness and hence uncertain cost effectiveness.

Table 6.1 **Summary of reviewed studies on cost and cost effectiveness of ABMT in the treatment and care of NHL patients**

Study	*Uyl-de Groot et al., 1995a*	*Bennett et al., 1995*	*Uyl-de Groot et al., 1995b*
Country of study	The Netherlands	USA	The Netherlands
Type of economic evaluation	Incremental direct cost assessment	Cost analysis	Cost effectiveness/ cost utility analysis
Comparison groups	ABMT v standard combination chemotherapy e.g. CHOP	ABMT or PSCT v nothing	High dose therapy and ABMT v standard chemotherapy with CHOP
Study design and year	Multi-hospital (5 university hospitals) observational assessment of resource use and costs for each group in 1992	Single hospital site (University of Nebraska Medical Center) observational assessment of costs and cost consequences associated with ABMT and PSCT 1987-91 (5 years)	Multi-hospital (10 major hospitals) prospective randomised controlled trial of costs and effects for each group, conducted between 1987-93. Markov model (model of natural history of the disease) used for modelling 8 year post treatment outcomes
Patients	25 advanced stage aggressive NHL patients in each group (unclear if or how patients were matched), with maximum 2 years follow-up	149 NHL patients selected as they had undergone high dose chemotherapy, treated with ABMT or PSCT	34 patients in the ABMT group v 35 patients in the CHOP group, with aggressive NHL who were newly diagnosed and untreated. 21 patients in each group selected for costs analysis, and at 2 year follow-up maximum of 7 ABMT v 13 CHOP patients completed each quality of life questionnaire

Table 6.1 **Summary of reviewed studies on cost and cost effectiveness of ABMT in the treatment and care of NHL patients** ***(continued)***

Study	*Uyl-de Groot et al., 1995a*	*Bennett et al., 1995*	*Uyl-de Groot et al., 1995b*
Costs measured	Costs of ABMT, hospital inpatient days, outpatient visits, diagnostic tests and investigations, drugs (including chemotherapy, antibiotics, antiemitics), blood transfusion, overheads	Not clearly specified, but includes cost of ABMT/PSCT, inpatient hospitalisation, high dose chemotherapy	Costs of ABMT, hospital inpatient, outpatient, day care diagnostic tests and procedures, drugs (including chemotherapy, antibiotics, antiemitics), overheads
Costs valuation	'Cost price studies, measuring real resource use' (actual words on p.606 of the paper) carried out in the participating hospitals (1992 $s)	Hospital resource use costs derived from University of Nebraska Medical Center financial database (calculated using Medicare 'cost to charge ratios') (1991 $s)	Costs valued 'reflecting the real use of resources' (actual words on p.464 of the paper) (1992 $s)
Outcomes measured	None	Resource savings. Predicted probability of reduction in mortality rates	Complete remission, survival, life years gained, quality of life scores/profiles, QALYs gained based on EuroQoL instrument (2 year prospective follow-up, 8 year modelled follow-up)
Results	ABMT has an incremental per patient cost of $27,410-37,100 v standard chemotherapy ($4.9 to $6.8 million for all NHL in The Netherlands)	Costs per patient declined by 8% per annum between 1987-91 (mainly due to shorter inpatient stay), and mortality rate predictions of a decline from 29% to 4% over the study period	Costs per patient of $56,512 for ABMT group v $20,397 for CHOP group. 8 year predicted outcomes = 4.49 v 5.04 life years per patient, 3.84 v 4.33 QALYs per patient, ABMT v CHOP respectively (5% discount rate for costs and effects (0% also used))

Table 6.1 **Summary of reviewed studies on cost and cost effectiveness of ABMT in the treatment and care of NHL patients** *(continued)*

Study	*Uyl-de Groot et al., 1995a*	*Bennett et al., 1995*	*Uyl-de Groot et al., 1995b*
Main limitations	1. Small patient numbers 2. Unclear criteria for matching patients in each treatment group 3. Uncertain method of cost valuation	1. Lack of control group to compare costs of ABMT v no ABMT 2. The types of costs included in evaluation were not specified 3. No discounting of costs	1. Small patient numbers, especially for the resource use and quality of life measurement 2. No baseline measurement of quality of life 3. Uncertain method of cost valuation

6.2 Autologous bone marrow transplantation

Three economic analyses of ABMT with NHL patients were identified. Only one represented a full cost effectiveness analysis (Uyl-de Groot et al., 1995b) according to the classification in Table 5.1. All the studies related to aggressive and not indolent NHL. The methods, results and main limitations of each study are summarised in Table 6.1.

A study by Uyl-de Groot et al. (1995a) had the objective of estimating the additional hospital resource requirements associated with the substitution of ABMT for standard chemotherapy (several regimens were used) in The Netherlands for patients with aggressive NHL who were at an advanced treatment stage. Resource utilisation for 25 patients receiving ABMT was compared with utilisation by 25 patients receiving standard chemotherapy. The estimated mean cost per patient associated with ABMT was $40,220 (1992 US dollars), which was between 2.5 to 10 times greater than the mean costs of conventional chemotherapy. Over 50% of ABMT costs were associated with inpatient and outpatient care. The authors used a figure of an expected 180 ABMTs required in The Netherlands per annum to estimate an incremental cost of $4.9 to $6.8 million if ABMT were to replace conventional chemotherapy in these cases.

Despite the small numbers in this study and unclear criteria for patient selection and matching, it does give some indication of the extra cost associated with the use of ABMT. Evidence of a positive incremental cost means that for ABMT to be considered cost-effective there needs to be sufficient benefits to justify the extra resources required (see section 5.4 and Figure 5.1). Evidence from two econom-

ic studies (one cost analysis and a cost effectiveness analysis) was reviewed to examine whether a case exists based on existing published evidence for the cost effectiveness of ABMT.

A US study examined the cost and cost consequences of the use of ABMT or peripheral stem-cell transplantation (PSCT – an alternative to ABMT), combined with high dose chemotherapy for patients with Hodgkin's disease or NHL (Bennett et al., 1995). Over the period 1987-91 the total mean costs of hospital treatment for 149 NHL patients treated with ABMT or peripheral stem-cell transplantations decreased by 8% per year from $91,000 per patient in 1987 to $74,000 per patient in 1991, due mainly to a reduction in inpatient utilisation. In the same study the mean costs over the same period for 178 Hodgkin's disease patients also decreased, by 10% per year from a higher cost per patient of $96,000 to $55,000. Alongside this a regression analysis predicted a mortality rate of 29% for patients with NHL in 1987, decreasing to 4% in 1991 (a similar decline was found for Hodgkin's Disease).

The results of this study are suggestive of the economic benefits of ABMT or PSCT as a treatment option for NHL. However, the study is insufficiently rigorous to conclude this, and to enable interpretation of the findings from this study using the cost effectiveness graph in Figure 5.1. Bennett et al. identified a reduction in mortality rate from ABMT/PSCT and the cost of treatment for later stage NHL patients, but a lack of control group receiving the best or standard alternative treatment (to represent point A), means it is not possible to assess into which segment of Figure 5.1 ABMT for these patients would fall, and thereby to determine its relative cost effectiveness.

In a second paper by the Dutch study team, Uyl-de Groot et al. (1995b) investigated the cost effectiveness and cost utility of high dose therapy and ABMT compared with standard CHOP chemotherapy for patients with aggressive NHL who were newly diagnosed and untreated. Using a prospective randomised controlled trial design, 69 patients between 1987-93 were randomised to the two treatment groups. Over a median follow-up period of 36 months there was no statistically significant differences between the CHOP and ABMT groups in the percentage achieving complete remission (71% v 68% respectively) and disease free survival (77% v 60% respectively).

The assessment of cost effectiveness and cost utility was similarly unfavourable for ABMT. There were improvements for both treatment groups in health related quality of life measured at 6 months, 1 and 2 years using two generic instruments, (the Karnofsky Performance Index and the Nottingham Health Profile), a disease specific measure (Rotterdam Cancer Symptom Checklist – this really measures disease symptoms rather than broader health-related quality of life) and a utility based instrument (EuroQol). As no baseline measure was reported it is difficult to assess total benefits although for six months

to two years the mean utility based quality of life scores from the EuroQoL showed a larger increase for the ABMT group. However, when the utility data were combined with survival data in a Markov model to estimate eight year survival and QALYs, mean outcomes were slightly better for the CHOP group (at 5.04 v 4.49 discounted life years and 4.33 v 3.84 QALYs) . Overall, the ABMT group demonstrated no better outcomes than the CHOP group whilst estimated hospital costs for the former were significantly higher. For ABMT, cumulative costs over this period were estimated at $56,512 compared to $20,397 for the CHOP group (1992 US dollars, 5% discount rate).

Interpreting the results from this study in terms of Figure 5.1, if standard chemotherapy is represented by point A, ABMT for previously untreated NHL patients is in segment III (not cost-effective) due to higher relative costs and poorer life years and QALY outcomes. As AMBT was found to be no more effective than existing treatment practice but far more costly, a cost per QALY gained estimate could not be generated and, on this basis, the treatment should not be considered for scarce health care resources.

However, this conclusion depends on the quality of the evidence. The main limitations of the Dutch study were the small numbers involved. Resource use data was abstracted from the medical records of only 21 patients in each of the ABMT and CHOP groups in order to estimate costs, although the difference in mean cost for the short-term follow-up period were statistically significant. The quality of life results were based on data for only seven patients in the ABMT and 13 patients in the CHOP group at two year follow-up, with no information on whether differences were statistically significant. The small numbers means it would be difficult to determine a clinically significant improvement in the quality of life scores, and therefore it is unlikely that the study would have sufficient power to detect a difference in QALY outcomes.

No published economic evaluations of ABMT for NHL were identified for the UK. Currently, the evidence for its cost effectiveness in this patient group in the UK is lacking, and the limited evidence from other countries is inconclusive. The studies reviewed in this section have suffered from small patient numbers, uncertain methods for estimating unit costs (see Table 6.1), and a lack of general rigour in the study design. It is therefore important that before this technology diffuses further within the UK NHS, a full and rigorous economic evaluation of the use of ABMT for lymphoma treatment is conducted (see section 8). A systematic review of the effectiveness of high dose therapy and ABMT by the NHS Centres for Reviews and Dissemination (York University) due to be published in 1998 could provide the first steps toward this end (Johnson et al., 1998).

6.3 Use of G-CSF in NHL treatment

The aim of adding G-CSF after a course of chemotherapy is to manage drug induced neutropenic fever, thereby reducing the probability of infections, related inpatient stays and use of antibacterial medication. In the literature search, two cost analyses and a cost-benefit analysis (according to the definitions in Table 5.1) were identified. The methods, results and limitations of each study are summarised in Table 6.2.

In a single hospital Canadian study resource use data was collected from the medical records of patients with NHL or Hodgkin's Disease (Dranitsaris and Sutcliffe, 1995). The hospital costs of 19 patients who received G-CSF were compared with a control group of 33 patients who received only chemotherapy (both patient groups received one to three courses of mini-BEAM salvage chemotherapy). Another study assessed the costs of adding G-CSF on an outpatient basis following chemotherapy for elderly patients with aggressive NHL (aged 60-70) in an Italian hospital during 1990-92 (Zagonel et al., 1994). A small controlled trial was used to compare the overall estimated hospital treatment costs (for hospital days, antibiotic/antifungal medication, diagnostic tests and investigations, and G-CSF) for 12 patients receiving G-CSF and 11 patients who did not, with patients matched according to age and clinical characteristics. All patients received CHVmP/VB chemotherapy (thought by the authors to be better tolerated than CHOP).

Despite different study designs, the main results from both studies were a reduction in hospitalisation, antibiotic use and level of patient monitoring in patients given G-CSF compared to control patients. However, any cost savings this produced were offset by the additional costs of G-CSF. In the Canadian study the main finding was of no statistically significant difference in net costs per patient for the two groups. In the Italian study the mean costs for the G-CSF group were 1.5 time higher than the control group (13,301 ECUs v 8,441 ECUs, cost year uncertain). Dranitsaris and Sutcliffe (1995) argued that G-CSF appeared to be a worthwhile use of resources as cost neutrality is likely to be coupled with benefits of improved quality of life for patients, and greater independence due to a reduced need for hospitalisation. Zagonel et al. (1994) concluded, somewhat optimistically, that if G-CSF became more routinely used in practice for NHL patients undergoing aggressive chemotherapy, the diffusion of this technology and experience in its effective use could reduce the cost gap identified in their study.

Similar findings have been found from cost analyses of G-CSF used in the management of Hodgkin's disease (Goa and Bryson, 1994). However, the evidence for both NHL and HD patients is not conclusive concerning the cost effectiveness for G-CSF due to small patient

Table 6.2 **Summary of reviewed studies on cost and cost-benefit of the use of G-CSF for the management of chemotherapy-induced febrile neutropenia in NHL patients**

Study	*Dranitsaris and Sutcliffe, 1995*	*Zagonel et al., 1995*	*Dranitsaris et al., 1997*
Country of study	Canada	Italy	Canada
Type of economic evaluation	Cost analysis	Cost analysis	Cost-benefit analysis
Comparison groups	300 mg G-CSF over 10 days v standard chemotherapy alone (with mini-BEAM salvage chemotherapy)	250mg G-CSF provided on an outpatient basis over 10 days v standard chemotherapy alone (with CHVmP/VB chemotherapy)	G-CSF provided over 11 days v CHOP chemotherapy alone
Study design and year	Single hospital observational design of resource use and costs. Data drawn from patient medical records, 1993	Single hospital site controlled trial of resource use and costs. Data collected June 1991-December 1992	Single hospital observational design for the resource use data and costs associated with febrile neutropenia (collected retrospectively from patient medical records between 1985-95), phase II trial for G-CSF efficacy data (febrile neutropenia incidence and outcomes), and modelling of the economic benefits of G-CSF

Table 6.2 **Summary of reviewed studies on cost and cost-benefit of the use of G-CSF for the management of chemotherapy-induced febrile neutropenia in NHL patients** *(continued)*

Study	*Dranitsaris and Sutcliffe, 1995*	*Zagonel et al., 1995*	*Dranitsaris et al., 1997*
Patients	19 patients in the G-CSF group and 33 patients in the chemotherapy only group. Patients were those with NHL who previously had at least received a course of mini-BEAM salvage chemotherapy. G-CSF given after each chemotherapy course, with up to 3 courses given. After 3rd course costs for 12 patients in G-CSF group v 8 in chemotherapy only	12 patients in the G-CSF group and 11 patients in the chemotherapy only group. Patients aged 60-70, with aggressive NHL, matched across the groups according to age and clinical characteristics. Each group received 3 courses of chemotherapy	24 patients randomly selected from medical records with aggressive NHL treated with CHOP chemotherapy provided the resource use data. 20 patients in a phase II trial provided the efficacy data
Costs measured	Costs of G-CSF, hospital inpatient care (including overheads), antibiotic support, patient monitoring, laboratory tests, chemotherapy. Measured after each chemotherapy course (up to 3 courses)	Costs of G-CSF, hospital inpatient care, antibiotic and antifungal support (for chemotherapy only group), neutropenia antibiotics, tests and investigations	Direct costs of G-CSF, hospital inpatient care, antibacterials, tests and investigations, and therapeutic drug monitoring costs. Indirect costs of lost work time and of patient transport to hospital

Table 6.2 **Summary of reviewed studies on cost and cost-benefit of the use of G-CSF for the management of chemotherapy-induced febrile neutropenia in NHL patients** *(continued)*

Study	*Dranitsaris and Sutcliffe, 1995*	*Zagonel et al., 1995*	*Dranitsaris et al., 1997*
Costs valuation	Costs of resources obtained from hospital departments. Retail prices used for antibiotics (1993 $Can)	Unit costs of resources stated in paper, but source not specified and year of costs unclear	Costs of resources obtained from hospital departments, hospital inpatient cost from Ontario Hospital Association, G-CSF acquisition cost from hospital outpatient pharmacy. Indirect costs valued using average wages using national Canadian wage data (costs in 1995 $Can)
Outcomes measured	Resource savings	Resource savings due to reduced hospitalisation. Courses of chemotherapy delayed due to infections from febrile neutropenia or toxicity, and mean days of delay	Three benefit measures: (1) Cost savings from preventing a case of febrile neutropenia. (2) Societal reduction in indirect costs of lost working time. (3) Reduction in cost of delaying further chemotherapy treatment due to febrile neutropenia

Table 6.2 **Summary of reviewed studies on cost and cost-benefit of the use of G-CSF for the management of chemotherapy-induced febrile neutropenia in NHL patients** ***(continued)***

Study	*Dranitsaris and Sutcliffe, 1995*	*Zagonel et al., 1995*	*Dranitsaris et al., 1997*
Results	After 3 courses maximum of chemotherapy, G-CSF costs per patient were $Can4,682 v $Can4,753 for chemotherapy only (not a statistically significant difference)	Costs per patient for the G-CSF group were 13,301 ECUs v 8,441 ECUs for the chemotherapy only group. Fewer delays in chemotherapy due to febrile neutropenia in the G-CSF group (10/83 delayed, mean days delayed 10.1) v chemotherapy group (20/83, mean days delayed 25.9). Differences statistically significant	In baseline analysis, cost of G-CSF and CHOP chemotherapy was $Can15,090 per patient. Benefits were: (1) $Can5,007 cost saving if a case of febrile neutropenia was prevented. (2) $Can8,016 indirect cost saving from reduction in lost working days. (3) $Can810 saving if delay in further CHOP therapy avoided. Net cost = $Can1,257. In a sensitivity analysis most optimistic result (lower G-CSF dose, greater benefits) was net benefit of $Can6,564. Most pessimistic result (for higher G-CSF cost) was net cost of $Can2,287
Main limitations	1. Small patient numbers 2. Unclear patient follow-up period	1. Small patient numbers 2. Uncertain source of costs and methods of cost valuation	1. Small patient numbers for efficacy and resource use data 2. Uncertain method of cost valuation

sample sizes in the studies. In terms of the NHL cost analyses reviewed above, assessment of cost effectiveness using the graphic representation of Figure 5.1 would require additional data on the relative outcomes of G-CSF and control groups to be presented and linked to the cost estimates provided.

Recently, the most extensive economic evaluation to date of G-CSF administered with standard chemotherapy for NHL patients has been conducted by Dranitsaris et al. (1997) in a Canadian setting. This study can be classified as a cost benefit analysis according to the definition in Table 5.1, as the major costs and benefits (measured in monetary units) to society of the intervention were evaluated. These include: the direct monetary benefits of reducing hospital inpatient and drug costs associated with a reduced number of episodes of neutropenia; savings associated with delaying further chemotherapy; and also the indirect work productivity benefits of enabling NHL patients receiving a course of chemotherapy to continue in employment. Data on the clinical efficacy of G-CSF in reducing neutropenia after a course of CHOP chemotherapy was derived from a small phase II clinical trial of 20 patients with NHL. Resource use data related to netropenia was derived from the retrospective records of 24 randomly selected NHL patients treated between 1985-95 in a single Canadian hospital.

The mean cost per patient of G-CSF associated with a course of CHOP was estimated at $15,090 (1995 Canadian dollars). Against this the value of benefits were estimated using different assumptions for number of G-CSF doses, dosage, and cost of treating neutropenia. In a baseline analysis, offsetting the costs of G-CSF by the value of benefits resulted in a net societal cost of $1,257, and under more optimistic assumptions in the sensitivity analysis net benefits of over $6,500 per patient were estimated.

Interpreting the results from this study in terms of Figure 5.1, under the best circumstances G-CSF represents a cost-effective option for NHL patients as the finding of net societal benefits locates the intervention in segment I of the graph. The adoption of a societal perspective increases the economic case in favour of G-CSF. However, the study suffers from a number of weaknesses which limit the strength of the findings, including the small patient numbers and the crude valuation of indirect productivity benefits using average national wages.

There is no published evidence for the UK of the cost effectiveness of prophylactic G-CSF in NHL patients. The general finding from the studies reviewed above supports an economic case for G-CSF in NHL patients, but until more extensive economic evaluation (ideally enabling a meta analysis) is carried out in this patient group this conclusion must be treated as illustrative rather than definitive.

7 ESTIMATES OF THE COSTS OF TREATMENT AND CARE FOR NON-HODGKIN'S LYMPHOMA

7.1 Costing methods

As no previous estimates exist, this section provides a first estimate of the direct costs in England and Wales of treatment and care for four categories of NHL:

(i) aggressive NHL in patients aged under 65 and given CHOP chemotherapy as first line treatment;
(ii) aggressive NHL in patients aged 65 and over and given CHOP chemotherapy as first line treatment;
(iii) indolent NHL in patients aged under 65;
(iv) indolent NHL in patients aged 65 and over.

Using Treeage decision analysis software, standard treatment pathways and clinical outcomes for 100 patients diagnosed with each category of NHL are shown in Figures 7.1 to 7.4 and are used as the basis for estimating direct costs. The pathways and proportions of patients following each path represent the typical management of NHL in the UK. They are based on literature evidence and clinical opinion, which has been summarised by one of this booklet's authors (GM).

Each tree consists of treatments and possible clinical outcomes. Each treatment/outcome has an estimated proportion of patients associated with it, i.e. the percentage of patients expected to receive a treatment and to achieve a specific outcome following treatment (e.g. 0.5 = 50% or 50 patients of the 100 diagnosed with a NHL sub-type). Each pathway ends with either: the patient's complete remission with or without cure and long term survival (no further treatment or care); complete remission and relapse to death; or the provision of palliative care to death. There is some uncertainty concerning whether high dose chemotherapy (HDT) with ABMT should be provided for patients aged under 65 (it would not be provided to patients older than 65 due to poor tolerance). Figures 7.1a and 7.3a represent treatment/outcome scenarios without HDT/ABMT, and Figures 7.1b and 7.3b show treatment/outcome scenarios with HDT/ABMT.

The expected resource inputs associated with the pathways in each tree were defined. The cost per patient of CHOP and other chemotherapy regimens, HDT/ABMT, radiotherapy and hospitalisations for febrile neutropenia associated with the toxic effect of chemotherapy, the cost per fraction for radiotherapy and the daily cost of palliative care were derived from published economic oncology studies from

Table 7.1 **Average and total costs of hospital treatment and care for NHL[1] (£1995/96)**

Type of NHL	*Expected cost per patient, £*	*Total annual incidence cost – males, £m (numbers)*	*Total annual incidence cost – females, £m (numbers)*	*Total annual incidence cost, £m (numbers)*
Aggressive, <65 years[2]	8,764 [13,200]	5.5 (627) [8.3]	3.2 (361) [4.8]	8.7 (988) [13.1]
Aggressive, >65 years	3,776	1.6 (436)	1.8 (475)	3.4 (911)
Indolent, <65 years[2]	5,429 [13,181]	2.9 (529) [7.0]	2.1 (386) [5.1]	5.0 (915) [12.1]
Indolent, >65 years	4,949	2.0 (401)	2.5 (503)	4.5 (904)
All aggressive & indolent NHLs[2]	5,728 [8,776]	12.0 (1,993) [18.9]	9.6 (1,725) [14.2]	21.6 (3,718) [33.1]

1. Based on: *Incidence data for 1984-88: an atlas of leukaemia and lymphoma*, Leukaemia Research Fund, 1990.

2. The figures in square brackets represent treatment scenarios including the use of HDT/ABMT, assumed in these cases to result in an additional 20% long term survivors (see Figures 7.1b and 7.3b).

North America and Europe. Unit costs for diagnostic inputs (biopsies, CT scan, biochemistry tests and full blood counts) were based on NHS price data from several hospitals in the Trent Health Region of England (Jane Wolstenholme, personal communication, 1997). The cost of an outpatient visit for oncology and an inpatient day was derived from the Office of Health Economics' Compendium of Health Statistics 1997. The costs of chlorambucil medication was estimated using British National Formulary (BNF) unit costs.

The full set of unit costs and assumptions used are listed in the appendix to this paper. The expected lifetime treatment and care cost (i.e. from diagnosis to death or cure and long term survival) per patient for each of the four categories of NHL were estimated using the decision analysis software and Excel spreadsheets. Based on the standard treatment pathways we have defined, Figures 7.1 to 7.4 show the expected costs for each treatment/outcome path and the proportion P of patients expected to achieve the end outcomes associated with each path (P is expressed to two decimal points – in some cases actual P is slightly higher or lower than that indicated).

The expected cost per patient and the total incidence costs (number

Table 7.2 **Expected costs per person by component of treatment and care[1]**

	Type of NHL			
Treatment	*Aggressive, <65 years[2]*	*Aggressive, >65 years*	*Indolent, <65 years[2]*	*Indolent, >65 years*
Radiotherapy	–	–	419 [318]	319
Chemo/CHOP	8,479	3,335	5,010 [4,269]	3,862
High dose therapy (ABMT)	[4,460]	–	[8,594]	–
Palliative care	285 [261]	441	–	768
Total	**8,764** **[13,200]**	**3,776**	**5,429** **[13,181]**	**4,949**

1,2. See notes for Table 7.1.

of new cases per year multiplied by the lifetime costs per patient) for males and females with NHL in England and Wales are presented in Tables 7.1 and 7.2. All costs are presented in 1995/96 values. Discounting was not performed due to the short time period of most of the costs.

7.2 Cost per patient with aggressive NHL

The expected lifetime cost per patient of the treatment and care for patients with aggressive NHL aged under 65 is £8,764, and £3,776 for patients aged 65 and over (Table 7.1). The major component of the expected costs per patient for patients with aggressive NHL aged under 65 is associated with CHOP and other chemotherapy (Table 7.2). Due to poor tolerance of chemotherapy, patients aged 65 and over are offered palliative care if first line chemotherapy using CHOP fails to produce complete remission. Depending on the treatment path followed, the cost range for patients with aggressive NHL aged under 65 is £3,335 for long term survivors due to cure after first line CHOP chemotherapy (50% of patients) to £29,660 for patients who have undergone three lines of chemotherapy followed by palliative care due to no remission or relapse (14% of patients) (Figure 7.1a). For patients with aggressive NHL aged 65 or over who do not achieve complete remission and long term survival following first line CHOP, only palliative care is provided, producing an expected cost of £3,965

Figure 7.1a **Aggressive NHL. Patients aged under 65. Without HDT/ABMT**

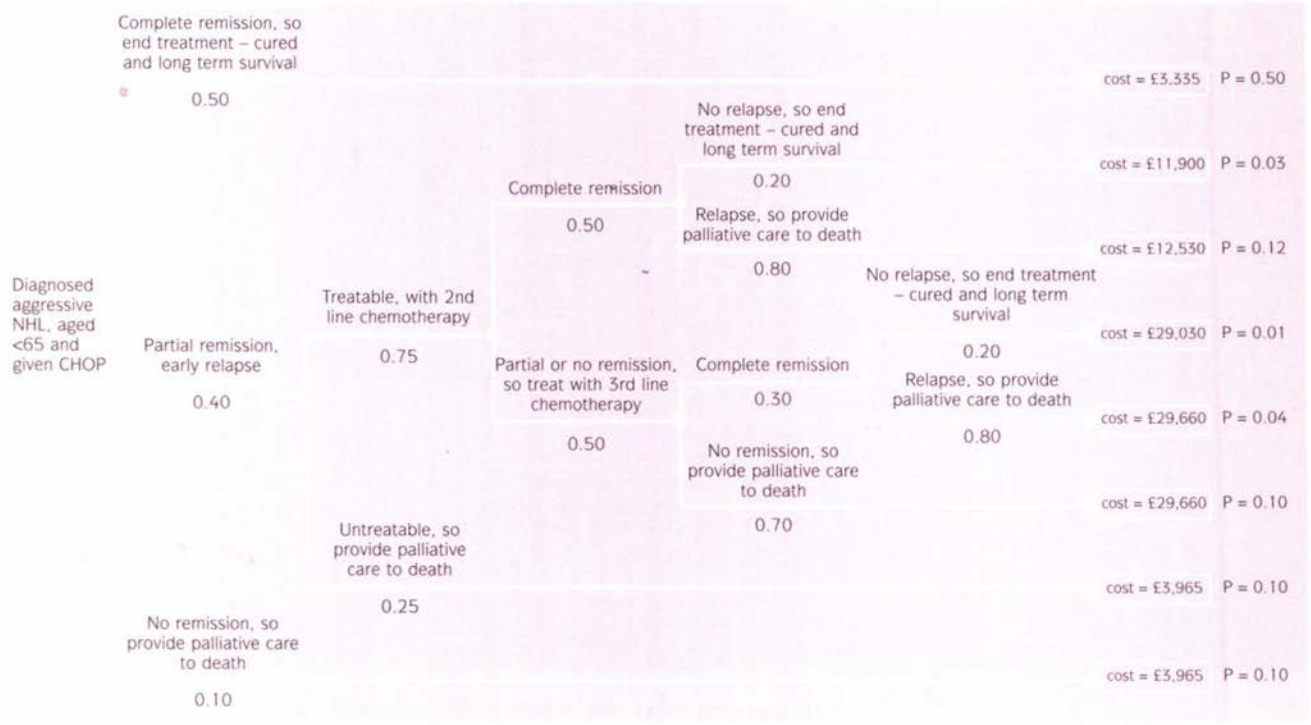


Figure 7.1b **Aggressive NHL. Patients aged under 65. With HDT/ABMT**

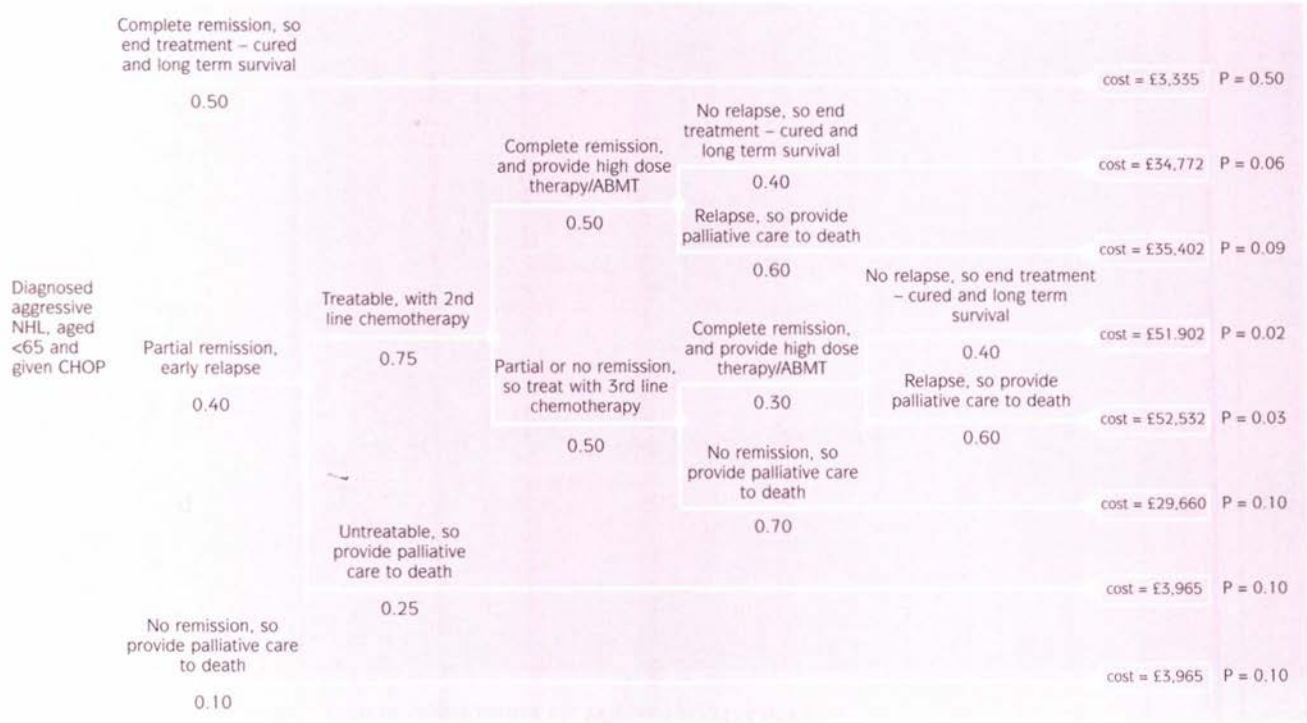
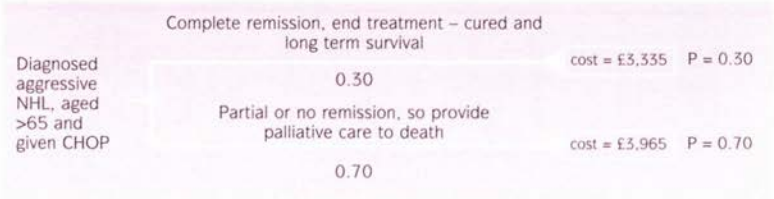


Figure 7.2 **Aggressive NHL. Patients aged 65 and over. Without HDT/ABMT**



for their treatment and care (Figure 7.2). This outcome is expected for 70% of patients.

7.3 Cost per patient with indolent NHL

The expected lifetime cost per case for patients aged under 65 is £5,429, whilst for patients aged 65 and over it is slightly lower at £4,949 (Table 7.1). For both groups the dominant cost is associated with chemotherapy. However, due to lower tolerance of chemotherapy, palliative care plays a more important part in the care of patients aged 65 and over with indolent NHL, representing approximately a fifth of the costs per patient. Only a tenth of patients with indolent NHL are assumed to be treatable with radiotherapy, and so represents a relatively low expected cost per patient (Table 7.2).

The treatment path with the lowest expected cost for patients with indolent NHL is associated with cure after initial radiotherapy (£1,100 per patient). However, this represents only 6% of patients (Figures 7.3a and 7.4). The highest expected cost treatment path is £8,254 per patient for the provision of radiotherapy, chlorambucil therapy if the patient is not cured, followed by further treatment with chlorambucil and CHOP on relapse (three relapses expected). This is provided for only an expected 1% of patients aged under 65 (Figure 7.3a) and slightly under 1% of patients aged 65 and over (Figure 7.4). For patients who do not have radiotherapy, the expected cost for both age groups is lower (£7,154), but is provided for a much greater proportion of patients: 27% of those aged under 65 and 18% of those aged 65 and over.

Figure 7.3a **Indolent NHL. Patients aged under 65. Without HDT/ABMT**

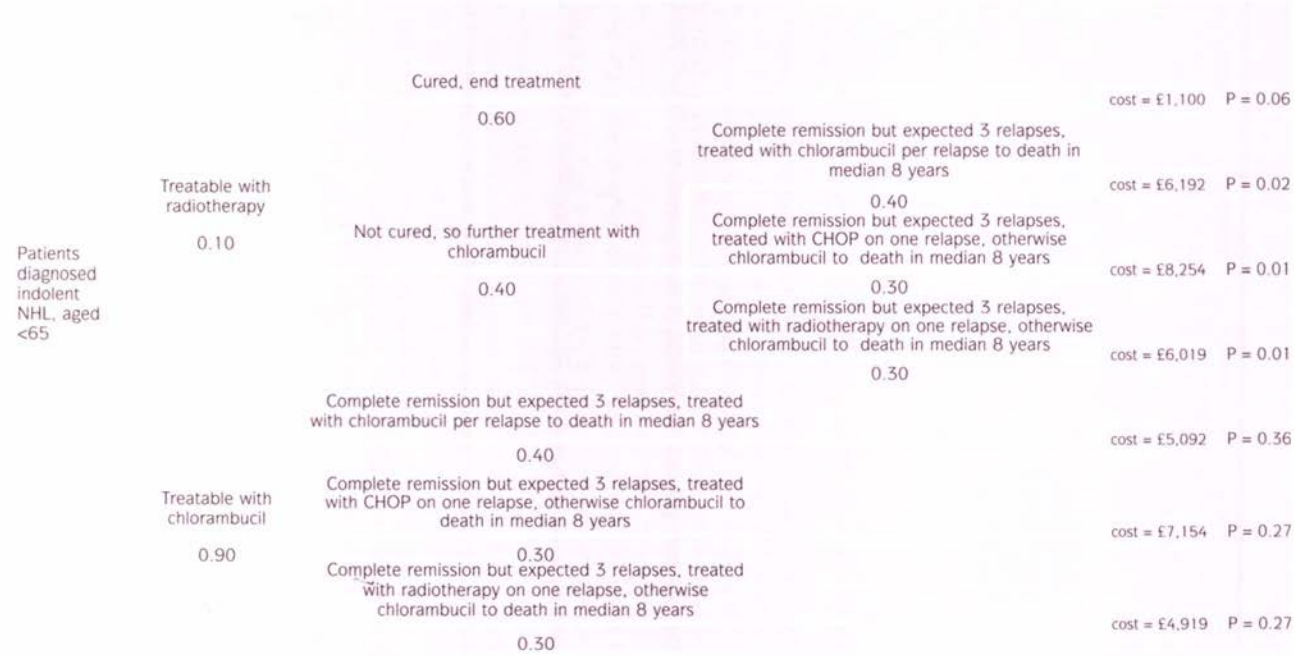


Figure 7.3b **Indolent NHL. Patients aged under 65. With HDT/ABMT**

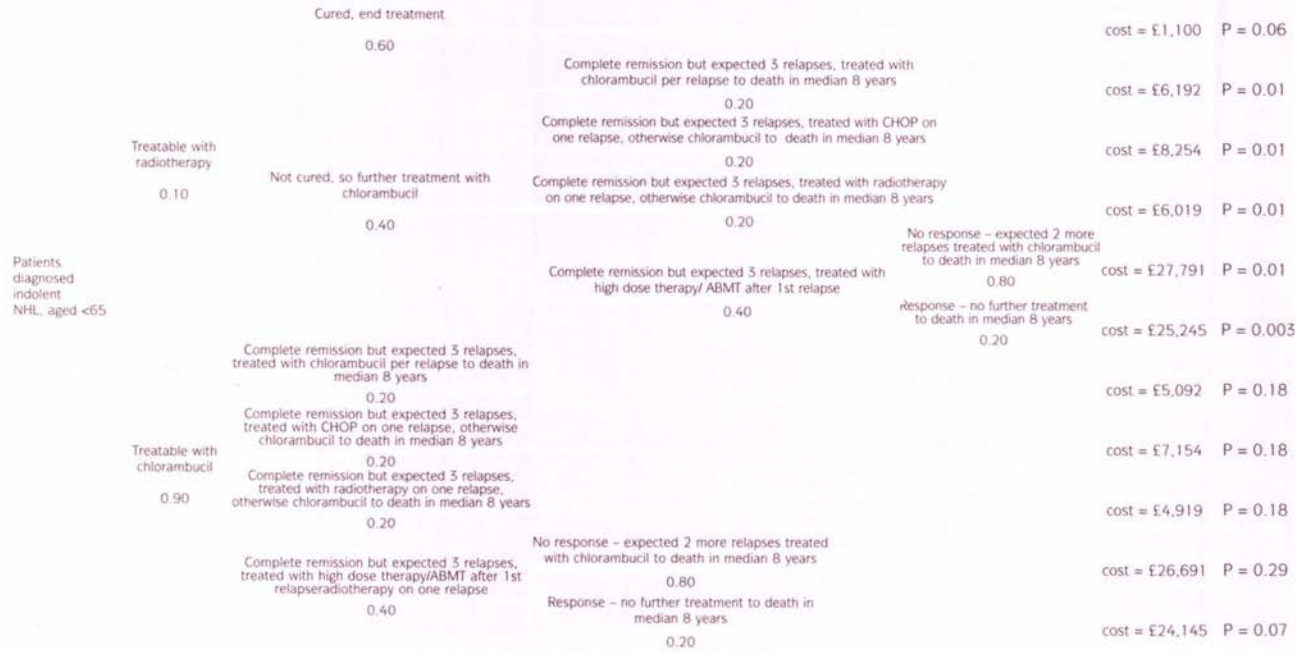
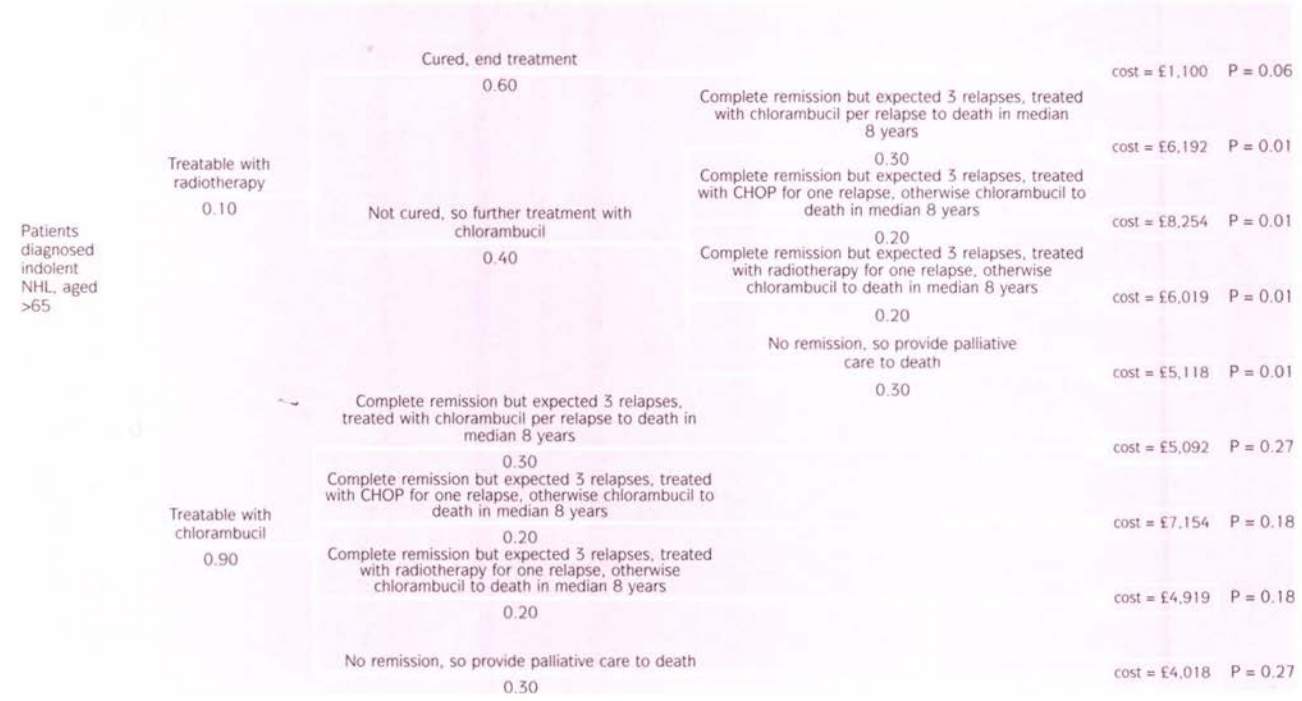


Figure 7.4 **Indolent NHL. Patients aged 65 and over. Without HDT/ABMT**



7.4 Cost per patient of including high dose therapy with autologous bone marrow transplantation

The provision of HDT/ABMT in the treatment of patients aged under 65 with aggressive or indolent NHL represents a new, rapidly diffusing and expensive treatment technology. HDT/ABMT could be provided as consolidation treatment on the first relapse after response to second line chemotherapy. Figures 7.1a and 7.3a present outcomes and costs based on treatment/outcome pathways in which HDT/ABMT is not provided. Alternatively, Figures 7.1b and 7.3b represent the expected cost and outcome associated with the provision of this treatment, assuming that there is a 20% outcome improvement e.g. 20% improvement in number of long term survivors in Figure 7.1b (representing the outcome that would be expected from clinical trials - see section 4). The effect of including HDT/ABMT is to raise expected lifetime costs per patient to over £13,000 for patients with aggressive and indolent NHL (Table 7.1). High relative costs per patient are associated with each treatment path containing HDT/ABMT in Figures 7.1b/7.3b. There is therefore an issue of whether the expected improvements in patient outcomes are worth the increased cost associated with HDT/ABMT.

7.5 Total incidence costs of NHL

Combined with epidemiological data, the expected cost estimates in the first column of Table 7.1 can be used to estimate the total cost of NHL treatment and care. Epidemiological data on the incidence of aggressive and indolent NHL are produced by the Leukaemia Research Fund for reference regions in England and Wales. The last published data covered the period 1984-88 (Leukaemia Research Fund, 1990). Standardised incidence rates by five-year age group were available, which are used to derive an estimated annual incidence for the whole of England and Wales. These are presented in round brackets in columns 2 to 4 in Table 7.1. Multiplying the annual incidence data by the expected costs per patient for each category of NHL produces an estimate of total annual incidence costs. For the whole of England and Wales this is nearly £22 million (and over £33 million if HDT/ABMT is provided). For the four categories of NHL, the highest total cost is associated with patients diagnosed with aggressive NHL aged under 65 (£8.7 million per year), due to relatively high treatment costs per case for this group. If HDT/ABMT is provided, the total incidence costs of treatment and care for patients with aggressive NHL aged under 65 is £13.1 million per year. Including HDT/ABMT in the treatment of indolent NHL raises the total cost for the under 65 group from £5.0 million to £12.1 million.

Table 7.1 also provides a breakdown of costs by males and females. The incidence of aggressive NHL in the younger patient categories is higher amongst males, resulting in greater total incidence costs. Due to the age distribution of the population, the incidence and total annual cost for patients aged 65 and over with NHL, whether aggressive or indolent, is higher for females (£1.8 million and £2.5 million respectively) than males (£1.6 million and £2.0 million respectively).

7.6 Limits to the analysis

The cost estimates presented in Figures 7.1a to 7.4 and Tables 7.1 and 7.2 are tentative estimates and should be interpreted cautiously for several reasons.

First, the cost data have been derived from several sources, in particular previous studies of the costs and cost effectiveness of standard chemotherapy and ABMT for NHL. As was shown in section 6, there have been few such studies published, and none in the UK. Most of the data were, therefore, derived from two Dutch studies and a North American study. Due to different international cost structures existing for the treatment and care of NHL patients, these estimates are not directly generalisable to the UK context. Third line chemotherapy for aggressive NHL is more intensive in the UK than in many countries, so the Dutch cost data for this has been adjusted to more closely reflect UK treatment practice and costs (see the appendix). However, in general, the published cost estimates have been used for ease of availability and to allow a general indication of the magnitude of costs for the UK.

Second, our estimates represent a minimum cost. This is because only the direct hospital treatment and care costs have been included. A complete cost estimate would include costs of primary care, social care, personal costs to the patient, family and friends and the costs of hospice care (which may be expected to be more greatly needed and so higher for more elderly patients). These costs could be substantial, especially with the shift in NHS policy to a primary care led health service. Estimates were not included as the probabilities for treatment and care and resource implications could not be reliably included in the treatment/outcome trees. In addition, not all the costs of hospital treatment and care have been included. For example, patient follow-up costs after remission from chemotherapy or ABMT have not been (fully) estimated, the cost of emesis prevention, G-CSF prophylaxis, and the costs of NHL diagnosis are not included (only costs for patients already diagnosed with NHL are estimated).

Third, the cost estimates used reflect average costs per patient treated, which is appropriate for calculating the total costs of NHL in England and Wales. Marginal costs (i.e. the additional costs associat-

ed with additional patients treated) would be more useful for assessing the cost consequences of an increase (or decrease) in the number of patients treated, for instance with a particular aggressive chemotherapy regimen (Goddard and Hutton, 1991). This is a task for further analysis.

Fourth, some cost data for resource inputs into the treatment and care of NHL patients were not directly available from literature sources. Hospital prices were used to estimate the costs of assumed numbers of outpatient visits and diagnostic tests associated with this treatment. For some resources, NHS price data have been used. These may be a poor proxy for actual costs. Although in the NHS internal market NHS prices are meant to reflect actual costs, the accounting systems in many hospitals are not sufficiently sophisticated to ensure this. In addition, NHS prices may more closely reflect local contracting arrangements rather than the actual costs of providing treatment and care.

Fifth, the treatment/outcome trees in Figures 7.1a to 7.4 are based on a combination of the authors' knowledge of the literature and clinical opinion on standard treatment and outcomes for NHL treatment and care. They may to some extent reflect 'ideal care' rather than actual care practice. Our judgement is that the scenarios in each tree represent a reasonable generalisation of the current UK and European practice. In particular, it would be expected that there would be inter-hospital variation in treatment practice. We have only produced two total cost scenarios – with and without the provision of HDT/ABMT. Other scenarios could be modelled, varying treatment assumptions and patient numbers. The details provided regarding the treatment pathways and cost assumptions in this booklet offer a basis for other researchers to conduct such further analysis. It could also be possible in further analysis to assess cost effectiveness by developing the tree to model, for example, the costs per successfully treated case.

Sixth, the total incidence costs of NHL for England and Wales (i.e. costs from NHL diagnosis to end of treatment or death for new cases diagnosed between 1984-88) have been estimated, rather than prevalence costs (the costs for each NHL patient over a defined time period, typically one year). Discounting (not undertaken) would only have a very a small impact on the estimated costs due to the short 'lifetime' period for most cases and the small proportion of costs that are incurred after the first year of treatment. An important motivation for the adoption of an incidence costing approach was the availability of disaggregated incidence data for NHL from the Atlas of Leukaemia and Lymphoma compiled by the Leukaemia Research Fund Centre for Clinical Epidemiology at the University of Leeds. Incidence costs are also seen as superior in cost-of-illness studies as they reflect the full costs of treating a disease, and so can be used as a basis for esti-

mating the potential cost (reduction) impact of new treatments or prevention benefits (Hodgson, 1994; Drummond, 1992). Prevalence costs can be useful for estimating the annual costs of treatment for a disease for budget planning purposes.

New estimates of the incidence of lymphomas covering a more recent time period are due to be published by the Leukaemia Research Fund Centre. When available, these could be used to update the cost estimates in Tables 7.1 and 7.2.

7.7 Further economic analysis using the treatment/outcome trees

The treatment/outcome trees presented in this section are useful for identifying the costs of alternative treatment routes for patients with different types of NHL, and in different age groups. The type of study we conducted was a direct cost assessment in terms of the classification in Table 5.1. However, the approach used also provides a good basis for exploring other economic issues in the treatment and care of NHL. For example, the use of ABMT with HDT in Figures 7.1b and 7.3b adds to direct costs but, if effective, improves patient survival and removes the (immediate) need for palliative care so reducing these costs. Cost effectiveness in terms of the cost per life year or QALY gained for ABMT v no ABMT could be determined given certain assumptions concerning the life years gained and data on the patients health related quality of life over these years. The use of prophylactic G-CSF could be incorporated to assess the potential resource savings from a reduction in chemotherapy related infections this may achieve. The treatment/outcome trees also offer much scope for conducting sensitivity analysis of alternative NHL management strategies. For instance, whilst Figures 7.1 to 7.4 are designed to reflect current treatment practice in the UK, alternative trees could potentially be constructed, for example to assess the cost of treatment and care if only cost-effective options were used (if such knowledge existed). The cost consequences of adopting such strategies could then be assessed.

8 DISCUSSION AND CONCLUSIONS

There has been no previous estimate of the costs of treatment and care for lymphoma in the UK. Focusing on NHL, our preliminary and tentative estimate demonstrates a cost per case for hospital treatment and care of between £3,700 and £8,800 depending on the type of NHL and age group of patients, and an average cost of £5,728 for all NHLs. Including HDT/ABMT produces an upper cost estimate of over £13,000 per patient for both aggressive and indolent NHL in those aged under 65 years. Although comparisons are difficult due to differences in costing methods, the NHL costs are reasonably similar to those for breast cancer at £3,500 to £7,000 per case depending on disease stage (Wolstenholme et al.,1996), and Hodgkin's disease at £12,500 per case (Norum et al., 1996). Based on 1984-88 data (Leukaemia Research Fund, 1990) the incidence of aggressive and indolent NHL was similar, at just under 2,000 new cases per year for each tumour type (see Table 7.1). There were more new cases of both clinical types of NHL among men than women under 65, and more new female cases over 65, although the incidence rate is higher for men than women in both age categories (at about 5/100,000 population for males v 3.4/100,000 for females).

Based on a total annual incidence for NHL in England and Wales of just over 3,700 cases, we have estimated the total lifetime cost of treating these new cases at £22-33 million, with the higher cost estimate associated with the use of ABMT. These estimates are a minimum as potentially important care components such as hospice care and the use of G-CSF therapy for preventing chemotherapy-induced infections have been excluded. Although a sizeable cost, it may not be considered exceptionally large in comparison to some of the most common cancers. However, there are a number of factors that are likely to contribute to substantially higher total treatment and care costs in the near and more distant future. The cost pressures come from two main sources.

Firstly, the epidemiological evidence suggests there will be a large increase in the annual number of new cases of NHL over the next 30 years both in the UK and elsewhere, which can only partly be attributed to the ageing of the population. NHL can occur at any age, although the highest prevalence rates are in people aged over 65. If a trend rate of at least 4% per annum growth in incidence of NHL in the over 30's in the UK continues, then the future total number of cases in 30 years will be similar to the current number of cases of major cancers such as breast and lung cancer (see section 2.3, Table 2.2). The total economic cost of treatment and care for new cases, even in the unlikely event of no new technological developments, could be four

times the current cost, suggesting an annual incidence cost of at least £100 million in 2025 (in current prices). In addition to this cost there will be the burden from the additional lost life years, the increased morbidity and the community care costs borne by formal service providers, and patients' families and friends.

Secondly, cost pressures exist from recent developments in the treatment and care of NHL patients, such as ABMT which is rapidly diffusing into standard clinical practice for cancer management in the UK. In the treatment/outcome tree analysis, the cost of using ABMT with high dose chemotherapy (using an estimated cost of £22,872) in the treatment of NHL patients under 65 is estimated to add £11.5 million to the total annual incidence cost, with improved outcomes attained for 5% of all diagnosed aggressive and indolent NHL patients. Research is also being conducted on several new approaches which if used in practice may also add to the costs of treatment and care (e.g. 'antisense' treatment, which is an attempt to use DNA molecules to target the lymphoma and improve the effectiveness of standard chemotherapy – see section 4). Further, as yet unknown, developments could further increase costs in the future.

Health care policy makers and purchasers face the problem of controlling the costs of NHL (and all other cancer) care whilst ensuring that the maximum health benefits are obtained from the allocation of resources to cost-effective NHL treatment and care options. The particularly high cost patients can be identified from the treatment/outcome trees of Figures 7.1-7.4. For example, the highest costs per patient are for NHL patients under 65 with an aggressive tumour who are given ABMT after a third course of chemotherapy. This cost is estimated at over £50,000 per patient (Figure 7.1b). Even without the use of ABMT, the cost for some patients who are given three courses of chemotherapy due to relapses is nearly £30,000. In contrast, if aggressive NHL can be cured by first line chemotherapy then the cost is estimated at only £3,335 per patient (Figures 7.1a and 7.2). In the treatment/outcome trees, the cure rate for aggressive NHL is estimated as 50% and 30% respectively for patients under 65 and those 65 or over, after first line CHOP chemotherapy. Hence, if these cure rates could be increased through earlier and better diagnosis of aggressive tumours or the discovery of even more effective chemotherapy regimens, some extra direct costs might be incurred, but there could be potentially large resource savings (especially for patients under 65 years) from avoiding further courses of chemotherapy, ABMT and other treatment. Coupled with the gains in patient health outcomes that could be obtained, the cost effectiveness of chemotherapy for NHL would be improved.

For indolent NHL, cure is improbable so that the main objective might be to increase the patient survival time without need for treat-

ment (which can be considered any duration which increases the current median of eight years). Compared to aggressive NHLs, there appears to be less scope for resource savings in the treatment and care of indolent NHL. However, if survival and quality of life outcomes can be increased through improved chemotherapy and other treatment efficacy, the cost effectiveness of treatment for these patients could be increased. Of course, for both aggressive and indolent tumours, the greatest economic and health gains would be from the prevention of NHL, but given poor knowledge of the primary risk factors for NHL this prospect still seems distant.

If the potential economic and health burden of NHL is to be controlled and resources for treatment and care efficiently managed, there is much need to invest the research and development resources of the Government, health authorities, pharmaceutical companies and health care research funding agencies effectively in a number of strands of research. Alongside research, provision of an integrated and high quality network of hospital and community cancer services is important, and plans are currently being implemented to try and achieve this (Expert Advisory Group on Cancer Services, 1994).

The research needs are several and multi-disciplinary. Firstly, there is a need for more epidemiological research into the causes of NHL which, as outlined in section 3, are complex and uncertain. If effective screening programmes could be developed, the opportunities for early diagnosis would increase and the survival prospects of some patients with NHL might be improved.

Secondly, despite the use of well worked out treatment/outcome trees to estimate the costs of NHL treatment and care in section 7, these represent tentative first estimates. There is much uncertainty about the future potential costs of the disease. More detailed research on the costs of NHL with the use of UK patient-specific data could verify our initial estimates. Until such research is undertaken, the cost estimates produced in this booklet could be used for projecting the future per patient and total incidence costs of NHL using modelling techniques such as scenario analysis. In this a reference scenario is developed to estimate the future costs (in five to 30 years' time) given no new treatment developments and a steady trend in demography and incidence of NHL. Alternative 'what-if' scenarios would then be generated to compare against the reference scenario the costs associated with various epidemiological, treatment, preventative or service developments (Postma et al., 1997).

Thirdly, much of the treatment and care provided for NHL patients is based on limited evidence of efficacy and cost effectiveness. Our review of economic studies of NHL treatment and care in section 6 identified only one Dutch study of the cost effectiveness of ABMT for NHL patients, which was not particularly favourable to the interven-

tion compared to CHOP chemotherapy. The results of economic studies of G-CSF for the prevention of chemotherapy-induced febrile neutropenia in NHL patients produced more favourable results for the intervention, but none of these were UK based and the studies had several weaknesses. As well as a need for good quality randomised controlled trials of interventions such as high dose chemotherapy and ABMT for NHL, good quality economic evaluations also need to be conducted within or alongside these to help resource allocation decisions. Such economic evaluations should conform to latest 'quality' standards (e.g. Drummond et al., 1996), make good use of the available validated cancer specific and generic quality of life instruments (Carin et al., 1994; Padilla et al., 1996; Aaronson et al., 1996), and explore the possibility of modelling designs prior to collection of prospective data within a randomised controlled trial (Sculpher et al., 1997). The treatment/outcome trees in this booklet could provide a basis for modelling the cost effectiveness of treatment options, although their value for this purpose would be enhanced with good quality efficacy data from well conducted meta analyses.

Increasingly, the value for money of NHL treatment and care (especially new developments) is likely to be compared with interventions for other cancers and health care interventions for other therapeutic areas (e.g. cardiology, mental health). As long as it is properly designed, the use of cost utility analysis to estimate the incremental cost per QALY gained for alternative treatment options for NHL should aid such comparisons. Therefore, a priority for economic research should be the commissioning of cost utility analyses (and, where appropriate, other types of economic evaluation) in a UK setting for evaluating key aspects of NHL treatment and care, such as the use of ABMT, alternative chemotherapy regimens, palliative care options and G-CSF.

NHL is a rapidly growing epidemiological, economic and human problem, so priority should be given to investment in research to improve knowledge of risk factors and possible preventative measures, achieving early and accurate diagnosis, and identification of cost-effective treatment and care interventions.

Appendix – Estimates, assumptions and sources used for the costs of NHL

1. CHOP chemotherapy

The cost per person per course used was £3,106. The costs of CHOP were taken from source (2), and converted from 1992 Dutch guilders to 1996 £'s. The original cost from source (2) was based on a four cycle course. We have therefore adjusted average costs to reflect typical UK practice of the administration of CHOP three-weekly on an outpatient basis for a six cycle course. The cost estimate includes outpatient visits, inpatient administration, diagnostic tests and investigations including CT scans, antibiotics, transfusions and overhead costs.

2. Hospitalisation following CHOP

The cost per person used was £2,290. It is assumed that hospitalisation is due to febrile neutropenia treatment from the effects of CHOP chemotherapy. The costs of inpatient treatment and care, including diagnostic tests, antibiotics and overheads are available from a Canadian study, source (6), with costs converted from 1993 Canadian dollars to 1996 £'s.

3. Other intensive chemotherapy for second and third line treatment of aggressive NHL

The cost per person per course used was £8,565 for second line chemotherapy and £17,130 for third line chemotherapy. Several alternative intensive chemotherapy regimens exist with cost estimates available from a Dutch study, source (2): e.g. DHAP – dexamethason, cisplatine, Ara C, prednisone; or IMVP – ifosamide, methotrexate, etoposide/VP-16; with costs converted from 1992 Dutch guilders to 1996 £'s. The costs of IMVP have been used in our analysis for second line chemotherapy. This estimate is based on a four cycle course, with administration on an inpatient basis. The cost estimate includes outpatient visits, inpatient administration, diagnostic tests and investigations including CT scans, antibiotics, transfusions, overhead costs. In the UK, third line chemotherapy is more intensive than second line, often involving several weeks of hospitalisation. As no cost data were available for such chemotherapy, we have used an arbitrary estimate of double the cost of second line chemotherapy.

4. Palliative care

The unit cost per day used was £45. The cost per person was £630 for

patients with aggressive NHL, based on an expected patient survival of four weeks (28 days), and £2,520 for patients with indolent NHL, based on an expected patient survival of four months (122 days). Palliative care for terminally ill patients with NHL generally consists of Macmillan/district nurse home visits, GP care, counselling and pain relief. Identification of a unit cost for such care from the literature was difficult. The estimate we used represents the average unit cost (including overheads) of a palliative care home visit to cancer patients by GPs, Macmillan/district nurses, Marie Curie nurses, and a member of a home care team (nursing sister plus medical support) in a London borough, available from source (7). The cost was inflated from original 1987-88 prices to 1996 costs. Patients do not receive a visit every day, so an assumption was made that one visit would be made every two days, producing a total of 14 visits for patients with aggressive NHL and 61 visits for patients with indolent NHL. This may be an overestimate of the actual number of visits, but in other ways the cost used underestimates the full cost of palliative care that is likely to be provided as it does not include the costs of pain relief, and the use of more expensive inpatient or hospice stays were not estimated.

5. Chlorambucil therapy

The cost per person per course used was £1,272. As no information on the full cost of chlorambucil therapy was found from literature sources, an estimate of this cost was made using available price data. This was based on the price of chlorambucil from the British National Formulary (September 1996, source (5)), assuming a dose of 20mg per day (unit cost of £3.40 per day) for six days per cycle. A course consists of eight cycles, producing a cost per person of £163.20 for a course. In addition, it was assumed that the patient would receive an outpatient consultation per cycle, producing a total of eight visits per course (at a unit cost of £72 per visit – source (4)), and at each visit patients receive a full blood count (NHS price of £2.88 – source (1)) and biochemistry test (NHS price of £7.14 – source (1)). The cost of three CT scans per course of chlorambucil was included (unit cost of £74 per scan derived from source (1)), and one surgical biopsy requiring an inpatient admission (NHS price for biopsy of £16.54 – source (1), and £215 for an inpatient day – source (4)).

6. Radiotherapy for indolent NHL

The unit cost per fraction used was £55. The cost per person per course was £1,100. It was assumed that 20 fractions over five outpatient visits would be provided per patient with indolent NHL. A UK cost estimate per fraction for 1991 was obtained from source (8), and inflated to 1996 £'s. This estimate includes outpatient visits, diagnos-

tic tests and investigations and overhead costs. The cost estimate we have used may be low for some cases, particularly elderly patients, who may receive radiotherapy as an inpatient procedure.

7. High dose therapy and ABMT for patients under 65

The cost per person used was £22,872. The cost of HDT/ABMT was available from source (3), with costs converted from original 1992 Dutch guilders to 1996 £'s. The cost estimate includes high dose therapy (cyclophosphamide), outpatient visits, inpatient administration, diagnostic tests and investigations including CT scans, antibiotics, transfusions and overhead costs. Hospital price data in the UK indicate a lower cost for HDT/ABMT (in the region of £13,000) although such prices are highly unreliable indicators of true cost as they do not include many on-costs and are not necessarily based on accurate cost identification methods. Therefore, the Dutch estimates have been used.

8. Follow-up outpatient visits for patients with indolent NHL

The costs of outpatient visits, typically every three months, with a full blood count and biochemistry test each visit until death, have not been included in the cost estimates.

Note:

Dutch/Canadian costs were converted to 1996 £'s using the 1996 exchange rates and health care price index. UK cost estimates were inflated to 1996 £'s using the health care price index.

Sources of cost estimates

1. Mean of NHS prices from eight Trent Hospitals (figures supplied by Jane Wolstenholme, Trent Institute for Health Services Research, Nottingham University).
2. Uyl-de Groot CA, Hagenbeek A, Verdonck LF, Lowenberg B, Rutten FF (1995b). Cost effectiveness of ABMT in comparison with CHOP chemotherapy in patients with intermediate and high grade malignant non-Hodgkin's lymphoma. *Bone Marrow Transplantation;* 16, 3: 463-70.
3. Uyl-de Groot CA, Okhuijsen SY, Hagenbeek A et al. (1995a). Costs of introducing autologous BMT in the treatment of lymphoma and acute leukaemia in The Netherlands. *Bone Marrow Transplantation;* 15, 4: 605-10.

4. Office of Health Economics (1997). *Compendium of health statistics, 10th edition.* Office of Health Economics, London.

5. British Medical Association and Royal Pharmaceutical Society of Great Britain (1996). *British National Formulary.* September 1996.

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