CHAPTER 25 COST EFFECTIVENESS

25.1 Economic burden of lymphoma in Australia

In Australia, lymphoma is a common cancer with serious health consequences. It includes more than 20 lymphoproliferative diseases classified into two main groups, non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). In 2000, the annual incidence of all lymphomas was 18.3 per 100,000 males and 13.5 per 100,000 females, making it the sixth most common cancer for men and women.[1] For both men and women, lymphoma (all) is the sixth most common cancer, and in children aged 0–14, it is the third most common cancer.[1] Treatments for lymphoma include radiotherapy, chemotherapy, transplantation and antibody therapy.

The estimated burden of disease attributable to lymphoma in Australia is outlined in Table 25.1. Years of Life Lost (YLL) due to lymphoma are considerably higher than Years Lost due to Disability (YLD). This reflects the fact that the 'burden of cancer' is dominated by mortality rather than lengthy periods of disability'.[2]

Table 25.1 Burden of disease attributable to lymphoma in Australia, 1996

	Total		Males		Females	
	Number	Per cent	Number	Per cent	Number	Per cent
Deaths	1 595	1.2	810	1.2	785	1.3
YLL	19 535	1.4	9 848	1.3	9 687	1.6
YLD	3 915	0.3	2 116	0.3	1 799	0.3
DALY*	23 451	0.9	11 964	0.9	11 487	1.0

Source: Australian Institute of Health and Welfare[2]
* disability adjusted life years

The Australian Institute of Health and Welfare have estimated the costs of lymphoma at a macro level. In 1993–94, cancer was estimated to account for 6% of health care system costs in Australia, with lymphoma accounting for 5.5% of the cost of cancer care. It ranked sixth in terms of the most 'expensive' cancers in Australia, with total health care expenditure on lymphoma estimated at $105.7 million in 1993–94.[31] Lymphoma ranks as the fourth and fifth most costly cancer for males and females respectively aged 0–24, and the third most costly cancer for males aged 24–44.[3] Total treatment costs per case of lymphoma were estimated at A$18,519 in 1993–94, which ranks sixth in terms of the most costly cancer to treat.[3] However, there is relatively little micro-level information available in Australia about treatment patterns and resource use for lymphoma, particularly in terms of resource use by stage at diagnosis.

25.2 Economic evaluation

Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences. Cost-effectiveness evaluation (CEA) is the form of economic evaluation in which the consequences of interventions, procedures or programs are measured in the most appropriate natural units, such as life-years gained, complications avoided, or cases correctly diagnosed. While many CEAs consider a single measure of output, others present an array of output or outcome measures alongside cost, allowing the decision maker to form his or her own view of the relative importance of each measure.

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[1] This estimate includes hospital, medical, pharmaceuticals, nursing home and allied health services, public health programs, research, other institutional and non-institutional and administration expenditure (Mathers et al. 1999[3]).

In a cost-utility analysis (CUA), the consequences of an intervention, procedure or program are adjusted by health state preference scores or utility weights. This means that the quality of the life years gained can be assessed, which is particularly useful for interventions that extend life at the expense of side effects (such as some chemotherapy for cancer), or produce reductions in morbidity rather than mortality (such as some treatments for chronic conditions such as arthritis).

Whatever form of economic evaluation is used, an intervention, procedure or program can be considered efficient relative to the alternatives if it can be shown to produce a given level of benefit for the minimum cost.

25.3 Role of economic evidence in the development of guidelines

The NHMRC has identified two main areas where economic evidence is important in the development of clinical practice guidelines:

- determination of which treatment alternatives are the most cost effective
- determination of whether a proposed clinical practice guideline is cost effective.

In the development of these guidelines, the emphasis has been in the first instance on identifying those interventions for which there is evidence of effectiveness, before addressing questions of cost effectiveness. There is limited evidence available within Australia to assess the costs and cost effectiveness of alternatives for management of lymphoma. However, there is a range of international literature that provides information about the relative cost effectiveness of alternatives, and this information can be used to inform the development of these guidelines.

The approach taken in reviewing the economic evidence involved:

- identifying those areas where economic evidence is likely to be important
- identifying those areas where economic evaluation evidence is available
- reviewing and summarising the economic evaluation literature.

However, it is important to note that international economic evaluation literature is limited in its relevance to Australia because of differences in cost structures and reimbursement arrangements, and because the comparator in international studies may not reflect current practice in Australia.

A search was conducted using the databases Pre-Medline, Medline and Embase, covering the period 1994–April 2004. Economic evaluation literature that pre-dates 1994 was considered to be of limited relevance because of changes in technology, cost structures and management practices. The key words included *lymphoma*, *economic evaluation*, *cost-effectiveness analysis*, *cost benefit analysis*, *cost analysis* and *cost*. Articles were included if they were judged to be economic evaluations, that is, if they involved comparison of alternative interventions in terms of costs and consequences. Articles were classified into eight main areas:

- diagnosis
- follow up
- treatment of Hodgkin's lymphoma
- treatment of low-grade non-Hodgkin's lymphoma
- treatment of aggressive and high-grade non-Hodgkin's lymphoma

- treatment of childhood lymphoma
- treatment of immunodeficiency-associated lymphoma
- treatment of non-Hodgkin's lymphoma (where type of lymphoma was not specified, or several types of lymphoma were combined in the study sample).

These groupings reflected the main areas in which economic evaluations of interventions have been undertaken.

It should be noted that of the 45 articles included in these guidelines, the majority investigated the effect of an intervention on some type of clinical outcome such as haematological engraftment, treating complications, or output, for example, length of stay (LOS). Only 13 articles investigated the effect of an intervention on outcomes such as mortality, survival, quality of life on utility (QALY), or lifeyears saved (LYS).

These 13 articles were reviewed using the criteria recommended in *How to compare the costs and benefits: evaluation of the economic evidence (NHMRC).*[4]

Table 25.2 NHMRC's criteria: Assessing evidence using shadow prices

	Ranking of evidence on effects	
Ranking of evidence on costs	High	Low
Strong	Recommend if: < $70,000 per life year Do not recommend if > $100,000 per life year	Recommend if < $30,000 per life year Do not recommend if >$70,000 per life year
Weak	Recommend if < $30,000 per life year Do not recommend if > $70,000 per life year	Recommend if < $30,000 per life year Do not recommend if >$30,000 per life year

Source: *How to compare the costs and benefits: evaluation of the economic evidence* (NHMRC)[4] Table 6.1 pg 67.

The NHMRC provides comprehensive guidelines for evaluating the economic evidence for clinical practice guidelines. The evidence on both effectiveness and costs can be compared, providing a range of possibilities shown in the Table above. The threshold cost per life year should vary with the quality of evidence. The *lower* the ranking of the evidence, the more likely the decision will be to not recommend an option where the cost per life year falls between $30,000 and $100,000.

Table 25.2 shows that 'if highly ranked evidence is available on effects and there is strong evidence on costs, then options that cost less than $70,000 per life year saved are recommended and those that cost $100,000 are rejected. Those that cost between $70,000 and $100,000 should be considered.'

'If effectiveness evidence is ranked as low and the cost evidence as weak, options that cost more than $30,000 per life year saved are rejected.'

'If neither of the above cases applies [that is, where one of the criteria (costs or effects) is weak and the other is strong], then options of less than $30,000 are recommended and those greater than $70,000 are rejected. Those that are between $30,000 and $70,000 should be considered.'[4]

Health care alternatives require further consideration if they fall between $70,000-$100,000 per life year saved and rank highly for effects and costs, or if they fall between $30,000-$70,000 per life year saved and rank highly on one but not the other. Issues that enhance the attractiveness of a health care option and move the threshold towards a higher price include equity implications, prevention of adverse flow on effects to other sectors, rare diseases with no other health options, improvement of survival and quality of life and severe and preventable conditions.[4]

This methodology has not been applied in the development of these Guidelines. Rather, the economic information has been summarised and presented, but not graded. Hence they have not been assessed applying NHMRC's criteria and shadow prices framework.

However, assessment of overseas economic evaluations and even some Australian economic evaluations in these terms should be treated with caution. Whether these costs and outcomes would be realised if the intervention were adopted in the Australian context depends upon a number of factors, but particularly on whether the comparator for the study reflects current practice in Australia. This also applies where cost-effectiveness evaluations are made in terms of clinical comparators, as is the case in the majority of studies.

Cost effectiveness results from studies are presented as reported in the relevant studies, but also, for comparative purposes, converted to 2004 Australian dollars. The conversion was undertaken using the OECD purchasing power parity estimates (<www.oecd.org/std/ppp/>) for the relevant year of the study to convert to Australian dollars, then using the Australian Bureau of Statistics Health Price Index (weighted average of eight capital cities) (ABS, 2004; Consumer Price Index Catalogue 6401.0) to convert the relevant costs to 2004 Australian dollars. Results in terms of 2004 Australian dollars are reported in parentheses following the original results. However, in comparing across studies it should be noted that the results from different studies are not directly comparable. In particular, the scope of the studies may differ in terms of the range of costs and consequences considered, the perspective of the study, and the choice of comparator. In addition, particularly for earlier studies, there may be important changes in cost structures and technology that limit comparability. The indicative cost-effectiveness estimates in 2004 Australian dollars should be treated as providing a guide to the likely cost effectiveness of the interventions in the Australian setting.

The findings of the literature review are summarised below. In a number of studies, the subject sample involved more than one patient group. Where this has occurred, the studies have been included in each of the relative sections. Detailed results from these studies have only been given in the sections where they are first discussed. In all subsequent sections the reader is referred back to the first section in which the study is reported for the relevant results.

25.3.1 Diagnosis

There have been relatively few papers assessing the cost effectiveness of different diagnostic procedures and these are primarily related to staging.

In a German study, Klose et al. 2000[5] compared FDG-PET to CT scanning and found FDG-PET to be more accurate in the primary staging of lymphomas, with an effectiveness of 100% compared to 81.88% for CT scanning. The incremental cost-effectiveness ratio (ICER), interpreted as the additional costs of a more effective strategy per additional correctly-staged patient, was €3133 (A$5496) per correctly-staged patient. Sensitivity analysis indicated the potential for more cost saving with optimal utilisation of PET facilities. The authors concluded that the use of FDG-PET might result in cost savings because of better planning of further diagnostic procedures and of treatment. However, more research is needed to assess the long-term treatment and cost effects of more accurate staging.

A further study in the United States by Hoh et al. 1997[6] found that whole body PET-based staging, when used to guide further conventional diagnostic strategies, is cost effective compared to current conventional staging. It may reduce the total cost of staging work by focusing procedures only to necessary regions. Accurate staging was performed in 17 of 18 patients using whole body PET, compared to 15 of 18 with conventional methods. PET correctly increased the stage in 17% of patients. The total cost of PET was US$37,850 (A$67,915) compared to US$68,192 (A$122,358) for conventional staging.

In Japan, Kosuda et al. 2003[7] conducted a study investigating the diagnostic impact of combined ^{201}T1 and ^{67}Ga brain SPECT on the management of patients suspected of having central nervous system (CNS) lymphomas. They found that it was useful for differentiating CNS lymphomas or germinomas from other cerebral tumours, and that it could potentially determine whether patients have stereotactic biopsy or craniomotomy. Expected cost savings in the 1–50% range of pretest probability of CNS lymphoma or germinoma would be from minus US$842 (A$1342) to plus US$2047 (A$3263) per patient, indicating it would be cost effective only in patients highly suspected of having CNS lymphoma or germinoma.

The studies are limited in that they rely on estimates of sensitivity and specificity of PET based on small sample sizes rather than randomised controlled trials. Results should be used as an indication of the costs and cost effectiveness of the alternative interventions only.

25.3.2 Follow up

Only one study evaluating follow-up strategies was identified and involved a basic costing comparison conducted in the United States. Edelman et al. 1997[8] compared the costs of utilising a literature-supported suggested follow-up regimen, developed by the authors, with current typical follow up for patients with HD and NHL. The total cost of follow up was obtained by first multiplying the number of patients at risk each year by the cost of follow up for that year. The cost was then calculated from the sum of all years (five) of follow up. The number of patients at risk in the first year of follow up was obtained by multiplying the number of patients with the disease by the percentage anticipated to achieve complete remission. For subsequent years, the relapsed patients in the preceding years were subtracted.

They found that for both patient groups, the cost of the literature-supported strategy — US$900,000 (A$1.7M)/1000 HD pts and US$500,000 (A$900,000)/1000 NHL pts — was lower than for current typical follow up — US$1.4M (A$2.6M)/1000 HD pts and US$1.8M (A$3.4M)/1000 NHL pts. However, a number of assumptions were made in this study. First, follow-up testing would only be obtained during periods of maximal risk of recurrence. Second, the rate of recurrence would be constant over the study period. Third, there would be no further surveillance testing after the study period. Fourth, all stage I and II HD patients would receive radiation therapy as part of their treatment and require routine thyroid testing. Further, as no sensitivity analysis was conducted, the results should be viewed with caution.

25.3.3 Treatment of Hodgkin's disease

A number of studies have evaluated costs and outcomes and cost effectiveness of various treatment alternatives. In the main, these studies have been conducted using specific patient groups and will be discussed accordingly.

Relapsed, refractory, resistant, progressive or poor/slow responding patients

Several studies investigating costs and outcomes have been undertaken since 1994, although there is considerable variation in terms of treatments evaluated, evaluation type, and the trial and other data used to evaluate effectiveness. The majority of studies were cost and outcome studies, with only one cost-effectiveness evaluation. The results are summarised in Table 25.3.

In general, these studies indicate that blood stem cell transplantation may result in better clinical and quality of life outcomes at lower costs than bone marrow transplantation. Some chemotherapy regimens also appear to result in better clinical outcomes and cost savings. The only cost-effectiveness study conducted indicated that the cost effectiveness of high-dose chemotherapy (HDC) is below the A$30,000 per-life-year-gained threshold. The use of granulocyte colony-stimulating factor (G-CSF) in addition to either transplantation or chemotherapy appears to be clinically effective and cost saving.

As these studies evaluate different treatment approaches and are predominately cost and outcome evaluations, it is not possible at this stage to recommend any one treatment over another on the basis of cost effectiveness. At best, the studies provide an initial indication of possible cost savings for certain treatment options.

Table 25.3 Results of studies investigating costs and outcomes of alternative treatments for relapsed, refractory, resistant, progressive, or poor/slow responding patients

Study	Country	Study question	Conclusion
Vellenga et al. 2001[9]	The Netherlands	Comparison of PSCT versus ABMT transplantation for relapsed/poorly responding patients	PSCT results in significantly better clinical outcomes (faster engraftment, fewer transfusions), less supportive care requirements, and better reported QoL. PSCT is more cost effective than ABMT, with total transplantation costs of US$13,954 (A$22,724) versus US$17,668 (A$28,772).
Van Agthoven et al. 2001[10]	The Netherlands	Comparison of PBPCT versus ABMT transplantation for chemo-refractory or relapsed patients	PBSCT is associated with better QoL and lower costs. The average total treatment costs were €22,560 (A$38,721) versus €28,428 (A$48,792), a relative cost advantage of 21%.
Tarella et al. 1998[11]	Italy	Comparison of PBPCT transplant + G-CSF versus PBPCT alone for relapsed patients	PBPCT + G-CSF significantly accelerated haematological recovery, significantly reduced incidence and severity of fever and infectious complications, and significantly reduced post-transplant hospital days. Average treatment cost for PBPCT + G-CSF was US$3627 (A$5906) lower than for PBPCT alone — US$18,241 (A$29,705) versus US$21,868 (A$35,611).
Smith et al. 1997[12]	USA	Comparison of PBPCT transplant + filgrastim versus ABMT transplant for relapsed patients	PBPCT + filgrastim is safe and more effective than ABMT and represents significant cost savings. It resulted in similar short-term survival, significantly better haematological recovery, LOS and lower total costs — US$45,792 (A$85,502) versus US$59,314 (A$110,750). Sensitivity analysis confirmed the robustness of the results.
Mazza et al. 1999[13]	Italy	Comparison of HDC + PBPCT transplant in non ICU setting versus ICU setting	HDC + PBPCT in a non ICU setting resulted in an overall response rate of 71%, and treatment-free rate (3–27mth) of 56%. At a mean cost of US$18,092.60 (A$29,463), the procedure is affordable without strict ICU-setting precautions.
Bennett et al. 1995[14]	USA	Assessment of cost of care and outcomes for HDC + ABMT or PBSCT over time for relapsed or refractory patients	Survival rates improved and cost of care decreased over time. The most significant factor for survival was the experience of the transplant team. Costs decreased at a rate of 10% per annum.

Beard, Lorigan and Sampson 2000 [15]	UK	Comparison of HDC versus Std chemotherapy for relapsed patients	HDC is clinically and cost effective. Additional life years gained were 1.1 (trial data) and 5.5 (20yr projection). Cost/LYG were £12,636 (A$31,159) (trial data) and £2527 (A$6231) (20yr projection). Sensitivity analysis shows that cost effectiveness remains under £25,000 (A$61,648)/LYG even when the marginal cost of HDC is increased to £20,000 (A$49,318).
Dranitsaris and Sutcliffe 1995[16]	Canada	Comparison of miniBEAM chemotherapy + G-CSF versus miniBEAM alone for patients with progressive disease	G-CSF reduced LOS and hospital, antibiotic and management costs. Total costs were CAN$4682.08 (A$8124.86) versus CAN$4753.54 (A$8248.86), a saving of approx CAN$1580 (A$2742) for hospitalisation and CAN$70 (A$121) when the cost of G-CSF is included.

Patients in remission

Only one paper was identified that specifically evaluated the cost effectiveness of treatments for patients in remission. Faucher et al. 1994[17], in a French cost-effectiveness analysis, compared transplantation methods with or without G-CSF. They found that PBPCT plus G-CSF had significantly better clinical outcomes (shorter engraftment rate and better haematological recovery), shorter LOS (15 versus 20 versus 20 days), and lower cost — US$197.7 (A$450.4) versus US$255.2 (A$581.3) versus US$245.1 (A$558.3) — than ABMT plus G-CSF or ABMT alone.

Cost effectiveness, evaluated in terms of haematological recovery, was in favour of PBPCT plus G-CSF. The cost-effectiveness ratios (CERs) for granulocyte and platelet recovery were US$9360 (A$21,232) and US$14,830 (A$33,783) for PBPCT plus G-CSF, versus US$11,450 (A$26,083) and US$21,550 (A$49,092) for ABMT +G-CSF, versus US$13,350 (A$30,412) and US$22,220 (A$50,618) for ABMT alone. The results of sensitivity analysis did not affect the findings.

This study provides some evidence that PBPCT plus G-CSF may be cost effective, but additional evidence from further research is needed before a definitive recommendation can be made.

Patient status not specified/varied

Three cost and outcome studies compared different transplantation methods with or without G-CSF. The results are summarised in Table 25.3. As the transplantation methods (and/or the use of G-CSF or IL-3) compared were different for each of the studies, it is not possible to recommend one method over another and the results should be used as an indication only.

Table 25.4 Results of studies investigating costs and outcomes of alternative treatments/interventions for patients where studies do not specify status or where patients of varied status are included in the study sample

Study	Study country	Study questions	Conclusion
Souetre, Quing and Penelaud 1996[18]	France	Comparison of ABMT transplant +G-CSF versus ABMT alone	Use of G-CSF is associated with improved therapeutic efficacy (reduced length/severity of infection, neutropenia, mucosity) LOS, and a moderate reduction in direct medical costs. Av. total cost/patient was US$43,341 (A$92,602) versus US$44,656 (A$95,412), a saving of US$1315 (A$2810). Sensitivity analysis indicates the evaluation is robust.
Luce et al. 1994[19]	USA	Comparison of ABMT transplant +GM-CSF versus ABMT alone	Use of GM-CSF resulted in lower costs — US$70,300 (A$150,303) versus US$82,500 (A$176,270) — a saving of US$12,200 (A$26,067), mainly due to difference in initial hospitalisation (21% lower than for no GM-CSF). (Note: This study was retrospective and no efficacy data were included.)
Uyl-de-Groot, Huijgens and Rutten 1996[20]	The Netherlands	Comparison of transplant methods with or without G-CSF (review) PBPCT versus ABMT PBPCT versus ABMT PBPCT versus ABMT + G-CSF	PBPCT resulted in improved efficacy and reduced hospital costs. Treatment costs were 15–30% lower than for ABMT — US$19,770–$21,809 (A$45,037–49,682) (PBPCT) versus US$23,290–30,592 (A$53,055–69,690) (ABMT) versus US$24,140–32,443 (A$54,992–73,906) (ABMT + G-CSF). Sensitivity analysis indicates the dominance of PBPCT is robust.
Schulman et al. 1998[21]	USA	Comparison of ABMT transplant + CM-CSF +IL-3 versus ABMT transplant + CM-CSF	For patients undergoing bone marrow transplant, Il-3 + CM-CSF resulted in no significant clinical or survival benefit (survival probability of 78% versus 76%) compared to CM-CSF alone. There was no significant effect on costs — US$89,651 (A$167,395) versus US$79,892 (A$149,173) — or quality-adjusted life-months (QALM) (6.26 mths versus 6.57mths) during the 13-month study period.

25.3.4 Treatment of low-grade non-Hodgkin's lymphoma

A number of studies have been undertaken evaluating costs and outcomes, and cost effectiveness of various chemotherapy treatments and the management of complications resulting from treatment. A further study investigated the effect of setting on treatment cost.

Chemotherapy

A few studies were found that evaluated costs and outcomes of different chemotherapy regimens or agents. Only one of these was a cost-effectiveness study. The others only compared costs and clinical outcomes.

Wirt et al. 2001[22], in a combined French and United States study, used a Markov model to compare the cost effectiveness of CHVP+interferon alfa-2b with CHVP alone. They found that the addition of low-dose interferon is cost effective, with a marginal cost effectiveness of US$16,900 (A$28,961)/QALY (simple model), and US$17,049 (A$29,217)/QALY (two-stage model). Sensitivity analysis showed that the results were robust, and the marginal cost effectiveness to be best expressed in the range of US$12,000–$17,000 (A$20,564–$29,133)/QALY.

A United Kingdom study by Sweetenham et al. 1999[23] compared the cost and clinical outcomes of CHOP, fludarabine and rituximab, and found rituximab to have similar efficacy but fewer adverse events (AE) and lower total cost than the other interventions. The total AE-related treatment costs per patient were £5049 (A$12,450) (CHOP), £2953 (A$7282) (fludarabine) and £109 (A$269) (rituximab). The total treatment costs per patient were £7210 (A$17,779) (CHOP), £10,022 (A$24,713) (fludarabine) and £6080 (A$14,993) (rituximab), with sensitivity analysis ranges of £5892–6267 (A$14,529–15,454) (rituximab), £5975–8445 (A$14,734–20,825) (CHOP) and £8917–1126 (A$21,989–7436) (fludarabine).

A review by Wake et al. 2002[24] concluded that rituximab appears to be clinically effective, with lower overall treatment cost due to fewer adverse events. However, they concluded that the extent to which beneficial effects are outweighed by adverse events is impossible to quantify, and that the absence of direct comparative data makes it difficult to assess whether the ratio of benefits to disbenefits with rituximab is better, worse or the same as currently used alternatives.

In Germany and Switzerland, Herold and Hieke 2002[25] compared the costs of toxicity for CHOP, COP/CVP and fludarabine in Canada, Germany and Italy. In Canada, all three regimens were compared; in Germany, CHOP and COP/CVP were compared; and in Italy, CHOP was compared with fludarabine. Results indicated that toxicity costs were substantial for all regimens and are likely to be substantial cost drivers. In Canada, CHOP-associated AE costs — €5.036 (A$7.824) — were higher than for COP/CVP — €3.252 (A$5.052) — and fludarabine — €1.273 (A$1.978). In Germany, CHOP-associated AE costs — €2.515 (A$3.907) — were comparable to COP/CVP — €2.658 (A$4.130). In Italy, CHOP-associated AE costs — €2.179 (A$3.385) — were considerably less than for fludarabine — €4.908 (A$7.625). Neutropenia and fever/infection were the most common and most expensive AEs to treat. The costs for chemotherapy-associated neutropenia and fever/infection for each of the regimens were as follows: in Canada, CHOP — €3.873 (A$6.017) — was higher than COP/CVP — €1.452 ($2.256) — and fludarabine — €1.149 (A$1.785); in Germany, CHOP — €0.9420 (A$1.463) — was lower than COP/CVP — €1.429 (A$2.220); and in Italy CHOP — €1.625 (A$2.525) — and fludarabine — €1.655 (A$2.571) — were comparable. Sensitivity analysis indicated that the results were robust.

Although these studies indicate that some regimes or agents appear to be relatively more cost effective or cost saving, at this stage there is insufficient evidence to recommend one regime or agent over others on the basis of cost effectiveness. It should also be noted that extrapolating these results to the Australian context is not appropriate, as relative cost effectiveness is driven largely by the costs of the different chemotherapy regimes and modes of delivery, which can vary internationally.

Setting

Mazza et al. 1999[13], in an Italian study, investigated the effect on costs and outcomes when patients receiving HDC plus PBPC transplantation were treated in a non-ICU instead of the usual ICU setting. For information on the results of this study, see Section 25.3.3.

Managing complications in advanced-stage patients

One Canadian study by Bobey and Woodman 1998[26] used predictive modelling to assess the potential cost effectiveness of combination chemotherapy plus G-CSF compared to combination chemotherapy alone. The results showed that with combination chemotherapy, 19% of advanced-stage patients experienced febrile neutropenic events, and 43% required chemotherapy dose modifications. The authors also found that 36% of patients could be identified as high risk for neutropenic complications and that administration of G-CSF for high-risk patients resulted in an estimated incremental cost per life-year-saved of CAN$3300 (A$4446). While these results suggest potential cost effectiveness, recommendations cannot be based on the findings of only one study. The findings should be taken as indicative of potential cost savings, with further research required.

25.3.5 Treatment of aggressive and high-grade non-Hodgkin's lymphoma

A number of studies have been undertaken evaluating costs, costs and outcomes and cost effectiveness of various treatment alternatives. In the main, these studies have been conducted using specific patient groups. They will be discussed accordingly.

Newly diagnosed patients

One Dutch study was identified that investigated the costs of treatment. This was a costing comparison by Van Agthoven et al. 2002[27], who compared the cost of CHOP-like chemotherapy according to trial protocols[2] with standard local practice (SLP). The results indicated that the costs for the trial protocols are comparable to those for SLP. Total costs (for diagnosis, treatment and follow up) were Prot1-yng — €16,901 (A$29,008); Prot2-yng — €19,136 (A$32,844); SLP-yng — €16,064 (A$27,572); Prot-eld — €20,296 (A$34,835); SLP-eld — €16,587 (A$28,469). This study provides basic information. It does not allow for definite conclusions, but may suggest cost savings with trial regimens. It is not known whether the findings can be extrapolated into the Australian context.

Relapsed, refractory, resistant, progressive or poor/slow responding patients

A number of studies evaluating cost effectiveness and costs and outcomes have been undertaken since 1994. These are, however, varied in relation to the treatments evaluated, evaluation type and the trial and other data used to evaluate effectiveness. Only two of the studies were cost-effectiveness evaluations. The majority were cost and outcome studies. The results are summarised in Table 25.5.

The findings from the studies generally indicate that blood stem cell transplantation may result in better clinical and quality of life outcomes at lower cost than bone marrow transplantation, and that some chemotherapy regimens appear to be more clinically effective at lower cost. The cost-effectiveness studies indicate that both HDC and HDC plus ABMT have a cost-effectiveness ratio below the A$30,000 per life-year-gained threshold.

However, because of the variation in the treatments evaluated, the approaches used, and the difficulty in extrapolating results to the Australian context due to international variation in treatment delivery mode, at this stage it is difficult to recommend potential cost effectiveness of any one treatment over another. At best, the studies provide an initial indication of possible cost savings for particular treatment options.

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[2] The trial protocols consisted of Prot1-yng (8x CHOP q 3wk or 6 x CHOP q2wk plus G-CSF), Prot2-yng (8 x (q 3 wk, CHVmP on day 1m BV on day 15) for patients under 65 years of age and Prot-eld (6 or 8 x CHOP q 3wk +G-CSF) for patients over 65 years of age. The Standard local practice treatments consisted of (6 or 8 x CHOP q 3wk).

Table 25.5 Results of studies investigating costs and outcomes of alternative treatments for relapsed, refractory, resistant, poor/slow responding patients or poor mobilisers

Study	Study country	Study questions	Conclusion
Vellenga et al 2001.[9]	The Netherlands	PSCT versus ABMT for relapsed/poorly responding patients	See Section 25.3.3.
Van Agthoven et al. 2001[10]	The Netherlands	PBPCT versus ABMT for chemo-refractory or relapsed patients	See Section 25.3.3.
Beard, Lorigan and Sampson	UK	HDC versus Std chemotherapy for relapsed patients	See Section 25.3.3.
Messori et al. 1997[28]	Italy	Comparison of HDC + ABMT transplant versus Std salvage chemotherapy for relapsed patients	Cost effectiveness of ABMT is very favourable, with an ICER of US$9229 (A$16,660)/discounted LYG — 95% CI of US$5390–24,012 (A$9671–$43,085), and US$4623 (A$8295)/undiscounted LYG — 95% CI of US$4297–19,138 (A$7710–34,340). Sensitivity analysis confirmed upper limits always below cut off line of US$50,000 (A$89,716) (Note: Study sample comprised highly selected pts and effectiveness data were obtained from different studies.)
Uyl-de-Groot, et al[29]	The Netherlands	Comparison of CHOP chemotherapy + ABMT transplant versus CHOP alone for slow responders to CHOP	Despite no significant difference in complete remission, overall disease-free survival or long-term QoL, cumulative costs for ABMT are significantly higher. Av. treatment cost of ABMT is significantly more — US$34,445 (A$78,467) versus US$3118 (A$7103). Long-term costs of ABMT are US$34,580 (A$78,774) more expensive. ABMT patients experienced .14LY and .22 QALY less than CHOP patients.
Uyl-de-Groot et al. 1995[29]	The Netherlands	Comparison of chemotherapy + ABMT transplant versus chemotherapy alone for relapsed patients	Cost of chemotherapy ranges from US$3120–12,900 (A$7107–29,387). Total ABMT cost is US$40,220 (A$91,623). Average cost of introducing ABMT in to the Netherlands is US$27,410–$37,100 (A$62,441–$84,515)/patient.
Stockerl-Goldstein et al. 2000[31]	USA	Comparison of chemotherapy + transplantation for good mobilisers versus poor mobilisers	Total cost was significantly higher for poor mobilisers, but there was no significant difference in survival or relapse. Total costs for bone marrow-related care/patient were US$140,264 (A$246,852) for poor mobilisers versus US$80,833 (A$142,559) for good mobilisers.

Mazza et al. 1999[13]	Italy	HDC+PBPCT in non ICU setting versus ICU setting	See Section 25.3.3.

Patients in remission

Two studies were found that investigated the costs and outcomes of several different treatment methods. In a French study, Limat et al. 2000[32] investigated the effect of cell dose on the cost and consequences of PBSCT. They found that CD34+ cell dose >5 x 10^6 appears to be optimal clinically and economically compared to cell dose <5 x 10^6. The higher cell dose resulted in significant earlier engraftment, with a total cost saving of US$4210 (A$7409). The cost savings were principally related to reduction in hospital stay — US$3010 (A$5297) — and number of transfusions — US$815 (A$1434). Sensitivity analysis showed the analysis was robust and that infusion of cell dose >5 x 10^6 would result in cost savings of more than US$2750 (A$4840). This study provides some evidence that higher cell dose may result in cost savings, but more evidence is required.

In Belgium, Van Tiggelen et al. 1999[33] conducted an exercise comparing the effectiveness and costs of three treatment options: methotrexate plus CVB chemotherapy plus ABMT, induction chemotherapy plus LNH84, and CHOP. They concluded that CHOP — 2060 to 2745 ECU (A$4440–5916) — is less costly than induction chemotherapy plus LNH84 — 7232 ECU (A$15,587) — or chemotherapy plus ABMT — 19,262 ECU (A$41,515), yet as effective. This was, however, a basic costing study using effectiveness results from previous studies and applying expected costs to the treatments considered. The results need to be viewed with caution.

Patients with a poor prognosis

Only one study evaluating treatment methods was identified. A cost and outcomes study conducted by Lee et al. 1998[34] in the United Kingdom compared PBPC transplantation plus G-CSF (following high-dose chemotherapy) with PBPC transplantation alone. The results indicate that the use of G-CSF leads to more rapid haematological recovery and is associated with more predictable and shorter hospital stays. Despite the additional cost of G-CSF, there was no increase in overall health care expenditure but a trend towards reduced expenditure. The mean expenditure per inpatient stay was £6500 (£5465–8101) (A$16,967 — $14,265–$21,146) for the PBPC plus G-CSF group compared to £8316 (£5953–15,801) (A$21,707 — $15,539–41,245) for the PBPC alone, a mean saving of £1816 (A$4740) per patient. This study provides some evidence of cost saving, but more evidence is required.

Managing complications in advanced-stage patients

For information on studies in this area see Section 25.3.4.

Patient status not specified

Two studies evaluating treatment methods were found. A French cost and outcome study by Limat et al. 2000[35] investigated the effect of cell dose on the cost and consequences of PBSCT. They compared CD34+ cell dose >5 x 10^6 with CD34+ cell dose ≤5 x 10^6, and found that CD34+ cell dose >5 x 10^6 leads to increased hematopoietic engraftment with consequent cost savings. There was a large reduction in procedure costs — US$2740 (A$4279) or 11% — directly related to hospitalisation — US$680 (A$1062) — and the number of platelets transfused — US$1340 (A$2043). Sensitivity analysis indicated that the results are robust.

In a United Kingdom study, Hackshaw, Sweetenham and Knight 2004[36] compared chemotherapy plus G-CSF with chemotherapy alone. They undertook a meta-analysis of six randomised and one non-randomised trial to determine the effectiveness of the treatments, and conducted a simple cost-effectiveness analysis. Results showed that the inclusion of G-CSF was associated with a significant reduction in the incidence of severe neutropenia (44%) and in patients with clinically relevant infections, but there was no evidence of an effect on remission rates or survival. The cost-effectiveness model indicated that a relatively large proportion of patients need to be hospitalised several times in the absence of G-CSF for routine G-CSF to become cost effective. For instance, if 15% of patients were each hospitalised twice during their course of treatment, G-CSF would have to be purchased at a cost 85% lower than the list price; if 45% of patients were each hospitalised five times during treatment, no reduction in the purchase price is required for the cost to the health service to be less than the cost of using it. They concluded that given the current cost of G-CSF, it would only be cost effective among patients for whom high rates of hospital stay due to neutropenia or infection are expected. However, extrapolating these findings to the Australian context may not be appropriate.

Older patients

Only one cost and outcomes study was identified that evaluated treatments in this population. An Italian study by Zagonel et al. 1994[37] compared chemotherapy plus G-CSF with chemotherapy alone. They found that overall response rates, percentage of complete remissions, and incidence of chemotherapy-related side effects (neutropenia and related infections) were comparable. There was, however, significantly less chemotherapy delay, duration of delay, and infection-related hospital days, with consequent lower costs in the G-CSF group — 8440.97 ECU (A$26,215.34) versus 13,300.98 ECU (A$41,309). The authors concluded that G-CSF for older patients, at high risk of prolonged hospitalisation due to neutropenia and/or fever, appears safe and cost effective. However, the sample size in this study was very small and there was limited information on pricing, so the results need to be viewed with caution.

25.3.6 Treatment of childhood lymphoma

Economic analyses of treatments for childhood lymphoma have concentrated on interventions aimed at treating or preventing complications resulting from treatment. The majority of the studies have been cost and outcome studies, with only one cost-effectiveness study identified. The results are summarised in Table 25.6.

In general, the studies suggest that the use of G-CSF does not appear to be cost saving, although G-CSF administration, based on individual timing of blood count, that is, blood counts measured at times individual to each patient and depending on their neutrophil count and the duration of previous cycles of G-CSF, may have an effect. Ceftriaxone plus amikacin may be cost saving and rasburicase appears to be cost effective for prevention and treatment.

It is not possible to recommend any one treatment over another as the studies evaluate different treatment approaches and are predominately cost and outcome studies. At best, the studies provide an initial indication of possible cost savings for certain treatment options.

Table 25.6 Results of studies investigating costs and outcomes of interventions/treatments aimed at treating or preventing treatment complications

Study	Study country	Study questions	Conclusion
Rubino et al. 1998[38]	France	Comparison of chemotherapy + G-CSF versus chemotherapy alone for prevention/ treatment of febrile neutropenia	No significant difference in clinical endpoints. Treatment cost with G-CSF — US$29,675 (A$53,247) — was lower than the cost without G-CSF — US$30,774 (A$55,218). Sensitivity analysis showed no difference in results.
Bennett et al. 2000[39]	USA	Comparison of chemotherapy + G-CSF versus chemotherapy alone for prevention/ treatment of neutropenia	Despite better clinical outcomes, there was no significant difference in overall resource use and costs — US$34,190 (A$55,677) with G-CSF versus US$28,653 (A$46,660) without). Sensitivity analysis confirmed the findings.
Ammann et al. 2002[40]	Switzerland	Comparison of G-CSF using individual timing of blood count versus standard twice weekly treatment	Individual timing resulted in a clinically relevant and significant reduction in the number of G-CSF injections and blood counts, with consequent less pain and lower costs (reduction of US$152 (A$260)/cycle).
Annemans et al. 2003[41]	Belgium, UK, Spain, The Netherlands	Comparison of rasburicase versus no rasburicase for prevention and treatment of hyperuricaemia and tumour lysis syndrome	Rasburicase is highly cost effective for the prevention of hyperuricaemia and tumour lysis syndrome in all countries — ICER €425–1710 (A$982–2780)/LYS. Treatment is cost saving (authors stated that results not shown because for cost saving strategy, figures are not informative). Sensitivity analysis shows the results are robust.
Pession, Prete and Paolucia 1997[42]	Italy	Comparison of ceftriaxone + amikacin versus ceftazidime for treatment of febrile granulocytopenic children	Ceftriaxone + amikacin is as effective, but is associated with a more favourable cost-benefit ratio. Extrapolated from a previous study, the savings for single treatment (1 and 6 day) are US$11 and $65.60 (A$20 and $117.70). Applied to the study sample of 183 pts, the cost reduction for antibiotics and injection material would be US$12,009 (A$21,548).
Castagnola et al. 1999[43]	Italy	Comparison of ceftriaxone + amikacin versus ceftazidime for treatment of febrile granulocytopenic children	Ceftriaxone + amikacin is effective in 72% patients and is associated with cost savings. Extrapolated from a previous study, the savings for single treatment (1 and 6 day) are US$11 and $65.60 (A$20 and ($117.70).

25.3.7 Treatment of immunodeficiency-associated lymphoma

Only one relatively old study was found that investigated the costs and outcomes of treatments in this area. Tirelli and Vacher 1994[44], in a small, one-centre, United States study, evaluated the economic and clinical benefits of the prophylactic use of G-CSF following chemotherapy. They found that the use of G-CSF was associated with a significant reduction of treatment-related myelosuppression (mean duration of nadir was 8.4 days compared to 10.8 days for the control group), resulting in shorter hospitalisation and a decrease in the overall cost of treatment, although not significant. The total cost of treatment with G-CSF was US$2282 (A$4578) compared to US$3232 (A$6480) for patients treated with chemotherapy alone. However, as this is a relatively old study, conducted with a sample of consecutive patients at a single institution, the results should be viewed with caution and should only be considered as an indication of possible cost saving.

25.3.8 Treatment of non-Hodgkins's lymphoma (where type of lymphoma has not been specified or several types of lymphoma were combined in the study sample)

A number of studies have been undertaken evaluating costs and outcomes and cost effectiveness of various treatment alternatives. In the main, these studies have been conducted using specific patient groups and will be discussed accordingly.

Relapsed, refractory, resistant, progressive or poor/slow responding patients

Although several studies investigating cost and outcomes have been undertaken since 1994, there is considerable variation in terms of treatments evaluated, and the trial and other data used to evaluate cost effectiveness. All of the studies were cost and outcome studies. The results are summarised in Table 25.7.

It appears that blood stem cell transplantation may result in improved clinical outcomes at lower cost and that the use of G-CSF, either with transplantation or chemotherapy, is clinically and cost effective. Some chemotherapy regimens may also result in better clinical outcomes and cost savings.

However, as these studies are only cost and outcome studies, and all evaluate different treatments, it is not possible to recommend one treatment over another. The studies do, however, give an indication of possible cost savings.

Table 25.7 Results of studies investigating costs and outcomes of alternative treatments for relapsed, refractory, resistant or poor/slow responding patients

Study	Study country	Study question	Conclusion
Uyl-de-Groot et al. 1999[45]	The Netherlands	Comparison of PBPCT transplant + filgrastim versus ABMT transplant	It appears that PBPCT + filgrastim is more cost effective than ABMT. PBPCT + filgrastim resulted in significantly accelerated granulocyte recovery and lower cost — US$16,890 (A$31,537) versus US$20,713 (A$38,675), an implied cost reduction of 18%.
Tarella et al. 1998[11]	Italy	PBPCT + G-CSF versus PBPCT (relapsed)	See Section 25.3.3.
Smith et al. 1997[12]	USA	PBPCT+ filgrastrim versus ABMT (relapsed)	See Section 2.3.3.
Jerjis et al. 1999[46]	The Netherlands	Comparison of APSCT versus ABMT transplantation	APSCT results in improved haematological recovery, less supportive care needs (less fever, transfusions, and medications) and significant cost savings — 34,178 NLG (A$61,650) versus 43,469 NLG (A$78,410).
Bennett et al. 1995[14]	USA	Assessment of cost of care and outcomes for HDC + ABMT or PBSCT over time for relapsed or refractory patients	Survival rates improved and cost of care decreased over time. Most significant factor for survival was the experience of the transplant team. Costs decreased at a rate of 8% per annum.
Dranitsaris and Sutcliffe 1995[16]	Canada	miniBEAM+ G-CSF versus miniBEAM (progressive)	See Section 2.3.3.
Souetre and Quing 1994[47]	France	Comparison of lenograstim versus none for treating complications	Lenograstim is associated with a reduction of total direct medical costs as a result of reduced morbidity and shorter LOS for reasons other than chemotherapy. Total cost was FF115,534 versus FF122,831 (A$255,064 versus $271,175), a reduction of FF7297 (A$16,110). Sensitivity analysis varying per diem room costs support the findings of cost savings — cost savings of FF3667–16,377 (A$8096–36,156).

Patients in remission

For information on studies in this area see Section 25.3.3.

First-line therapy

A French cost and outcome study by Woronnoff-Lemsi et al. 1997[48] compared PBPCT with ABMT transplantation and found that PBPCT resulted in significantly better engraftment, fewer days of intravenous antibiotics, fewer transfusions, and shorter LOS. Overall costs for PBPCT — US$35,381 (A$70,939) — were less than for ABMT — US$41,759 (A$83,726) —a saving of US$6378

(A$12,788). Sensitivity analysis indicated that the results are robust. This study provides some evidence of cost saving, but more evidence is required.

Patient status not specified/varied status

Several studies evaluating different treatments have been identified, although there is considerable variation in terms of treatments evaluated and evaluation type. These include one cost-effectiveness study and one cost-benefit analysis, with the remainder being cost and outcome studies. The results are summarised in Table 25.8. As the treatments evaluated were all different, it is not possible to recommend one method over another. The results should be used as an indication of the effect of interventions on costs and outcomes only.

Table 25.8 Results of studies investigating costs and outcomes of alternative treatments/interventions for patients where studies do not specify status or where patients of varied status are included in the study sample

Study	Study country	Study questions	Conclusion
Souetre, Quing and Penelaud 1996[18]	France	ABMT+ G-CSF versus ABMT	See Section 25.3.3.
Luce et al. 1994[19]	USA	ABMT + GM-CSF versus ABMT alone	See Section 25.3.3.
Uyl-de-Groot, Huijgens and Rutten 1996[20]	The Netherlands	Review — PBPCT versus ABMT, PBPCT versus ABMT+G-CSF	See Section 25.3.3.
Schulman et al. 1998[21]	USA	ABMT + CM-CSF + IL-3 versus ABMT + CM-CSF	See Section 25.3.3.
Dranitsaris, Altmayer and Quirt 1997[49]	Canada	Comparison of chemotherapy + G-CSF versus chemotherapy alone	Administration of G-CSF dosage 5 *ug*/kg/day for 11 doses following CHOP resulted in an overall net cost of CAN$1257 (A$1920), which is close to cost neutrality. Sensitivity analysis shows a dose reduction to 2 *ug*/kg/day would result in a net benefit of CAN$6564 (A$10,025), which is a societal cost saving. Cost-benefit analysis resulted in an institutional cost saving (neutropenic events avoided) of CAN$5007 (A$7647), and a societal cost saving (lost production avoided) of CAN$8016 (A$12,243).
Elting et al. 2003[50]	USA	TCP versus control cycle	Incremental cost attributed to thrombocytopenia is US$1037 (A$1825). However, only 40% of cycles were considered high/very high cost. Interventions targeted at this subset would significantly reduce the cost of thrombocytopenia.

Study	Study country	Study questions	Conclusion
Annemans et al. 2003[41]	Belgium, UK, Spain, The Netherlands	Comparison of rasburicase versus no rasburicase for prevention and treatment of hyperuricaemia and tumour lysis syndrome	Rasburicase is cost effective for the prevention of hyperuricaemia and tumour lysis syndrome in all countries — ICER = €30650–41383 (A$67,273–70,858/LYS). For treatment, it is highly cost effective — ICER = -€9776–2059 (-A$22,600–3347). Sensitivity analysis indicates that for prevention, it is sensitive to the risk of hyperuricaemia and tumour lysis.

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