therapy-related nausea and vomiting in children. *J Pediatr* 1988, 113, 146–149.
5. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. *Arch Dis Child* 1986, **61**, 502–505.
6. Leibundgut U, Lancranjan I. First results with ICS 205-930 (5-HT_3 receptor antagonist) in prevention of chemotherapy-induced emesis. *Lancet* 1987, **i**, 1198.
7. Dogliotti L, Faggiuolo R, Berruti A, Antonacci RA, Ortega C, Lancranjan I. Prevention of nausea and vomiting in cisplatin-treated patients by a selective 5-hydroxytryptamine (5-HT_3) receptor antagonist, ICS 205-930. *Tumori* 1990, **76**, 595–598.
8. Seinen H, Zonnenbeg BA, Tija P, Neijt JP. The effect of three dose levels of ICS 205-930 (a selective $5HT_3$ antagonist) on cisplatin-induced nausea and vomiting. *Eur J Clin Oncol* 1989, 25, 1333–1335.
9. Leventhal BG, Wittes RE. *Research Methods in Clinical Oncology*. New York, Raven Press, 1988, 211–212.
10. Data on file, Sandoz Pharma Ltd, Basle, Switzerland.

Acknowledgement—This study was carried out with the support of Sandoz Pharma Ltd and monitored by Véronique Laveix-Dietrich and David M. Fowler.

Pergamon

European Journal of Cancer Vol. 30A, No. 10, pp. 1441–1447, 1994

0959–8049/94 $7.00 + 0.00

0959-8049(94)00284-3

How Relevant is Secondary Leukaemia for Initial Treatment Selection in Hodgkin's Disease?

C.F. Hess, R.D. Kortmann, H. Schmidberger and M. Bamberg

Specific tools of decision analysis, a set of mathematical rules for simplifying complex decisions, were applied to evaluate the impact of secondary leukaemia on the selection of initial treatment in Hodgkin's disease (HD). For this purpose, a combined 'expected utility' considering survival, relapse free survival, and secondary leukaemia was determined for different treatment strategies. Our analysis revealed that considerations of secondary leukaemia for initial therapy should include the *a priori* estimation of all possible events which may occur after initial treatment, e.g. the probabilities of recurrence and success of salvage therapy. In early and intermediate stage HD, for example, the minimal risk of leukaemia after successful radiotherapy (RT) must be weighed against the increased risk after treatment failure and subsequent salvage therapy. Thus, the difference of expected risk of leukaemia between RT and combined modality treatment (CMT) is within 4% for HD, stage II B and near to 0% in stage III A. In advanced stage HD, the addition of RT to chemotherapy has no adverse effect on the expected utility of initial treatment. These conclusions are only marginally affected by reported differences in rates of recurrence, salvage success, and secondary leukaemia. Subjective quality of life considerations, such as the latency period between treatment and leukaemia and patients' attitudes towards the occurrence of leukaemia, did not significantly affect expected utilities. In summary, our results strongly suggest that presently there is no sound basis for reducing the intensity of initial treatment in HD to avoid secondary leukaemia.

Key words: decision analysis, quality of life, leukaemia, Hodgkin's disease, radiotherapy, chemotherapy
Eur J Cancer, Vol. 30A, No. 10, pp. 1441–1447, 1994

INTRODUCTION

THE MAJOR late complications in cured patients with Hodgkin's disease (HD) include secondary haematological disorders and solid cancer. Whereas the risk of second solid tumours seems to be equally influenced by chemotherapy and radiotherapy (RT), the incidence of leukaemia is clearly linked to the use of chemotherapy [1–10]. A higher association with intensive therapy, such as combined modality treatment (CMT) or salvage therapy for recurrence of HD has been suggested [2, 5, 10, 11].

Currently, there is a great variation in the reported rates of secondary leukaemia in the literature (Table 1). Consequently, considerable controversy exists whether the potential induction of leukaemia should influence the selection of the initial treatment strategy. Some authors concluded from their results that the risk of secondary leukaemia is so high that less intensive therapy should be considered [2, 12, 13, 14]. Other authors have recommended that the risk of leukaemia should be completely ignored for initial treatment selection [3, 7, 15–17]. In many publications, however, no specific recommendations were included [4, 5, 18, 19]. In particular, there is no detailed analy-

Correspondence to C.F. Hess at Universitätklinik, Robert-Koch-Str. 40, D-37075, Göttingen, Germany.
All other authors are at the Radiologische Klinik, Abt. für Strahlentherapie, Hoppe-Seyler-Str. 3, D-72076 Tuebingen, Germany.
Revised 24 May 1994; accepted 31 May 1994.
EJC 30:10-C

Table 1. Leukaemia rate for patients having received radiotherapy (RT) alone, continued modality treatment (CMT) and salvage therapy for relapse of Hodgkin's disease (HD)

Treatment	Cumulative rate (mean ± standard deviations* or rates† of secondary leukaemia) (minimum follow-up in years)	References
RT alone	0–1.4% (10)†	[2, 3, 5, 13, 16, 17, 19, 24, 27]
Chemotherapy alone	1.3% (5), 1.8% (10)	Baccarini [3]
	3.9 ± 1.3% (5), 9.9 ± 2.9% (10)*	Bjergaard [24]
	0.2–22.8% (15)†	Devereux [15]
	2–3% (10,MOPP), 3–6% (10,BCNU)†	Hellman [5]
	2.0% (10)	Lavey [16]
	6.3% (15)	van Leuuwen [27]
	5.6% (10)	van Rijswijk [17]
	1.4 ± 2.3% (12)*	Valagussa [19]
CMT	3.5 ± 2.7% (15)*	Andrieu [2]
	2.3% (5)	Baccarini [3]
	3.9 ± 13% (5), 9.9 ± 2.9% (10)*	Bjergaard [24]
	3.1 ± 0.9% (10), 8.1 ± 4.0 (20)*	Cimino [4]
	0.2–22.8% (15)†	Devereux [15]
	2.9% (10)	Hancock [18]
	2–8% (10)†	Hellman [5]
	12.4% (10)	Henry-Amar [13]
	0.9% (10)	Lavey [16]
	3.0% (10)	van Rijswijk [17]
	0% (ABVD) – 10.5 ± 5.2% (MOPP)*	Valagussa [19]
Salvage chemotherapy after recurrence of HD	1.8 ± 1.0% (10), 16 ± 8 (20)*	Cimino [4]
	2.9% (10)	Hancock [18]
	5–15% (10)†	Hellman [5]
	4.7% (10)	van Rijswijk [17]

sis available, considering both benefit and complications of the competing treatment strategies, in the various clinical settings. This should be of specific interest when choosing between RT alone or chemotherapy ± RT in early or intermediate stage HD (e.g. HD, stage II B or III A).

The goal of the present analysis was to examine quantitatively the expected therapeutic gain of different treatment strategies considering survival, relapse free survival and treatment-related leukaemia. For this purpose, specific tools of decision analysis, a set of mathematical rules for simplifying complex decisions, are applied [20–23]. The following questions are assessed.

(1) Can we make a rational choice between RT, chemotherapy and CMT in early or intermediate stage of HD, considering both survival and treatment-related leukaemia?
(2) How does this choice vary within the range of probabilities known from the literature (e.g, survival, recurrence rate, rate of leukaemia)?
(3) How is this choice altered, if the patient weighs the occurrence of leukaemia less heavily than death after tumour recurrence? This more subjective aspect should be considered since secondary leukaemia may occur late (3–11 years) after initial therapy, and is not necessarily an inevitably fatal event [1, 7, 13, 15, 24–29]. The preferences of the patients are difficult to quantify, but they can be of decisive importance in the choice which a patient and a doctor will have to make [30].

MATERIAL AND METHODS

Expected risk of treatment-related leukaemia

Patients with HD can be treated with curative intention by initial RT, chemotherapy or CMT. In the literature, various probabilities of treatment-related leukaemia have been reported, describing the proportion of patients that have experienced leukaemia during their course of the disease. Usually, these probabilities have been assessed retrospectively for patients having received RT alone, chemotherapy only, CMT or chemotherapy for relapse of HD (Table 1).

However, these figures do not indicate the expected risk of leukaemia after a specific initial therapy. If, for example, RT alone is initiated in a patient with HD stage II B, the expected risk of leukaemia should consider the possibility of recurrence—with subsequent salvage therapy and increased risk of leukaemia. Therefore, the probabilities of all possible events during the further course of the disease must be considered for the choice of the initial treatment (Figure 1).

Depending on individual prognostic factors, such as stage, presence of B symptoms etc., patients will have different initial treatments and different courses of disease. A varying number of patients will be cured without any further treatment. Patients with tumour recurrence after primary treatment may undergo a salvage procedure. Patients eligible for salvage therapy may become free of disease or the tumour will persist and they will die. A certain proportion of surviving patients will experience leukaemia (Figure 1).

In particular, the rates of recurrences with subsequent salvage therapy are of considerable importance. For HD stage II B, these events have been structured and visualised in a decision tree presented in Figure 1, including recurrence and survival rates at 7 and 10 years, respectively, which have been reported by the Stanford group [31]. The leukaemia rates used in Figure 1 are mean cumulative incidences at 10 years estimated by Hellman and colleagues [5]: 0, 6 and 10% for cured patients after

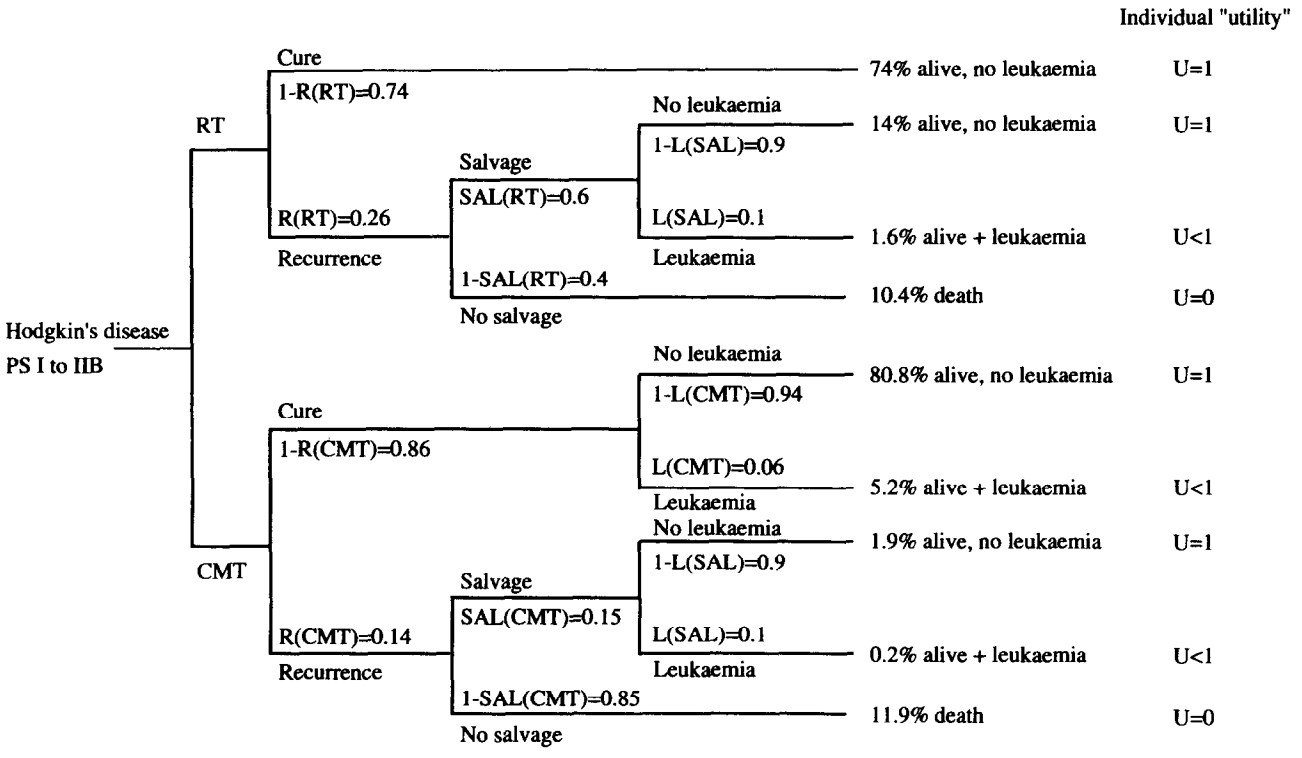

Figure 1. Decision tree for the treatment of patients with HD, stages I to II B. The recurrence and survival rates are given at 7 and 10 years, respectively [31]. The used cumulative incidences (L) of leukaemia at 10 years after radiotherapy (RT) alone, combined modality treatment (CMT) and salvage therapy (SAL) are L(RT) = 0, L(CMT) = 0.06 and $L(SAL)$ = 0.10, respectively [5]. U, 'utility'.

initial RT, initial CMT and after salvage therapy following recurrence of HD, respectively. The overall probability of each particular event can easily be calculated by multiplying the probabilities in each branch of the tree [21–23]. From these data two conclusions can be drawn as follows.

(1) After initial RT, there is only a risk of leukaemia in the subgroup of patients who suffer from a recurrence and who are cured by salvage therapy. Consequently, for the total group with initial RT, the expected cumulative risk of leukaemia at 10 years is $0.26 \times 0.6 \times 0.1 = 1.56\%$ (recurrence rate × cure rate after recurrence × leukaemia rate after salvage therapy).

(2) After initial CMT, all cured patients have a significant risk of developing leukaemia. However, the risk differs between the patients with and without recurrence. For the total group of patients initially receiving CMT, the expected cumulative risk of leukaemia at 10 years is $0.86 \times 0.06 + 0.14 \times 0.15 \times 0.1 = 5.2\% + 0.2\% = 5.4\%$ (cure rate × leukaemia rate after CMT + recurrence rate × cure rate after salvage therapy × leukaemia rate after salvage therapy).

Occurrence of leukaemia: subjective patient-oriented considerations

Thus, in the particular situation shown in Figure 1, the expected cumulative risk of treatment-related leukaemia at 10 years is 1.6% after initial RT and 5.4% after initial CMT. However, the clinical impact of these figures is also determined by the importance ('utility', U: $0 \leq U \leq 1$) that is given by the individual patient to the occurrence of leukaemia (Figure 1), as compared with successful treatment without leukaemia ($U = 1$) and to death following recurrence of HD ($U = 0$). As the latency period after initial treatment is greater for leukaemia than for death after recurrence of HD, $U > 0$ may be assumed. Taking into account, however, that acute non-lymphocytic leukaemia is almost always uncurable, U should be closer to 0 than to 1. In any case, different values may be attached by individual patients.

With the quantification of utilities for a given patient, a rational decision can be made on the patient's behalf without requiring that the patient possesses detailed knowledge of the probabilities for all possible outcomes. This analysis (decision analysis [20–23]) does not reduce uncertainty, but does enable a decision maker to make rational choices between alternative strategies, each with uncertain outcomes. If the problem is appropriately described and the probabilities and weights are assigned as accurately as possible, then any finite difference in 'expected utility' should tilt the decision in favour of the apparently better strategy [21–23].

Consideration of survival and treatment-related leukaemia: the concept of 'expected utility' for initial treatment strategies

In general, for competing therapies in HD, expected rates of survival or of recurrence free survival are considered. Expected survival rates (S) can be easily calculated from recurrence rates (R) and salvage rates (SAL):

$$S = 1 - R + R \times SAL. \quad (1)$$

For example, in Figure 1, for initial RT, survival is determined by $S = 0.74 + 0.26 \times 0.60 = 0.896$.

For additional consideration of secondary leukaemia, the branches with leukaemia are weighed by the incidence (L) and the individual 'utility' (U) of leukaemia. Consequently, the

'expected utility' (EU) of each initial treatment can be calculated by

$$EU(\mathrm{RT}) = (1\text{-}R(\mathrm{RT})) + R(\mathrm{RT}) \times SAL(\mathrm{RT}) \times (1\text{-}L(SAL)+L(SAL)\times U) \quad (2a)$$

and

$$EU(\mathrm{CMT}) = (1\text{-}R(\mathrm{CMT})) \times (1\text{-}L(\mathrm{CMT})+L(\mathrm{CMT})\times U) + R(\mathrm{CMT}) \times SAL(\mathrm{CMT}) \times (1\text{-}L(SAL)+L(SAL)\times U). \quad (2b)$$

In Figure 1, we have assumed $L(\mathrm{RT}) = 0$ and $L(\mathrm{CMT}) = 0.06$ for cured patients after initial RT and after CMT, respectively, and $L(SAL) = 0.1$ for patients successfully treated after tumour recurrence (see Table 1).

For the data shown in Figure 1 (HD, stage II B), for example, expected utilities for initial RT and for initial CMT are 0.880 and 0.827, respectively, if the occurrence of leukaemia is weighted as heavily as death tumour recurrence ($U = 0$). If a patient assigns an intermediate 'utility' value, $U = 0.5$, to the occurrence of leukaemia, the resulting figures are 0.888 and 0.854.

For $U = 1$, EU is identical to survival (S in equation 1).

Different treatment results in the literature: how do they affect expected utilities of competing treatments?

It is obvious from the decision tree in Figure 1 that changes of the recurrence and salvage rates should influence the expected utilities of competing therapies. If, for example, the recurrence rate after initial RT increases, there is a decrease in survival, but also an increase in the risk of treatment-related leukaemia. It is also clear from Figure 1 that varying rates of leukaemia and different attachments of utility values affect expected utilities.

Quantitative evaluation of the relationship between these issues is important, since considerable differences between treatment results have been reported in the literature for a variety of clinial settings. The consequences of different data in the literature can easily be demonstrated by appropriate analysis of equation 2 (see Results).

RESULTS

Impact of different recurrence rates on the expected utilities

In Figure 2a, expected utilities are calculated for varying recurrence rates, with and without consideration of treatment related leukaemia. For the calculation of the utility lines in Figure 2a, the same rates for successful salvage therapy and for secondary leukaemia are used as in Figure 1 [5, 31]. The upper lines in the diagrams represent a situation in which the induction of leukaemia is completely disregarded ($U = 1$ in Figure 1). For the lower line, it is assumed that the occurrence of leukaemia is weighted as heavily as death after tumour recurrence ($U = 0$ in Figure 1).

It is obvious from Figure 2 that the consideration of treatment-related leukaemia has a considerably different impact on the expected utility for initial radiotherapy and initial combined modality treatment. For initial RT, the lines are divergent. This means that with increasing recurrence rates, consideration of leukaemia becomes more important. This is due to the increasing rates of leukaemia after successful salvage chemotherapy (see Figure 1). For initial CMT, the lines are convergent. Therefore, with increasing recurrence rates, there is a minor effect on expected utility. The reason for this phenomenon is that, in this group, leukaemia is mainly caused by the initial treatment, and

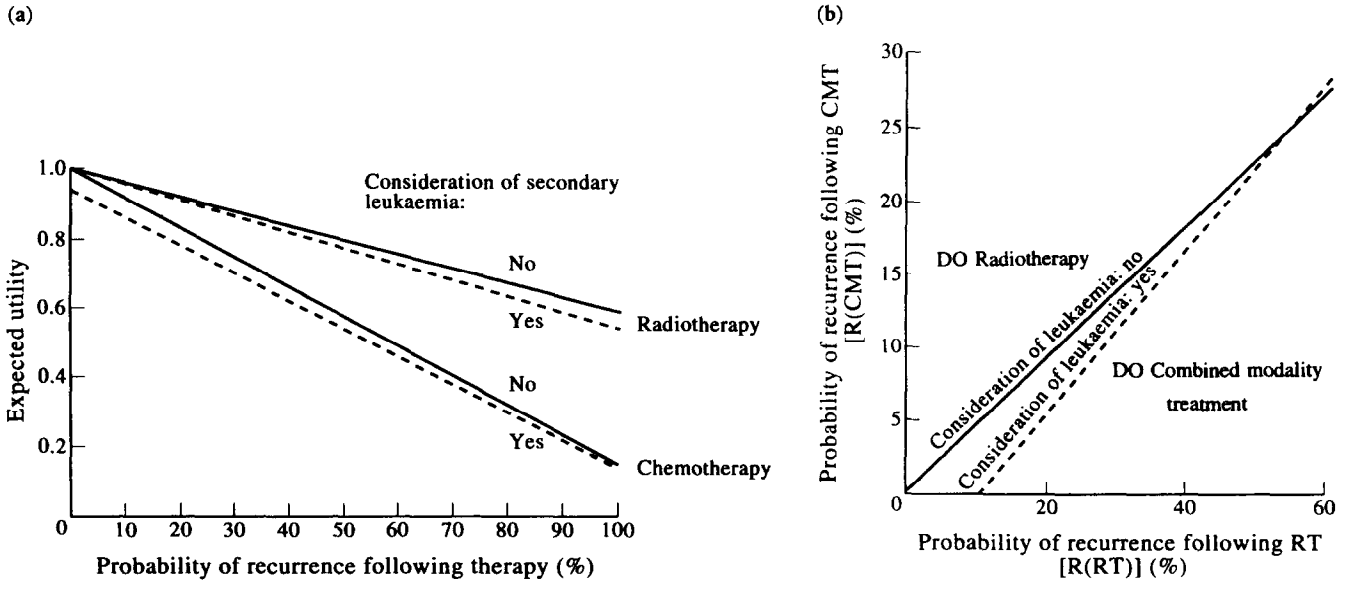

Figure 2. Consideration of secondary leukaemia for initial treatment selection in early and intermediate stage HD. The quantitative evaluations are based on the same probabilities of successful salvage therapy and the same cumulative incidences of secondary leukaemia as in Figure 1. Expected utilities are determined for $U = 1$ (consideration of survival only) and for $U = 0$ (occurrence of leukaemia weighed as heavily as death after tumour recurrence). (a) With increasing recurrence rate after initial therapy, the difference between the expected utilities for $U = 1$ and $U = 0$ become more prominent for initial RT alone and less prominent for initial CMT. (b) 'Decision lines' which separate the areas in which RT alone and CMT should be preferred (with and without consideration of secondary leukaemia). For each particular pair [R(RT),R(CMT)] which is located above the decision line, the expected utility is greater for RT ('do RT'). For each pair below the decision line, the expected utility is greater for CMT ('do CMT'). If the recurrence rate following RT is less than 50% (e.g. early or intermediate stage HD) consideration of secondary leukaemia results in an increase of the 'RT area'. With increasing recurrence rates, the decision lines are converging and crossing at (55, 26%).

that most patients with recurrent disease do not experience leukaemia because of unsuccessful salvage therapy (see Figure 1).

In Figure 2b recurrence rates after initial radiotherapy and after CMT that result in identical expected utilities are arranged on a decision line, for $U = 0$ (leukaemia considered) and $U = 1$ (leukaemia disregarded). As an example, for $U = 1$ recurrence rates of 0.26 and 0.14, after radiotherapy and CMT, lead to identical expected utilities of 0.88. All pairs of recurrence rates above the decision lines should favour initial RT and all pairs below should favour CMT. The details of the calculations for the determination of the decision lines are given in the Appendix.

For $U = 0$, the decision line is below the line for $U = 1$, and the region for RT is enlarged. As discussed above, this effect is most prominent for low rates of recurrence. From this analysis, it is obvious that patients with HD stage III A cannot substantially benefit from initial RT in terms of treatment-related leukaemia, since recurrence rates after RT alone are higher than 30% [5]. For patients with HD, stage II A/B, there may be a benefit for patients with initial RT. However, compared with survival, this benefit is within 4% (Figure 2a).

Impact of different salvage rates on the expected utilities

For Figure 2, salvage rates of 0.6 and 0.15 are assumed after initial RT and CMT, respectively. For RT, these figures are in the upper range of the reported data, and for CMT in the lower range [5]. If the salvage rate after RT was actually lower and if the salvage rate after CMT was actually higher, divergence of the curves after initial RT and convergence of the curves after initial CMT become less prominent. Thus, the consideration of leukaemia would become even less important. The same conclusion can obviously be drawn, if the occurrence of leukaemia is weighed less heavily (e.g. $U = 0.5$).

Impact of the leukaemia rate on the expected utilities

The conclusions drawn from Figures 1 and 2 are based on mean cumulative incidences at 10 years which have been reported by Hellman and colleagues: 0, 6 and 10% after RT alone, CMT, and salvage therapy, respectively [5]. However, in the literature, different rates have been reported for very similar clinical and therapeutic situations (Table 1). For CMT, for example, most figures are in the range between 2 and 10%.

In Figure 3, it is demonstrated how differences in this range may result in different conclusions on the appropriate initial therapy. Expected utilities are presented for different assumptions on the rate of treatment related leukaemia. For the calculation of the 'utility lines' in Figure 3, survival rates of 85 and 90%, recurrence rates of 30 and 15% and salvage rates of 50 and 33% are assumed for initial RT and CMT, respectively. These figures have been reported for the treatment of HD, pathological stage III A [5, 8]. In addition, it is assumed in Figure 3 that the rate of leukaemia after salvage therapy is twice the rate after CMT [5]. Treatment-related leukaemia is weighted as heavily as death after tumour recurrence.

For the assumptions made in Figure 3, initial RT is found to be superior to CMT, if treatment-related leukaemia exceeds a rate of 7.5% after CMT or 15% after treatment for tumour relapse. However, such a rate is only rarely reported (Table 1). Even for a 10% rate of leukaemia, the benefit in favour of RT is minimal.

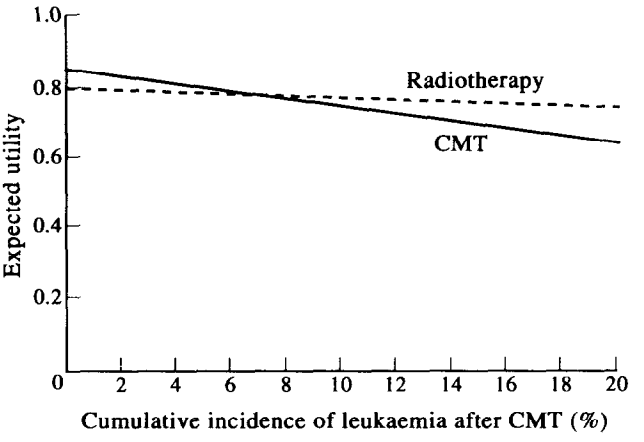

Figure 3. Expected utilities of initial RT alone and CMT in HD, stage III A, for varying rates of secondary leukaemia (at 10 years). For the calculation of the 'utility lines', survival rates of 85 and 90%, recurrence rates of 30 and 15%, and salvage rates of 50 and 33% are assumed for initial RT and CMT, respectively. If the leukaemia rate after CMT exceeds 7.5%, there is limited benefit for initial RT.

DISCUSSION

Within the past decades, wide-field RT and combination chemotherapy have become accepted approaches for the treatment of Hodgkin's disease. Because of the effectiveness of these two main treatment modalities, most patients diagnosed with Hodgkin's disease today enjoy a high probability of cure and, as they are generally young, a long life expectancy after treatment. Therefore, treatment decisions are increasingly influenced by the expected late sequelae of treatment, as well as the expected efficacy of particular treatment regimens [5, 8, 25, 32–34].

It is well accepted that the most serious complication of therapy of Hodgkin's disease is the risk of developing secondary leukaemia [4, 5, 13, 25, 28]. This risk is clearly linked to treatment with chemotherapy (particularly with alkylating agents), with a latency period between treatment and leukaemia between 3 and 11 years [1–19, 24–28, 35]. In addition, association with intensity of treatment has been suggested [1, 2, 5, 8, 13, 14]. Consequently, some authors have recommended that less intensive therapy in HD should be considered [2, 12–14]. In particular, considerable efforts have been undertaken to delineate the subset of patients that can be safely treated by RT alone [36, 37].

However, our analysis revealed, that the expected risk of secondary leukaemia after initial therapy for HD (e.g. RT alone) cannot be directly derived from the reported data in the literature, because the published rates of leukaemia have been retrospectively assessed for patients having received RT only, chemotherapy only, CMT or chemotherapy for relapse. Considerations of treatment-related leukaemia for initial therapy however, should include the *a priori* estimation of all possible events which may occur during the subsequent life of each patient.

After initial RT for HD, stage II B, for example, the minimal risk of leukaemia after successful initial RT must be weighed against the increased risk after treatment failure [14, 30]. This risk is not negligible, because about 30% of patients may recur, and 60% of these patients may be cured by salvage therapy [31]. In contrast, secondary leukaemia may occur in a higher proportion of patients successfully treated with initial CMT. After CMT, leukaemia is mainly caused by the initial treatment, and most patients with recurrent disease in this group do not experience leukaemia because of unsuccessful salvage therapy [5, 31, 38].

Therefore, the analysis of expected risk of leukaemia for competing initial therapies is complex, and the expected rates of

recurrence as well as of successful salvage therapy must be considered [21–23]. For this purpose, specific tools of decision analysis, a set of mathematical rules for simplifying complex decisions, were used. In the present quantitative approach, 'expected utilities' were determined for each treatment considering both, survival and secondary leukaemia. This approach may provide insights not available from clinical studies or expert opinion [20–23]. Since physicians have the responsibility of maximising the patient's probability of a successful outcome, the selection of therapy remains a 'probability issue' [36].

In contrast to other recommendations [2, 12–14], our analysis suggests that consideration of treatment-related leukaemia should not have a decisive impact on the selection of the initial treatment strategy in HD. In particular, it has been shown that—for all practical purposes—the intensity of initial treatment has only a minor influence on the expected risk of leukaemia in early or intermediate stage HD. For HD, stage III A, for example, the expected risk is similar after initial RT and CMT. For HD, stage PS I/II B, differences of the expected risks of leukaemia between initial RT and CMT are within 4%. For the analysis of survival, such a difference is within the statistical variability of most reported studies.

It is well known that a variety of solid tumours may occur after various treatment schedules in HD, at varying time points after therapy, and with varying cure rates after secondary treatment [1, 3–6, 8, 11, 12, 16, 19, 25, 27, 28, 35, 39]. Therefore, a decision analytical approach to the impact of secondary solid tumours on initial treatment selection in HD would require a large body of detailed data, which is presently not available in the literature. It has been suggested, however, that the potential development of secondary solid tumours should be of minor importance for initial treatment selection in HD, because these tumours seemed to be equally related to initial chemotherapy and RT [11]. A decision analytical approach to the importance of non-fatal side effects of HD, such as treatment-related infertility, would necessitate reliable information about subjective preferences of individual patients which are equally not available at the present time [5, 8, 40].

The expected utility of competing initial treatment strategies—considering both survival and treatment-related leukaemia—can be derived from our results for a variety of clinical situations. In early or intermediate stage HD disease, the expected utility may be slightly greater for initial RT than for initial chemotherapy or CMT regimens, if the recurrence rate after RT is below 30%. For chemotherapy in intermediate stage HD, one can similarly conclude from our results, that the substitution of MOPP by ABVD—which is apparently less leukaemogenic—should only affect the expected utility significantly if the recurrence rate after ABVD is low. In advanced stages of HD, the addition of RT to chemotherapy and the extent of RT should not have adverse effects on the expected risk of treatment-related leukaemia, since this risk is significantly determined by salvage therapy, which is frequently needed after any form of treatment [6, 16–18, 24, 26, 28].

In addition, our analysis demonstrates that the conclusions drawn on initial treatment selection are only marginally affected by differences in rates of recurrence or treatment-related leukaemia which have been reported by different institutions. Similarly, neither potential risk factors of secondary leukaemia such as age, more advanced stages and splenectomy, nor the latency period between treatment and leukaemia nor patients' attitudes to the occurrence of leukaemia should be of final importance for the selection of initial treatment [1, 3, 4, 10, 13, 24, 26, 27, 29].

In summary, our results suggest that in the treatment of HD even small gains in survival outweigh in importance the risk of treatment-related leukaemia. At present, there is no sound basis for reducing the intensity of treatment to avoid secondary haematologic disorders [6, 7, 15, 26, 28, 30]. Controversies about the incidence of treatment-related leukaemia after different treatment modalities are of scientific interest, but of limited practical importance for the selection of initial treatment. Further investigations are necessary, however, to evaluate the impact of non-fatal, but more frequent side-effects, such as chemotherapy-related infertility [5, 8, 20, 33, 37, 40].

1. Abrahamsen JF, Andersen A, Hannisdal E, *et al.* Second malignancies after treatment of Hodgkin's disease: the influence of treatment, follow-up time, and age. *J Clin Oncol* 1993, **11**, 255–261.
2. Andrieu JM, Ifrah N, Payen C, Fermanian J, Coscas Y, Flandrin G. Increased risk of secondary nonlymphocytic leukaemia after extended-field radiation therapy combined with MOPP chemotherapy for Hodgkin's disease. *J Clin Oncol* 1990, **8**, 1148–1154.
3. Baccarani M, Bosi A, Papa G. Second malignancy in patients treated for Hodgkin's disease. *Cancer* 1980, **46**, 1735–1740.
4. Cimino G, Papa S, Tura S, Mazza P, Rossi-Ferrini PL, Bosi A, *et al.* Second primary cancer following Hodgkin's disease. Updated results of an Italian multicentric study. *J Clin Oncol* 1991, **9**, 432–437.
5. Hellman S, Jaffe ES, De Vita VT. Hodgkin's disease. In De Vita VT, Hellman SA, Rosenberg SA, eds. *Cancer. Principles and Practice of Oncology*, 3rd edn. Lippincott, Philadelphia, 1989, 1696–1740.
6. Henry-Amar M. Second cancer after the treatment for Hodgkin's disease: a report from the International Database on Hodgkin's Disease. *Ann Oncol* 1992, **3**, (Suppl. 4), S117–128.
7. Henry-Amar M, Dietrich P-Y. Acute leukaemia after the treatment of Hodgkin's disease. *Hematol Oncol Clin North Am* 1993, **7**, 369–387.
8. Santoro A, Valagussa P. Advances in the treatment of Hodgkin's disease. *Curr Opin Oncol* 1992, **4**, 821–828.
9. Somers R, Henry-Amar M, Meerwaldt JH, Carde P, eds. *Treatment Strategy in Hodgkin's Disease.* Colloque Inserm no 196. London, Paris, Les Editions Inserm/John Libbey Eurotext, 1990.
10. Tura S, Fiacchini M, Zinzani PL, *et al.* Splenectomy and the increased risk of secondary acute leukaemia in Hodgkin's disease. *J Clin Oncol* 1991, **11**, 925–930.
11. Swerdlow AJ, Douglas AJ, Vaughan Hudson G, Vaughan Hudson B, Bennett, Mac Lennan KA. Risk of second primary cancer after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. *Br Med J* 1992, **304**, 1137–1143.
12. Arsenau JC, Sponzo RW, Levin DL, *et al.* Nonlymphomatous malignant tumours complicating Hodgkin disease. Possible association with intensive therapy. *New Engl J Med* 1972, **287**, 1119–1122.
13. Henry-Amar M, Pellae-Cosset, Bayle-Weisgerber C, *et al.* Risk of secondary acute leukaemia and preleukaemia after Hodgkin's disease. The Institut Gustave-Roussy experience. *Recent Results in Cancer Res* 1989, **117**, 271–283.
14. Valagussa P, Santoro A, Kenda R, Fossate-Bellani F, Franchi F, Banfi A *et al.* Second malignancies in Hodgkin's disease: a complication of certain forms of treatment. *Br Med J* 1980, **280**, 216–219.
15. Devereux S, Selassie TG, Vaughan Hudson G, Vaughan Hudson B, Linch DC. Leukaemia complicating treatment for Hodgkin's disease: the experience of the British National Lymphoma Investigation. *Br Med J* 1990, **301**, 1077–1080.
16. Lavey RA, Eby NL, Prosnitz LR. Impact on second malignancy risk of the combined use of radiation and chemotherapy for lymphomas. *Cancer* 1990, **66**, 80–88.
17. van Rijswijk REN, Verbeek J, Haanen C, Dekker AW, van Daal, van Peperzeel. Major complications and causes of death in patients treated for Hodkin's disease. *J Clin Oncol* 1987, **10**, 1624–1633.
18. Hancock SL, Hoppe RT, Horning SJ, Rosenberg SA. Intercurrent

death after Hodgkin disease therapy in radiotherapy and adjuvant MOPP trials. *Ann Intern Med* 1988, **109**, 183–189. Erratum, *Ann Intern Med* 1991, **114**, 810.
19. Valagussa P, Santuro A, Fossati-Bellani F, Banfi A, Bonadonna G. Second acute leukaemia and other malignancies following treatment for Hodgkin's disease. *J Clin Oncol* 1986, **4**, 830–837.
20. Corder, MP, Ellwein, LB. Comparison of treatments for symptomatic Hodgkin's lymphoma employing decision analysis. *Am J Clin Oncol* 1984, **6**, 33–38.
21. Greenes RH. Computer-aided strategy selection. *Radiol Clin N Am* 1986, **24**, 105–119.
22. Pauker SG, Kassirer JP. Decision analysis. *New Engl J Med* 1987, **316**, 250–258.
23. Stalpers LJA, Verbeek ALM, van Daal WAJ. Radiotherapy or surgery for T2 N0 M0 glottic carcinoma? A decision analytic approach. *Radiother Oncol* 1989, **14**, 209–214.
24. Pedersen-Bjergaard J, Larson SO. Incidence of nonlymphocytic leukaemia, preleucemia, and acute myeloproliferative syndrome up to 10 years after treatment of Hodgkin's disease. *New Engl J Med* 1982, **307**, 965–971.
25. Henry-Amar M, Hayat M, Meerwaldt JB, Burgers M, Carde P, Somers P, *et al.* Causes of death after therapy for early stage Hodgkin's disease entered on EORTC protocols. *Int J Radiat Oncol Biol Phys* 1990, **19**, 1155–1157.
26. Kaldor JM, Day NE, Clarke EA, *et al.* Leukaemia following Hodgkin's disease. *New Engl J Med* 1990, **322**, 7–13.
27. van Leeuven FE, Somers R, Taal BG, *et al.* Increased risk of lung cancer, non-Hodgkin's lymphoma, and leukaemia following Hodgkin's disease. *J Clin Oncol* 1989, **7**, 1046–1058.
28. Mendenhall NP, Shuster JJ, Million RR. The impact of stage and treatment modality on the likelihood of second malignancies and hematopoietic disorders in Hodgkin's disease. *Radiother Oncol* 1989, **14**, 219–229.
29. Blayney DW, Longo DL, Young RC, *et al.* Decreasing risk of leukaemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. *New Engl J Med* 1987, **316**, 710–714.
30. Hopwood, P. Progress, problems and priorities in quality of life research. *Eur J Cancer* 1992, **28A**, 1748–1752.
31. Crnkovitch MJ, Leopold K, Hoppe RT, Mauch PM. Stage I to II B Hodgkin's disease: the combined experience at Stanford University and the Joint Center for Radiation Therapy. *J Clin Oncol* 1987, **5**, 1041–1049.
32. Longo DL, Glatstein E, Duffey PL, *et al.* Radiation therapy versus combination chemotherapy in the treatment of early stage Hodgkin's disease. Seven-year results of a prospective randomized trial. *J Clin Oncol* 1991, **9**, 906–917.
33. Lacher MJ, Redman JR. *Hodgkin's Disease: The Consequences of Survival*. Philadelphia, Lea & Febiger, 1990.
34. Vriesendorf HM, Order SE. Hodgkin's disease. New possibilities for clinical research. *Int J Radiat Oncol Biol Phys* 1989, **17**, 1119–1121.
35. Zarrabi MH, Rosner F. Second neoplasms in Hodgkin's disease. Current controversies. *Hematol Oncol Clin North Am* 1989, **3**, 303–318.
36. Raubitschek A, Glatstein E. The never-ending controversies in Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1989, **17**, 1115–1117.
37. Wasserman TH, Tubiana M. Lymphoma: radiation therapy in lymphoma treatment. *Int J Radiat Oncol Biol Phys* 1988, **14**, 187–201.
38. Longo DL, Duffey PL, Young RC. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. *J Clin Oncol* 1992, **10**, 210–218.
39. Tucker MA. Solid second cancers following Hodgkin's disease. *Hematol Oncol Clin North Am* 1993, **7**, 389–400.
40. Hohl RJ, Schilsky RL. Nonmalignant complications of therapy for Hodgkin's disease. *Hematol Oncol Clin of North Am* 1989, **3**, 331–343.

APPENDIX

The decision lines in Figure 2 can easily be calculated from equations 1 and 2.

For $U = 1$ survival only is considered. Assuming salvage rates $SAL(\mathrm{RT}) = 0.6$ and $SAL(\mathrm{CMT}) = 0.15$, identical survival (S) for RT and CMT is achieved, if

$$S(\mathrm{RT}) = S(\mathrm{CMT}) \text{ or if } 1\text{-}R(\mathrm{RT}) + 0.6 \times R(\mathrm{RT}) = 1\text{-}R(\mathrm{CMT}) + 0.15 \times R(\mathrm{CMT}).$$

From this equation the 'decision line'

$R(\mathrm{CMT}) = 0.40/0.85 \times R(\mathrm{RT})$ can be determined.

For $U = 0$ the occurrence of leukaemia is weighted as heavily as death after recurrence of HD. If cumulative risks of leukaemia of 0, 0.06 and 0.10 are assumed after initial RT, initial CMT, and after salvage therapy, respectively, the following expected utilities for inital RT and CMT can be calcualated from equation 2:

$$EU(\mathrm{RT}) = 1\text{-}R(\mathrm{RT}) + 0.6 \times 0.9 \times R(\mathrm{RT}) = 1 - 0.46 \times R(\mathrm{RT})$$

and

$$EU(\mathrm{CMT}) = (1\text{-}R(\mathrm{CMT}))(1\text{-}0.06) + 0.15 \times 0.9 \times R(\mathrm{CMT}) = 0.94 - 0.80\,R(\mathrm{CMT}).$$

Obviously, in this case,

$$EU(\mathrm{RT}) = EU(\mathrm{CMT})$$

if

$$R(\mathrm{CMT}) = 0.46/0.80 \times R(\mathrm{RT}) - 0.06.$$