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Safety, Tolerability, Efficacy and Plasma Concentrations of Tropisetron After Administration at Five Dose Levels to Children Receiving Cancer Chemotherapy

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In a double-blind, placebo-controlled, escalating dose study, 44 children receiving cancer chemotherapy of various degrees of emetogenicity were randomly allocated to once-daily treatment with tropisetron 0.05 mg/kg (6 patients), 0.10 mg/kg (5 patients), 0.20 mg/kg (6 patients), 0.33 mg/kg (6 patients), 0.50 mg/kg (6 patients) or placebo (15 patients). All doses of tropisetron were well tolerated; no tropisetron recipient discontinued treatment because of intolerance and no adverse effect could be plausibly correlated to tropisetron administration. Therapeutic plasma concentrations of tropisetron (> 3 ng/ml) were present for 9 h after administration of doses of 0.10 mg/kg or more. Tropisetron at doses of at least 0.20 mg/kg was significantly more effective in preventing vomiting than lower tropisetron doses or placebo, both in terms of treatment failure (> four vomits) ($P = 0.015$) and patient and investigator efficacy ratings ($P = 0.04$ for investigator rating; $P = 0.035$ for patient rating). Further comparative studies of the efficacy of tropisetron in chemotherapy-induced emesis in children are warranted.

Key words: tropisetron, adverse effects, children, therapeutic use, chemotherapy-induced emesis
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INTRODUCTION

THE TREATMENT of many childhood malignancies involves the administration of emetogenic agents and, therefore, control of chemotherapy-induced nausea and vomiting is an important part of paediatric oncological practice. Substituted benzamides, such as metoclopramide and alizapride, are widely prescribed, but their usefulness is limited by the distonic reactions that they produce at higher doses, and which are especially common in children and young adults [1, 2]. Other anti-emetic therapies (phenothiazines, benzodiazepines and cannabinoids) have been used [3–5] but are similarly handicapped by poor efficacy or unwanted effects.

Tropisetron (ICS 205930, Navoban®; Sandoz Pharma Ltd, France) belongs to a new class of anti-emetic agents, the 5-HT_3 receptor antagonists. It has been shown to prevent nausea and vomiting in adults receiving highly emetogenic chemotherapeutic regimens containing cisplatin, and to be well tolerated by adult patients [6–8]. In view of these encouraging results in adults, tropisetron is also of potential benefit to children receiving emetogenic chemotherapy.

This double-blind, placebo-controlled, escalating dose study was undertaken primarily to investigate the safety and tolerability of 5–7 days of treatment with tropisetron at five dose levels in children receiving cancer chemotherapy. In addition, plasma concentrations of tropisetron were assayed at three time-points after dosing, and the efficacy of the drug in controlling nausea and vomiting was assessed.

PATIENTS AND METHODS

Forty-four children aged between 2 and 18 years with a variety of malignant solid tumours were included in the study (Table 1). Patients with any current or previous medical condition that could interfere with the evaluation of the study drug or put patients at risk, such as severe hepatic, renal or cardiac insufficiency, uncontrolled infection, hypersensitivity or drug allergy, were not included. Administration during the study of anti-emetic agents other than tropisetron, drugs known to induce hepatic enzyme synthesis, neuroleptics and azole antifungal agents, were prohibited. The study was carried out in accordance with the Tokyo amendment of the Declaration of Helsinki and was approved by the local ethics committee. The assent of the

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Table 1. Baseline characteristics of the six treatment groups

		Tropisetron dose (mg/kg)					
	Placebo	0.05	0.10	0.20	0.33	0.50	Total
Patients (*n*)	15	6	5	6	6	6	44
Sex (*n*)							
Male	12	5	5	5	5	5	37
Female	3	1	0	1	1	1	7
Age (years)							
Mean	9.9	7.3	13.4	9.8	12.8	12.3	10.7
S.D.	5.5	2.8	3.3	3.5	3.3	2.8	4.4
Weight (kg)							
Mean	36.1	25.5	41.3	32.7	42.2	38.9	36.0
S.D.	20.3	9.5	10.6	12.5	9.7	11.0	15.0
Height (cm)							
Mean	139	123	155	136	151	148	141
S.D.	32	18	21	16	25	9	25
Tumour (*n*)							
Lymphoma	7	3	1	3	2	3	19
Rhabdomyosarcoma	4	0	2	1	1	2	10
Osteosarcoma	1	2	2	0	1	0	6
Cerebellar medulloblastoma	0	1	0	1	0	1	3
Ewing's sarcoma	0	0	0	1	1	0	2
Pineal tumour	1	0	0	0	1	0	2
Optic nerve tumour	1	0	0	0	0	0	1
Angiosarcoma	1	0	0	0	0	0	1

patients [9] (if old enough) was obtained, as well as the informed consent of their legal guardians.

The patients were scheduled to receive at least one course of cancer chemotherapy lasting 1–5 days. Because the study was designed to assess the safety and tolerability, rather than the efficacy of tropisetron, it was intended to involve only chemotherapy of low or moderate emetogenic potential, a procedure allowing the inclusion of groups receiving placebo and low doses of tropisetron that were thought likely to be ineffective. However, 21 patients received chemotherapy that included high doses of ifosfamide or cyclophosphamide and was, therefore, considered to be possibly of high emetogenic potential. For the remaining 23 patients, regimens of moderate or low emetogenic potential were used, i.e. single-agent or combination therapy with actinomycin, vincristine, methotrexate, cytarabine, etoposide, doxorubicin, daunorubicin, hydroxycarbamide, asparaginase, bleomycin, and/or vinblastine. There was no significant difference between the proportion of patients in each study group receiving potentially highly emetogenic therapy.

Patients were randomly assigned to treatment with tropisetron as a single daily dose of 0.05, 0.10, 0.20, 0.33, 0.50 mg/kg or to placebo. For each dose level of tropisetron, 6 patients were allocated to active treatment and 3 to placebo, according to a 2:1 unequal randomisation schedule. The study treatment was diluted in normal saline so that each patient received a volume of 1 ml/kg bodyweight, and was administered as a 15-min infusion immediately before the start of chemotherapy. The patients were treated daily with tropisetron for 5, 6 or 7 days for those receiving 1–3, 4 and 5 days cancer chemotherapy course, respectively. Children allowed home before the end of the study took later doses orally in a small quantity of orange juice. Tropisetron and matching placebo ampoules were provided by Sandoz Ltd.

23 patients took concomitant medication, other than their cancer chemotherapy. 5 (3 in the placebo group, 2 receiving tropisetron 0.10 mg/kg) were withdrawn because of lack of efficacy and received alternative anti-emetic treatment (alizapride with or without chlorpromazine). 4 patients (1 in each of the 0.05 mg/kg, 0.20 mg/kg, 0.33 mg/kg and placebo groups) were given benzodiazepines because of anxiety or insomnia or as a premedication, and 1 patient, who received tropisetron 0.20 mg/kg, took trimeprazine. One patient in the 0.50 mg/kg group received prednisolone. The majority of the other drugs administered concomitantly during the study were anti-infective agents or analgesics.

On the first day of the course of chemotherapy (day 1) and the last day of the study (day 7), the patients underwent a full physical examination, and blood samples were withdrawn for routine haematological and biochemical testing. Supine blood pressure, heart rate and axillary temperature were measured every 8 h while the patient was in hospital. Any adverse events that occurred were recorded, together with their severity and putative relationship to anti-emetic treatment. In addition, any other unusual symptoms or events were noted on diary cards.

The number of episodes of nausea and vomiting per day were also noted on the diary cards as a measure of anti-emetic efficacy, and at the end of the study, both patient and investigator provided overall evaluations of the efficacy and tolerability of the study treatment.

Patients were withdrawn from the study if they vomited more than four times a day, if intolerable adverse effects occurred, or if they or their legal guardian so wished.

On day 1, blood samples were obtained 3, 6 and 9 h after the start of tropisetron infusion for determination of plasma tropisetron level. Tropisetron concentrations were determined by high-pressure liquid chromatography. Briefly, plasma (1 ml)

added to internal standard (triethoxy 2-4-6 chlorhydrate pyrralidino-3-phenyl propyl-cetone) was extracted in alkaline medium by ether. The drug was back extracted in HCl 0.02 N (200 μl) to which was added 75 μl of a 0.5% triethylamine solution. The chromatographic conditions were the following: ultrasphere XL octyl (70 × 4.6 mm, Beckmann); eluent: CH_3CN (65%), H_2O (35%) with 0.05% triethylamine, flow rate 1.5 ml/min, wavelength 283 nm, injection volume 250 μl. The standard curve was linear from 2 to 50 ng/ml. The repeatability was 7.8, 4.6 and 1.8% at 4, 10 and 50 ng/ml, respectively. The reproducibility was 9.2% at 8 ng/ml. The limit of detection was 2 ng/ml.

Between-group comparisons of mean values were carried out using the Kruskal–Wallis test (for non-parametric variables), the Wilcoxon test or analysis of variance. Analysis of contingency tables was performed using the χ^2 test. For statistical comparison of efficacy data, two additional patient groups have been considered: a low-dose group comprising the patients receiving placebo, or tropisetron 0.05 or 0.10 mg/kg, and a high-dose group comprising those who were treated with tropisetron 0.20, 0.33 or 0.50 mg/kg.

RESULTS

14 patients stopped taking the study medication prematurely, 6 after 1 day, 6 after 2 days and 2 after 3 days of treatment. For 11 children (7 receiving placebo, 3 tropisetron 0.05 mg/kg and 1 receiving tropisetron 0.20 mg/kg), this was because of treatment failure. Most of these patients were receiving a regimen displaying usually moderate or high emetogenic potential. 2 children, both of whom were being treated with tropisetron 0.10 mg/kg, changed back to their usual anti-emetic treatment; in 1 case, the study treatment was stopped at the patient's request, while the other was to leave hospital and needed anti-emetic therapy of known efficacy to minimise the risk of vomiting and dehydration while at home. Finally, 1 child receiving tropisetron 0.20 mg/kg was withdrawn from the study by the investigator after 2 days because chemotherapy on the following day was to include carboplatin. Table 2 shows that the distribution of patients within each tropisetron group, relative to the emetogenicity of the chemotherapy received, was fairly equal. Data from all these patients were included in the final analysis. Of the remaining 30 patients, 1 was treated for 3 days, 19 for 5 days and 10 for 7 days.

Vital signs

In no study group did systolic or diastolic blood pressure, pulse rate or body temperature alter significantly during treatment when compared with baseline measurements. Diastolic blood pressure exceeded 95 mmHg on day 2 in the 3 patients (1 in the placebo group, 1 receiving tropisetron 0.05 mg/kg and 1 receiving tropisetron 0.20 mg/kg), and on day 3 in 1 patient taking tropisetron 0.20 mg/kg. 2 patients (1 on placebo and 1 on tropisetron 0.50 mg/kg) had a pulse rate higher than 120 beats/min on day 2; on days 3 and 5, 1 patient (from the 0.50 mg/kg group on both occasions) had a tachycardia. One patient treated with tropisetron 0.50 mg/kg developed a body temperature higher than 38.5°C on day 3 only.

Table 2. Number and distribution of patients within treatment groups in relation to emetogenicity of chemotherapy

Emetogenic potential of chemotherapy	Placebo	Tropisetron dose (mg/kg) 0.05	0.10	0.20	0.33	0.50
Low + moderate	7	3	3	4	3	3
High	8	3	2	2	3	3
Ratio: high versus low + moderate	1.1	1.0	0.7	0.5	1.0	1.0

Laboratory variables

In the whole study population, there were statistically significant reductions in mean haemoglobin concentration (from 11.1 g/dl at baseline to 10.4 g/dl on day 7; $P < 0.001$), leucocytes count (from 6.3 to 4.7 × 10^9/l; $P < 0.05$) and platelets count (from 391 to 326 × 10^9/l, $P < 0.05$). Mean levels of SGPT increased from 60 to 80 U/l ($P < 0.05$). The only statistically significant change in laboratory variables seen in isolated treatment groups was a reduction in mean haemoglobin concentration in the groups receiving placebo or tropisetron 0.20 mg/kg.

Leucopenia (leucocyte counts < 3.5 × 10^9/l) was detected at the final assessment in 19 patients, 14 of whom had a normal or raised leucocyte count at baseline. Leucopenia developed during treatment in 6 placebo recipients and 1, 1, 2, 2 and 3 patients, respectively, in the 0.05-, 0.10-, 0.20-, 0.33- and 0.50-mg/kg dosage groups. 3 tropisetron patients (2 treated with 0.20 mg/kg and 1 with 0.50 mg/kg) became anaemic (haemoglobin < 8.0 g/dl), the last of these had concomitant leucopenia and thrombocytopenia.

Abnormal liver enzyme tests (SGPT and/or SGOT > 80 U/l) were found at the final assessment in 7 patients. 2 of these, both in the placebo group, had normal levels at baseline while in another 2 (1 in the 0.33 mg/kg group and 1 in the 0.50 mg group) baseline values were missing. Liver enzyme abnormalities were generally associated with high-dose methotrexate treatment.

One child treated with tropisetron 0.50 mg/kg was found to have a raised alkaline phosphatase concentration (592 U/l) in the final sample. This was measured again 1 and 4 days later, and found to be near the pretreatment value on both occasions.

Tolerability

All adverse events that occurred during the study, both those formally reported by the investigators and those recorded on the diary cards, are summarised in Table 3. The most frequent events were headache, which occurred in 8 tropisetron-treated patients, and anxiety, which was reported by 7 placebo and 2 tropisetron recipients.

Seven adverse events, involving 6 patients, were reported by the investigators: in each case, the relationship of the event to treatment was described as uncertain. The events were anxiety (3 patients, 1 receiving placebo, 1 tropisetron 0.05 mg/kg and 1 tropisetron 0.10 mg/kg), abdominal pain (1 patient in the 0.05 mg/kg group), headache with arterial hypertension (1 patient in the 0.05 mg/kg group) and rash (1 patient in the 0.05 mg/kg group). Apart from the case of headache, which was severe, all events were of moderate or mild severity. The majority of patients and investigators described the overall tolerability of treatment as very good or good. Only in the placebo group was tolerability rated as poor or very poor.

Plasma tropisetron concentrations

Mean plasma concentrations of tropisetron 3, 6 and 9 h after intravenous (i.v.) administration are shown in Table 4. Results from 2 patients have been excluded; in 1 (who had received 0.10 mg/kg) levels were higher than 100 ng/ml and in the other (in the 0.50 mg/kg group), tropisetron was undetectable in plasma.

Table 3. Adverse events

	Tropisetron dose (mg/kg)						
	Placebo	0.05	0.10	0.20	0.33	0.50	Total
Anxiety	7	1	1				9
Headache		5		1		2	8
Abdominal pain		4					4
Tremor						3	3
Rash						3	3
Musculoskeletal pain				1		1	2
Sweating	1	1					2
Hypertension		1					1
Vertigo						1	1
Diarrhoea		1					1
Fever			1				1
Fatigue						1	1
Fall			1				1
Total no. of events	8	13	3	2	0	11	37
No. of patients treated	15	6	5	6	6	6	44

Control of nausea and vomiting

The numbers of patients in each study group who did not vomit or did not experience nausea on days 1 to 5 are presented in Figure 1. None of the 10 patients who remained in the study on days 6 and 7 experienced nausea or vomiting on those days. 10 (38%) of the 26 patients who received placebo or tropisetron 0.05 or 0.10 mg/kg (the low-dose group) were withdrawn from the study because of lack of efficacy, compared with 1 (6%) of 18 patients treated with tropisetron 0.20, 0.33 or 0.50 mg/kg (the high-dose group; $P = 0.015$).

The investigator's assessment of the overall efficacy was statistically significantly better for patients treated with one of the three higher doses of tropisetron than for those receiving either a lower dose or placebo ($P = 0.04$; χ^2 test). Efficacy was described as very good or good for 89% of patients in the high-dose group compared with 58% in the low-dose group. The investigators considered efficacy to be poor or very poor in 11 and 31% of patients in the high-dose and low-dose groups, respectively.

Similarly, patients in the high-dose group rated the efficacy of their anti-emetic treatment significantly better than those in the low-dose group ($P = 0.035$; χ^2 test).

Efficacy was considered to be good or very good by 83% of patients in the high-dose group and by 54% of those in the low-dose group; poor or very poor efficacy was reported by 11 and 35% of patients in the high-dose and low-dose groups, respectively.

DISCUSSION

The results of this study indicate that tropisetron is well tolerated by children undergoing cancer chemotherapy. No patient discontinued tropisetron treatment because of adverse effects and no adverse event was attributed to tropisetron administration. More placebo than tropisetron recipients complained of anxiety, whereas headache appears to be associated with tropisetron, but not placebo, administration. Headache has previously been described as an unwanted effect of tropisetron therapy in adults [6–8].

Unlike that of placebo, the tolerability of tropisetron was always rated as moderate to very good by both the patients and the investigators. In fact, the assessments of tolerability tended to parallel the overall efficacy evaluations, with treatment rated as ineffective also having a poor tolerability rating. This may reflect difficulty in distinguishing in children the effects of

Table 4. Plasma tropisetron concentrations at 3, 6 and 9 h after dosing (two outlying values have been excluded)

		Plasma tropisetron concentrations (ng/ml)						
Tropisetron dose (mg/kg)	Number of patients	3 h Mean	3 h S.D.	6 h Mean	6 h S.D.	9 h Mean	9 h S.D.	
Placebo	13	0.4	1.1	0.9	2.2	0.5	1.3	
0.05	5	2.5	1.5	2.4	1.9	2.3	1.6	
0.10	4	11.1	6.3	6.3	2.9	5.0	3.9	
0.20	6	24.8	8.6	17.1	6.8	15.3	5.6	▲
0.33	5	23.6	8.4	16.6	9.6	11.2	4.2	▲
0.50	5	51.2	5.5	36.4	11.6	35.9	19.3	●

▲ versus ● (those receiving 0.20 and 0.33 mg/kg versus those receiving 0.50 mg/kg): $P = 0.002$.

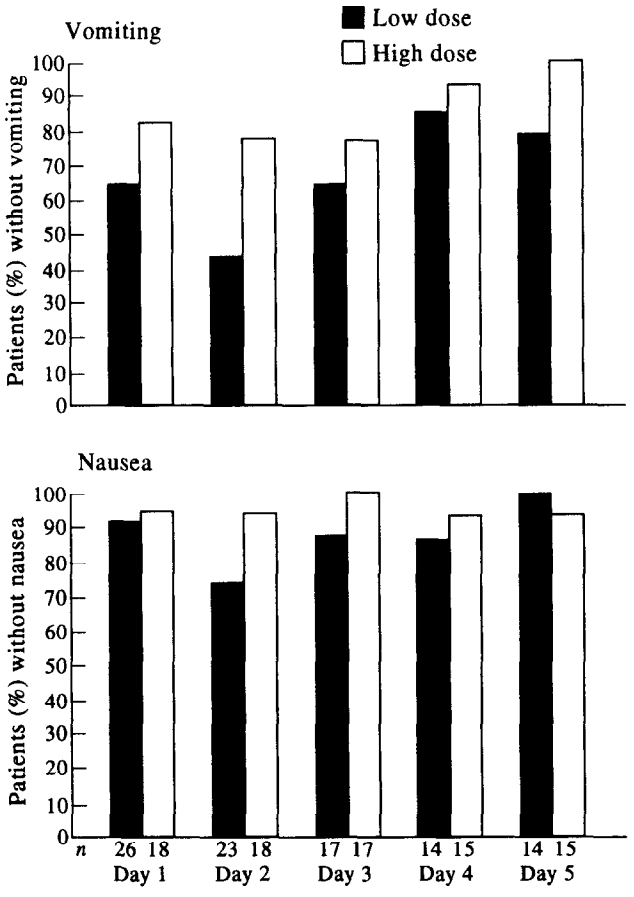

Figure 1. Control of vomiting and nausea on days 1 to 5 in the low-dose group (patients receiving placebo or tropisetron 0.05 or 0.10 mg/kg) and high-dose group (patients receiving tropisetron 0.20, 0.33 or 0.50 mg/kg). *n*, number of patients assessed.

chemotherapy with inadequate anti-emetic prophylaxis from the adverse effects of the anti-emetic treatment itself.

The observed changes in vital signs and laboratory variables were not different from those expected during a course of cancer chemotherapy. There was some evidence of myelosuppression and hepatic effects, but these were most likely a consequence of the cytotoxic agents used, particularly of high-dose methotrexate administration.

From these results, no relationship between tropisetron dose and the incidence of adverse events or abnormalities of laboratory variables is apparent. However, because of the small number of patients in each group, the data are inconclusive in this matter.

The measurement of plasma drug concentration at three time points after dosing does not constitute a full pharmacokinetic profile. However, the data obtained in this study demonstrate that plasma concentrations of tropisetron increase linearly with an increasing intravenous dose. Previous pharmacokinetic and pharmacodynamic studies have shown that plasma concentrations of at least 3 ng/ml of tropisetron are necessary for blockade of > 90% of 5-HT_3 receptors [10]. On this basis, it would seem that a tropisetron dose of 0.10 mg/kg or more is necessary to maintain therapeutic levels for 9 h after dosing. However, the efficacy data provided by this study indicate that only tropisetron doses of greater than 0.10 mg/kg are clinically effective and suggest that plasma concentrations higher than 3 ng/ml are needed for an adequate therapeutic effect.

This study was not designed with the primary aim of assessing the anti-emetic efficacy of tropisetron, and so it was intended that only patients receiving chemotherapy of low or moderate emetogenic potential should participate. For this reason, the inclusion of a placebo group was considered justifiable. If control of emesis was inadequate, patients were withdrawn from the study and alternate anti-emetic therapy provided.

In the event, 21 patients received chemotherapy considered to be possibly highly emetogenic, and on days 1 and 2 of chemotherapy, one-third of patients in the placebo groups vomited at least once. Of all the patients receiving tropisetron, 74% were free from vomiting on day 1, suggesting a possible benefit from the drug, although the difference was not analysed statistically.

Because of the small number of patients in each group, comparison of the efficacy of individual tropisetron doses would be of doubtful validity. However, the incidence of vomiting was noticeably greater in patients receiving tropisetron 0.05 or 0.10 mg/kg than in those receiving higher doses, especially on days 2 and 3 of chemotherapy. When results from all patients receiving the three higher doses of tropisetron (the high-dose group) were compared with results from the rest of the children (the low-dose group), a clearer difference in efficacy was evident, with 83% of the high-dose group compared with 65% of the low-dose group being free from vomiting on day 1. The difference between the incidences of vomiting in the two groups persisted on days 2–5. Furthermore, the proportion of patients who were withdrawn from the study because of inefficacy was statistically significantly greater in the low-dose than in the high-dose group. The global efficacy evaluations provided by both patients and investigators tended to favour the higher doses of tropisetron over the lower doses or placebo. The overall efficacy ratings for patients in the high-dose group were statistically significantly better than those for the low-dose group.

Nausea was a less frequent event than vomiting; indeed, on day 1 of the study, only 3 patients complained of nausea. The incidence of nausea was very low in comparison with that reported for adults, in whom nausea is often a greater problem than vomiting itself. However, symptoms were recorded not by the patients themselves, but by their carers, and so it is possible that nausea was under-reported in the present study. Because of the low reported incidence of nausea, an effect of tropisetron on this symptom is difficult to detect. Although the frequency of nausea was generally greater in the low-dose than in the high-dose group, the differences are small and their interpretation questionable.

In conclusion, tropisetron at doses of up to 0.50 mg/kg, administered once daily either as a 15-min i.v. infusion or orally, is well tolerated by children receiving cancer chemotherapy, with no evidence of dose-related adverse effects. There is some evidence that doses of 0.20 mg/kg or more reduce the incidence of acute vomiting in patients receiving chemotherapy of moderate to high emetogenic potential, but larger controlled trials are needed to provide clear evidence of efficacy.

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

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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
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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-

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