II: Prospective study

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Abstract

A prospective study of 120 patients newly diagnosed as having Hodgkin's disease and non-Hodgkin's lymphoma was conducted to determine the nature, extent, and timing of the psychiatric and social morbidity associated with the diagnosis and treatment. Patients were interviewed at diagnosis and two, six, and 12 months later by trained interviewers using standardised questionnaires. Psychiatric morbidity was greatest in the three months before treatment, but new episodes of anxiety and depression developed throughout the year of follow up. Altogether 39 patients suffered a depressive illness or anxiety state, or both, and a further 37 experienced borderline anxiety or depression, or both, during the 15 months of assessment. The most common adverse effects of treatment were hair loss, nausea, vomiting, sore mouth, and changes in perception of taste. Toxicity of treatment was associated with psychiatric morbidity. Conditioned responses to chemotherapy were experienced by 32 patients. Social morbidity was low, although difficulties in returning to work and to previous levels of leisure activity were noted. Although most patients were no longer receiving treatment and were free of disease at the one year follow up, 51 patients continued to complain of loss of energy, 24 of loss of libido, 38 of tiredness, 23 of irritability, 18 of poor concentration, and 23 of memory impairment.

These results confirm our retrospective study and suggest that a high price is paid for long term survival by a substantial proportion of patients receiving treatment for Hodgkin's disease and non-Hodgkin's lymphoma.

Introduction

Our retrospective study suggested that the diagnosis and treatment of Hodgkin's disease and non-Hodgkin's lymphoma were associated with substantial psychological and social morbidity (see accompanying paper). We therefore conducted a prospective study to determine the exact nature, prevalence, timing, and duration of problems occurring during the first year after diagnosis.

Patients and methods

All patients aged 70 or less who were newly diagnosed as suffering from Hodgkin's disease or non-Hodgkin's lymphoma and attended the Christie Hospital over 33 months were eligible for inclusion.

A trained interviewer (JD or PP) assessed each patient on four occasions: a week after diagnosis and two months, six months, and a year later. At the first, baseline interview shortened versions of the present state examination and the standardised social interview schedule were used to determine the nature and extent of any psychiatric symptoms and social morbidity in the three months before the patients attended the hospital.[1,2] In the three follow up interviews the same procedures were used to assess morbidity for each month since the previous interview. Symptoms and social adjustment were then rated for the three month baseline period before treatment and for each month in the first year of follow up.

Each patient was also asked in detail about the treatments given and the nature and extent of any adverse effects, with the same check list as in the retrospective study. The 13 adverse effects were rated according to their maximum severity over the year of follow up—for example, vomiting was considered severe if, at any stage, the patient had experienced more than 10 separate episodes in a day or six to 10 episodes a day for at least three days. Similarly, alopecia was considered of moderate degree if there were obvious bald patches covering from a quarter to three quarters of the surface of the scalp; and loss of appetite was considered mild if the patient had not wanted to eat for one day or had noticed a persistent decrease in appetite in comparison with his or her normal appetite.

Each patient's memory was assessed at the baseline, two month, and 12 month interviews with the Wechsler memory test.[3] Two versions were used alternately to minimise practice effects.

Results

Altogether 150 patients were entered into the study, but 19 died, six refused to continue, and five were subsequently found not to have Hodgkin's disease or non-Hodgkin's lymphoma. The remaining patients comprised 64 men and 56 women, and their mean age was 40·4 years (SD 16·1). Sixty three had Hodgkin's disease and 57 non-Hodgkin's lymphoma; table I gives details of the stages of the diseases and the treatments.

TREATMENT TOXICITY

Table II shows the severity of each side effect in the patients. Most patients experienced some degree of hair loss, nausea, and vomiting. Thirty two patients developed conditioned responses to chemotherapy. Of these, eight felt nauseous at the sight or smell of treatment, 15 vomited when they saw their infusion or injection, and nine vomited when they thought about treatment or were reminded of it by a doctor, relative, or friend. Conditioned responses were usually firmly developed by the fourth or fifth course of treatment.

Twenty three patients were treated with vincristine, doxorubicin, and prednisolone (VAP), 23 with cyclophosphamide, vincristine, and prednisolone (CVP); 22 patients in each group experienced hair loss. All 46 patients given mustine, vinblastine, prednisolone, and procarbazine (MVPP) suffered from vomiting, and 25 of them developed conditioned responses. Mustine, vinblastine, prednisolone, and procarbazine do not generally cause alopecia, but 20 of our patients reported slight thinning and a further two patients required a wig because of severe hair loss. Total toxicity scores were calculated by summing scores for the 13 adverse effects. The patients who obtained the highest scores were those treated with mustine, vinblastine, prednisolone, and procarbazine (mean 10·6, SD 3·9, maximum 19); vincristine, doxorubicin, and prednisolone (mean 9·4, SD 3·9, maximum 17); and radiation to the upper body (mean 8·0, SD 5·4, maximum 22).

At the one year follow up adverse reactions to treatment still persisting were loss of energy (51 patients), loss of libido (24 out of 74 sexually active patients), tiredness (38 patients), irritability (23), and poor concentration (18). At this time most patients were no longer receiving treatment (77) or were free of disease (87), or both (58), but they were as likely to be experiencing these symptoms as those still receiving treatment or with evidence of disease.

An unexpected finding was depression related to treatment. This took the form of episodes of depression lasting from one to three days, which occurred at the same time in relation to the administration of treatment and did not last long enough to be rated with the criteria of the present state examination. In total 25 patients experienced such episodes, most commonly those receiving mustine, vinblastine, prednisolone, and procarbazine (12 out of 46 patients).

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PSYCHIATRIC MORBIDITY

Symptoms of anxiety and depression were most evident in the baseline period, affecting 43 patients. Fifteen of these patients improved once they had attended the hospital and were informed of their diagnosis and treatment, but the 28 others continued to experience symptoms of anxiety or depression, or both, in the following months.

During the year of follow up 61 patients developed psychiatric morbidity as classified in our retrospective study. Twenty one patients had borderline depression, five borderline anxiety, and four borderline depression and anxiety combined. Nine patients had depressive illness, eight anxiety state, and 14 depressive illness and anxiety state combined. Table III shows the time of onset of the 89 episodes of depression and anxiety experienced by these 61 patients; half of the episodes began within the first three months after the start of treatment. Depression and anxiety state lasted for four months on average (range 1-12 months, median 2 months), and the duration of borderline anxiety and depression was similar. Although few anxiety states developed in the second six months of the year of follow up, new episodes of depressive illness continued to develop.

During the 15 months' assessment 76 patients developed psychiatric morbidity: 39 experienced depressive illness or anxiety state, or both, and a further 37 experienced borderline anxiety or depression, or both. We found no relation between type or stage of disease at diagnosis and the development of symptoms of either depression or anxiety. Depression and anxiety were, however, positively related to treatment toxicity scores over the one year follow up, particularly for loss of appetite, sore mouth, pain, and changes in taste (for depression Kendall's $\tau=0{\cdot}194$, $p<0{\cdot}01$; for anxiety Kendall's $\tau=0{\cdot}181$, $p<0{\cdot}01$).

Ten patients were seen by a psychiatrist, who prescribed antidepressants (eight patients) or anxiolytics (two). Two patients also received behaviour therapy. One patient needed to be seen only once because her conditioned vomiting responded rapidly to the anxiolytics; the nine others were seen for periods varying from six weeks to five months.

TABLE I—*Stage of disease and treatment for 120 patients with Hodgkin's disease or non-Hodgkin's lymphoma*

	No of patients	Treatment
Hodgkin's disease (n=63):		
Stage I/II	21	Radiation or radiation+MVPP
Stage III/IV	42	MVPP or MVPP+radiation
Non-Hodgkin's lymphoma (n=57):		
Stage I/II low grade	4	Radiation or radiation+chlorambucil
Stage I/II high grade	5	CMOPP or VAP+mercaptopurine, methotrexate, and cyclophosphamide
Stage III/IV low grade	26	CVP or CVP+chlorambucil
Stage III/IV high grade	18	VAP+cyclophosphamide+AC or VAP+cyclophosphamide+mercaptopurine, methotrexate, and cyclophosphamide
Miscellaneous	4	

MVPP=Mustine, vinblastine, prednisolone, and procarbazine.
CMOPP=Cyclophosphamide, vincristine, procarbazine, and prednisolone.
VAP=Vincristine, doxorubicin, and prednisolone.
CVP=Cyclophosphamide, vincristine, and prednisolone.
AC=Doxorubicin and cyclophosphamide.

TABLE II—*Ratings of adverse effects of treatment experienced by 120 patients over one year of follow up*

	None	Mild	Moderate	Severe
Hair loss	24	43	25	28
Nausea	27	31	30	32
Vomiting	34	28	25	33
Sore mouth	41	35	36	8
Change in perception of taste	45	33	40	2
Sore skin	55	53	12	
Loss of appetite	56	26	15	23
Pain	57	54	6	3
Constipation	64	43	8	5
Peripheral neuropathy	67	38	14	1
Increased appetite	75	38	6	1
Conditioned response	88	8	15	9
Diarrhoea	89	19	10	2

TABLE III—*Time of onset of episodes of depression and anxiety in 61 patients. Values are numbers (percentages) of patients*

	Months 1-3	Months 4-6	Months 7-9	Months 10-12	Total
Depressive illness	11 (48)	6 (26)	4 (18)	2 (8)	23
Anxiety state	16 (73)	3 (14)	2 (9)	1 (5)	22
Borderline depression	14 (44)	7 (22)	7 (22)	4 (12)	32
Borderline anxiety	6 (50)	3 (25)	1 (8)	2 (17)	12
Total No of episodes	47 (53)	19 (21)	14 (16)	9 (10)	89

MEMORY IMPAIRMENT

The Wechsler memory scores for the sample as a whole were comparable with those obtained in the normal population[3] and showed little change over time. Despite this 47 patients reported subjective memory impairment. Their scores for the Wechsler subtests were lower than those of patients reporting no impairment (table IV). Twenty three patients continued to report impaired memory at the one year follow up.

Patients reported that they had difficulty recalling simple facts that they had previously been able to recall at will, such as their home telephone number. They seemed especially vulnerable to being distracted while doing a task and found it difficult to remember the point they had reached before being interrupted. The 47 patients who reported transient memory impairment were significantly older (44·4 years) than those who did not (37·8 years) (difference between means 6·6 years, 95% confidence interval 0·7 to 12·5, df=118, $t=2{\cdot}2$, $p=0{\cdot}03$). None the less, memory impairment

TABLE IV—*Comparison of Wechsler subtest scores in patients with subjective memory impairment and those without (normal)*

	Normal patients			Patients with subjective impairment			Difference between mean scores	95% Confidence interval	Significance*	
	Mean score	SD	No of patients	Mean score	SD	No of patients			t	p
Month 2										
Logical memory	10·9	3·7	79	9·2	3·3	30	1·7	0·2 to 3·2	2·2	<0·025
Digit span	12·3	1·9	79	11·7	2·6	31	0·6	−0·3 to 1·5	1·3	NS
Associate learning	13·1	4·5	78	12·1	3·1	31	1·0	−0·7 to 2·7	1·1	NS
Visual reproduction	11·3	3·2	71	10·0	3·4	28	1·3	−0·1 to 2·8	1·8	<0·05
Month 12										
Logical memory	10·5	3·6	90	8·8	3·6	18	1·7	−0·6 to 4·1	1·8	<0·05
Digit span	12·3	2·0	91	11·9	2·3	18	0·4	−0·3 to 1·5	0·7	NS
Associate learning	13·6	3·8	90	11·9	4·6	18	1·7	−0·3 to 3·7	1·7	<0·05
Visual reproduction	11·5	2·8	83	11·3	3·2	17	0·2	−1·3 to 1·7	0·2	NS

*One sided Student's *t* test.

was a problem for 10 patients in their 20s. Although patients who were anxious or depressed tended to report memory impairment, albeit in only the latter months of follow up, the presence of an affective disorder did not explain it.

SOCIAL MORBIDITY

Understandably, patients reduced their leisure activities in the early months of treatment. In the baseline period 32 reported inadequate interest in leisure activities, and this number rose to 57, 55, and 55 in months 1, 2, and 3, respectively. At the one year follow up 48 patients still reported an inadequate interest even though 26 of them were no longer receiving treatment and were free of disease. Twenty one of the 86 patients who were in regular employment before they became ill stayed off work for from six to 11 months, 16 were off work for 12 months or more, and six retired early.

Discussion

We found a greater incidence of adverse effects of treatment in this prospective study than in the retrospective study. Patients reported conditioned responses three times more commonly, although similar treatments were given, which suggests that patients tend to forget over time what their treatments were like. Unfortunately, toxicity was greatest for the most commonly used treatments of mustine, vinblastine, prednisolone, and procarbazine; vincristine, doxorubicin, and prednisolone; and radiation to the upper body. In comparison with chemotherapy mantle radiotherapy may be less toxic, and it is often described to patients as a mild treatment after mustine, vinblastine, prednisolone, and procarbazine. Patients did, however, experience problems and were often devastated by the effects of this treatment.

Adverse effects were sometimes so serious that patients wanted to withdraw from treatment, although they realised that this could jeopardise their survival. Some patients dreaded relapse as it would mean further courses of chemotherapy and radiotherapy. Conditioned responses were firmly developed before they were recognised so we found it difficult to help patients continue through treatment with the use of anxiolytics, major tranquillisers, or anxiety management techniques such as relaxation. Earlier recognition and treatment of these responses might be more effective.[4,5] We were also concerned at the proportion of patients who continued to experience appreciable loss of libido, irritability, and tiredness that could not be attributed to the effects of disease or treatment. Loss of libido has been reported before and explained in terms of a reduction in testosterone or oestrogen concentrations and raised concentrations of follicle stimulating hormone and luteinising hormone induced by chemotherapy.[6,7]

The relation between gastrointestinal symptoms such as loss of appetite and sore mouth and the development of anxiety and depression is intriguing. The constant strain of trying to cope with adverse effects probably caused the morbidity in some patients, but others seemed to believe that these symptoms meant that their cancer was still there or spreading. Patients who are already anxious and depressed may also have a lowered threshold to experiencing such adverse effects. The strong relation between the toxicity of treatment and psychiatric morbidity, however, suggests that attempts to reduce toxicity would also reduce this morbidity. The close temporal relation in some patients between treatment and the onset of symptoms of depression suggests that there might also be a central effect on the brain.

As in the retrospective study, we found substantial psychiatric morbidity, which was similar to that reported by Lloyd *et al.*[8] The incidence of symptoms of depression was identical with that reported for patients after mastectomy,[9] but the lower incidence of symptoms of anxiety may reflect the better prognosis of lymphomas. Symptoms of anxiety and depression that developed before diagnosis often resolved once patients had been given a clear account of their diagnosis and treatment and a more hopeful prognosis.

The relatively short duration of psychiatric morbidity after diagnosis seemed to be due to two factors. Firstly, morbidity that was a reaction to adverse effects of treatment sometimes improved as the patient adapted or the dosage of drugs or radiation was reduced. Secondly, psychiatric treatment was usually successful. Further work is needed to distinguish those affective disorders that are transient and remit spontaneously from those that need prompt treatment by a doctor or psychiatrist.

The lack of any relation between hair loss and psychiatric morbidity was surprising. Most patients had been warned, however, that hair loss would be a transient phenomenon and could be compensated for by wearing a wig or a hat.

We were concerned at the proportion of patients who were free of disease and no longer receiving treatment who failed to return to work or resume their normal activities. Moreover, many of those who returned to work were assigned a lower level of responsibility than that before their illness. Although some patients purposely curtailed their activities, others seemed to develop "illness behaviour," behaving as if they were physically ill even though judged well by the doctors. This behaviour could not be explained by continued anxiety or depression. The prompt recognition by doctors of a discrepancy between disease state and performance at work or socially might enable these patients to be helped more effectively. The findings of retrospective studies that psychosocial problems are still evident some years after treatment gives little room for optimism that they will resolve over time.[10]

Although the formal memory scales failed to confirm impairment of short term memory, we were struck by the genuineness of the patients' complaints and their confirmation by relatives. Although memory impairment was associated with increasing age, depression, and anxiety, we believe that it may have represented minor brain damage due to a central effect of chemotherapy or a viral infection during periods of immunosuppression. The risk of organic brain damage is not restricted to patients who have received irradiation of the central nervous system but is also related to the use of certain drugs, especially methotrexate.[11] Objective evidence of brain damage has been shown by magnetic resonance imaging, which seems more sensitive than conventional means of neurological investigation.[11]

The similarity of our findings from the retrospective and prospective studies gives us confidence that they reflect what patients experience when receiving treatment for Hodgkin's disease and non-Hodgkin's lymphoma. A substantial proportion of patients pay a high price for the prospect of long term survival, and ways need to be found of reducing this cost

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