Eur J Cancer, Vol. 27, No. 2, pp. 170–174, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Randomised Controlled Study of Relaxation Training

S. Bindemann, M. Soukop and S.B. Kaye

In a study lasting 12 weeks, relaxation training was evaluated as a coping resource for cancer patients. 80 patients of both sexes were randomised to relaxation training and to a control (no training) group (40 in each). Scores for anxiety, depression and psychiatric morbidity were obtained at 0, 6 and 12 weeks with well-known questionnaires and a new anxiety and depression scale, the effects of serious illness (ESI) scale. 71 patients (32 men and 39 women) successfully completed the study. Results showed that relaxation training and control group scores were similar at 0 weeks. Higher anxiety, depression and psychiatric morbidity scores were reported by all patients at 6 and, to a lesser extent, at 12 weeks with greater differences in women. Female controls invariably reported significantly higher scores at 6 and 12 weeks on all indices. Male controls reported significantly higher anxiety scores only at 6 and 12 weeks.
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INTRODUCTION

THE NEED for prompt and appropriate psychosocial support and intervention in malignancy is well documented and understood. The aim is to increase self-control and to enhance patients' quality of life. However, although benefit has been claimed for several complementary approaches (e.g. counselling, cognitive therapy, relaxation therapy), systematic randomised studies are rarely reported. After our non-randomised investigation of the potential worth of relaxation training for cancer patients [1], we report a randomised controlled study.

PATIENTS AND METHODS

Patients and randomisation

Criteria for inclusion in the study were: newly diagnosed and histologically proven malignancy in patients aged 15 and over; life-expectancy of at least 6 months from the time of recruitment and informed consent to be randomised. Patients who had previously received anticancer treatment, who had a history of a psychiatric or neurological disorder or who were taking antidepressant or anxiolytic drugs were excluded.

Eligible patients were introduced to the study during their first clinic attendance and the following questionnaires were given to all patients to complete at home: the Eysenck personality questionnaire (EPQ) [2], Leeds self-assessment of anxiety (SAA) and of depression (SAD) general scales [3], general health questionnaire (GHQ-60) [4] and the state–trait anxiety inventory (STAI) [5]. We have developed two questionnaires which we also used: the effects of illness (ESI) scale (Appendix) and the actual/ideal-self inventory (AISI), which will be reported separately. Emphasis was given to the need for independent and accurate response to questions and confidentiality was assured. There were no refusals at this stage. Before leaving the clinic an appointment was made for one of us (S.B.) to visit the patients at home over the next few days. This two-stage design was adopted to ensure collection of some data from all patients, to show sensitivity toward patients attending an oncology clinic for the first time and to give the patient a fuller understanding of the study's aims where needed.

138 patients were originally recruited to the study, of whom 128 were potentially evaluable by virtue of their completion of all questionnaires and their willingness to be interviewed. Of these, 80 patients (62%—35 men and 45 women) gave informed consent. Randomisation assigned 40 patients to receive relaxation training and 40 to the control (no training) arm of the study. The relaxation training group comprised 18 males and 22 females of whom 3 did not complete the study: 1 man and 1 woman died and 1 man defaulted. The final number was therefore 16 men and 21 women. Mean ages were 39.7 years (S.D. 12.6) and 48.5 (11.65), respectively. The controls were 17 males and 23 females. 6 patients failed to complete the study: 1 man and 1 woman died and 4 women who expressed a desire to receive relaxation training were withdrawn from the study. The final composition of this group was therefore 16 men and 18 women; mean ages were 44.3 (S.D. 12.6) and 50.4 (11.87), respectively. In men, the most common tumours were testicular teratoma (n = 15) and lung (5). In women, the most common tumours were cancer of the ovary (16) and breast (15).

Relaxation training

We used a modified form of Jacobson's method for progressive muscle relaxation [6, 7]. Patients were encouraged to tense, then relax sequentially, groups of muscles while also attending to the somatic component of tension and relaxation being experienced. We also used a lightly-induced hypnosis with "ego-strengthening" [8], which reinforces the individual's self-perceived ability to adapt and to adjust to problems. Training began for all patients before treatment for physical disease commenced. Sessions lasted 25 min and took place twice weekly during the first 2 weeks, once weekly during the following 6 weeks and once fortnightly over the remaining period of the trial. An identical audiotape recording of relaxation training was given to patients in that group at the end of the first week, with instructions for use at home and a form on which to record frequency of use.

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Revised 5 Nov. 1990; accepted 7 Nov. 1990.

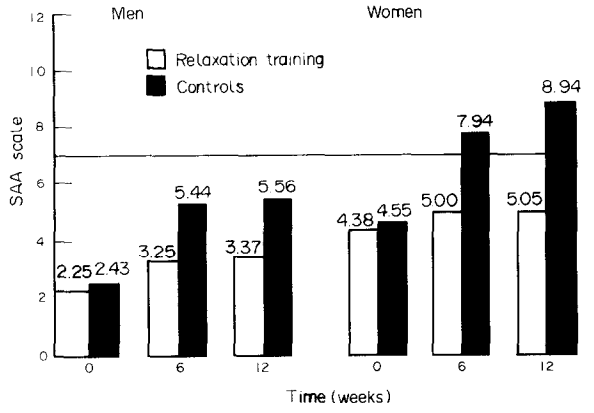

Fig. 1. Anxiety—mean Leeds SAA. Significant differences between groups for 0–6 weeks ($P < 0.0002$ in men and $P < 0.0001$ in women) and for 0–12 weeks ($P < 0.003$ and $P < 0.0001$, respectively). ——— = threshold for caseness.

Assessments

With the exception of the EPQ (0 and 12 weeks only), questionnaires and interviews were repeated at 6 and at 12 weeks. Assessments were made at 0, 6 and 12 weeks by medical staff for disease state (responding to treatment, stable, progressing disease, non-evaluable) nausea and vomiting, effect on working life (continuing to work full or part time), and coping status (very well-adjusted, reasonably adjusted, several problems, very disturbed). Evaluation was on a four-point scale during outpatient attendance.

Statistical analysis

Our data consisted of raw scores obtained at 0, 6 and 12 weeks. These were summarised by computing within group median and mean values of changes occurring from 0–6 to 0–12 weeks. Across group scores at these time points were compared using the Mann–Whitney U Test. There was strong agreement between medians and means and we therefore submitted the summarised data to the two sample t test. P values were also in substantial agreement and are given where significant.

RESULTS

The two principal research groups (both sexes) reported statistically similar psychoticism, extraversion and "lie" scores on the EPQ. Female controls had elevated neuroticism scores ($P < 0.02$). It has previously been noted that "normal" Glaswegians and people living in the West of Scotland have atypical EPQ scores compared with those reported in normal data for the questionnaire [2, 9, 10]. Comparisons were made therefore with Glasgow and West of Scotland and EPQ normal scores. These data will be reported separately.

Statistically comparison of anxiety trait showed similar mean male and female STAI scores in both groups at 0, 6 and 12 weeks. Anxiety state was measured by the STAI, the Leeds SAA and the ESI anxiety subscore. Analysis showed that the relaxation training and control male and female patients were statistically similar at 0 weeks. However, higher anxiety scores were reported by controls of both sexes (especially by women) at 6 and 12 weeks (Figs 1 and 2). Results of the STAI data are not shown but were consistent with SAA and ESI data.

Depression was measured by the Leeds SAD and the depression subscale of the ESI score. Both sexes were similar in the two groups at 0 weeks and for males only, at 6 and 12 weeks (Figs 3 and 4). Depression scores increased at 6 and 12 weeks in both female groups. However, control scores were significantly higher overall than those reported for patients receiving relaxation training.

For psychiatric morbidity (GHQ-60) the pattern and trend of responses were consistent with those reported for anxiety and depression. Female controls had scores which at 6 weeks approached and at 12 weeks exceeded the threshold for "psychiatric morbidity" (Fig. 5).

There was no significant difference between the groups in

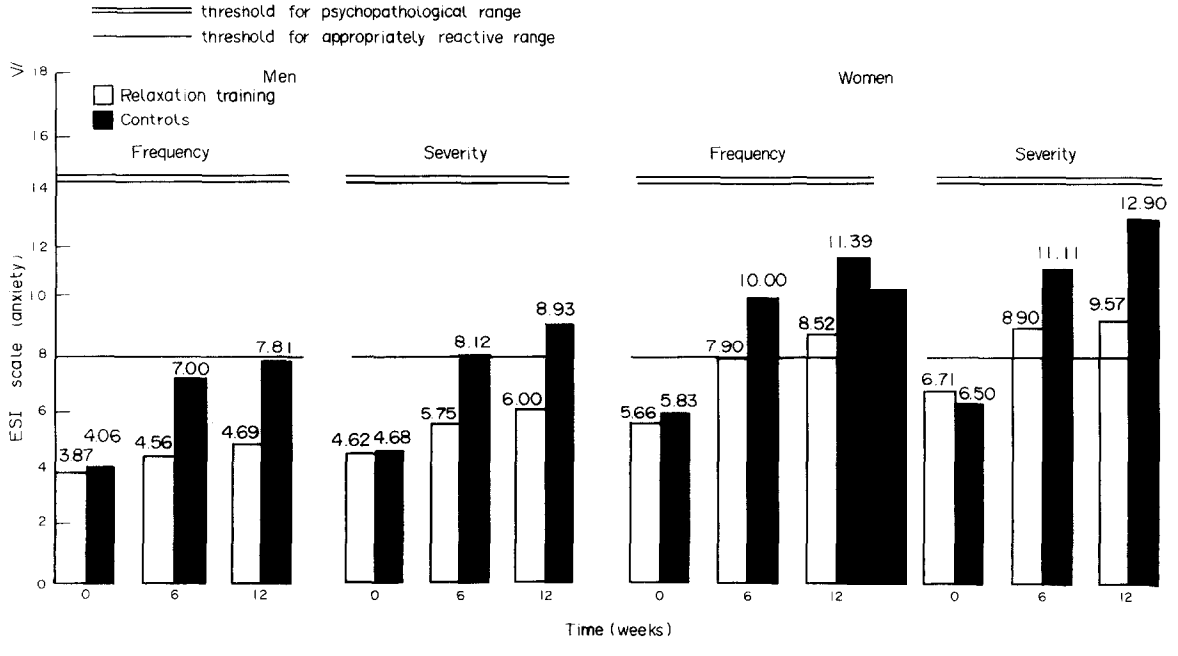

Fig. 2. Anxiety—mean ESI scores. For frequency, significant differences between groups: 0–6 weeks ($P < 0.0001$ in men and $P < 0.006$ in women) and 0–12 weeks ($P < 0.0001$ and $P < 0.0003$, respectively). For severity: 0–6 weeks ($P < 0.0004$ in men and $P < 0.005$ in women) and 0–12 weeks ($P < 0.0009$ and $P < 0.0001$, respectively). ═══ = threshold for psychopathological range and ——— = threshold for appropriately reactive range.

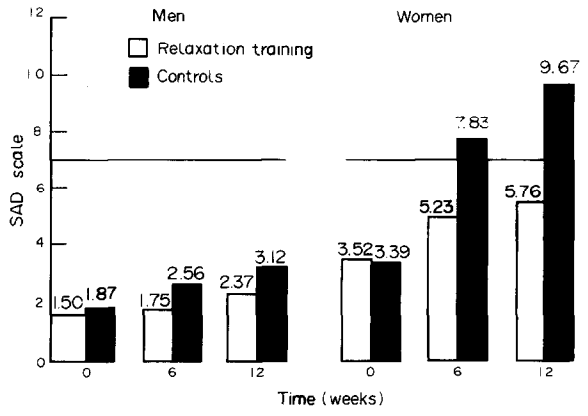

Fig. 3. Depression—Leeds SAD. Significant differences between women for 0–6 weeks ($P < 0.0001$) and for 0–12 weeks ($P < 0.001$). ——— = threshold for caseness.

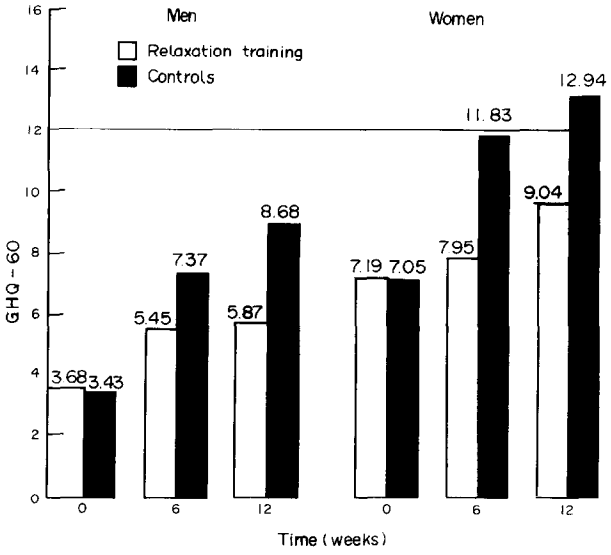

Fig. 5. Psychiatric morbidity—mean GHQ-60 Scores. Significant differences between groups. 0–6 weeks ($P < 0.004$ in men and $P < 0.003$ in women) and 0–12 weeks ($P < 0.001$ and $P < 0.009$, respectively). ——— = threshold for morbidity.

assessments made over the 12 weeks by medical staff for response to treatment or in effects on working life. However, patients who received relaxation training were considered to be coping better (males and females, $P < 0.01$), with a significant reduction in nausea and vomiting ($P < 0.01$ in men and $P < 0.003$ in women).

DISCUSSION

Relaxation training was offered solely as psychosocial support and not as a complementary therapy for the treatment of physical disease. The high frequency of non-compliance is worth noting in the light of our deliberate emphasis on real preference in choice. It may also reflect attitudes which, on the basis of our subsequent experience, increasingly favour participation. Such changes may in turn be a function of more informed public discussion of the need for psychosocial support for cancer patients. Patients with different tumours were studied, since there is no evidence that emotional response to cancer is tumour-specific. On the contrary, patient's perception, even of a good prognosis, may be restricted and hampered by an all-pervading fear of cancer.

Several studies of diverse patient groups have indicated that the cognitive manifestations of stress may be alleviated more readily with a form of relaxation training that naturally and comfortably "harnesses" and maximises its effect on both peripheral and central systems. Thus we used progressive muscle relaxation and ego strengthening.

Do our data provide evidence of value and of any implications for future use of relaxation training with cancer patients? How

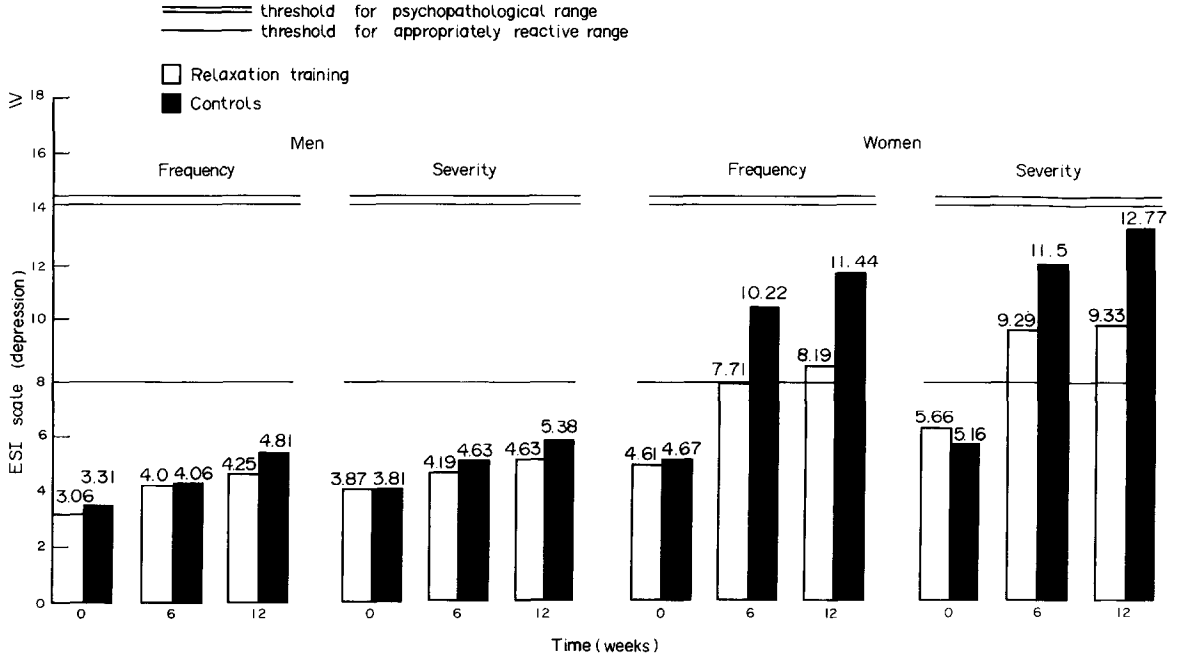

Fig. 4. Depression—mean ESI scores. For frequency, significant differences in women: 0–6 weeks ($P < 0.0001$) and 0–12 weeks ($P < 0.0007$). For severity in women: 0–6 weeks ($P < 0.0001$) and 0–12 weeks ($P < 0.0004$). ═══ = threshold for psychopathological range and ——— = threshold for appropriately reactive range.

should anxiety and depression in such patients be perceived and interpreted? And what, if any, is the significance of the sex-related differences we found?

To attribute such differences to relaxation training solely on the strength of these data would be premature. This is because we do not know what influence the training may have exerted merely as a diversion or as welcome evidence to patients that their psychosocial needs were being acknowledged. Any association between relaxation training and enhanced psychosocial wellbeing requires further investigation. What is clear is that without the audiotape, even a modified version of the training for 10–15 min might be unrealistically labour-intensive. On the other hand, relaxation-type strategies do seem to provide an aspect of self-help and self-control and may therefore be regarded as a valuable coping resource. This view is further reinforced by our earlier evidence [1] and our report here of a reduction in anticipatory nausea and vomiting in the relaxation training group.

Our data sharply focus on the need to distinguish between psychosocial distress and ensuing dysfunction which is an appropriate response to cancer and any such disorder which indicates psychopathology. Such a conclusion is consistent with the finding of Plumb and Holland [11] who have reported a surprisingly low level of severe anxiety (15%) and depression (15–20%) in cancer patients. Similarly Bloom *et al.* [12] in a study on psychosocial response to mastectomy, reported only transitory psychopathological symptoms and concluded that the diagnosis and treatment of breast cancer is not a cause of severe and lasting psychopathology. Hughson *et al.* [13] have referred to the absence of evidence to show that in breast cancer patients radiotherapy "... induced an excess of depression or anxiety at any time during the first year" following surgery. In similar studies designed to investigate depression as a risk for cancer morbidity and mortality, Cassileth *et al.* [14] and Zunderman *et al.* [15] have raised serious doubts of a causal association. In our study, although SAA and SAD mean scores exceeded the instrument's threshold score for "caseness", the ESI scale gave mean scores within its appropriately reactive range. This low frequency of genuine psychopathology in cancer patients is being confirmed and increasingly reported in clinical practice.

The third question focuses on sex-related differences and a seemingly greater vulnerability of female patients to psychological trauma. The two main tumour types among women were ovarian and breast, both of which may be perceived as being powerfully associated with sexual role, status and self-image. Any perceived threat to life may be expected to give rise to shock, anger, guilt, fear of adverse change or irrevocable loss. Is there a commensurate threat to males, given that the principal tumour was testicular teratoma? The impact on men seems to be less severe, although this may in part be because testicular teratoma, diagnosed and treated early, is potentially curable and less likely to result in changed body image. Once the shock of diagnosis has subsided in such patients, it may be treatment that presents the most acute psychosocial problem. Female patients appeared to handle relaxation training more comfortably as a daily or near daily routine than men, who seemed to perceive it in a narrower context—i.e. of the need for relief from unpleasant side-effects of treatment. In some men the training appeared to conflict with a "macho" self-image. The ESI scale shows potential for distinguishing appropriate and reactive response from maladaptive and biogenic state. Failure to detect the clinical features of this difference may lead to inappropriate prescribing of antidepressant drugs. Conversely, time and other resources may be used in providing psychosocial treatment where an antidepressant should have been prescribed. The ESI scale uses only psychosocial symptoms of anxiety and depression and excludes such somatic symptoms as fatiguability, loss of appetite and loss of libido, which may directly relate to advanced malignant illnesses.

1. Bindemann S, Milsted RAV, Kaye SB, Welsh J, Habeshaw T, Calman KC. Enhancement of quality of life with relaxation training in cancer patients attending a chemotherapy unit. In: Watson M, Greer S. *Psychosocial Issues in Malignant Disease*. Oxford, Pergamon Press, 1986.
2. Eysenck H, Eysenck SBJ. *Manual of the Eysenck Personality Questionnaire*. Hodder and Stoughton, 1975.
3. Snaith BP, Bridge GWK, Hamilton M. The Leeds scales for the self-assessment of anxiety and depression. *Br J Psychiatry* 1976, **128**, 156–165.
4. Goldberg D. *Manual of the General Health Questionnaire*. NFER-Nelson, 1978.
5. Speilberger CD, Gorsuch RL, Lushene RE. *STAI Manual for the STATE-TRAIT ANXIETY INVENTORY*. Palo Alto, Consulting Psychololgists Press, 1970.
6. Bernstein DA, Borkovek TD. *Progressive Relaxation Training: A Manual for the Helping Professions*. Champaign, Research Press, 1973.
7. Jacobson E. *Progressive Relaxation*. Chicago, University of Chicago Press, 1938.
8. Harland J. *Medical and Dental Hypnosis and its Clinical Application*. Balliere-Tindall, 1971.
9. Wells BWP, Fish F, Bindemann S, *et al.* An investigation of the incidence and characteristics of young drug takers. *Br J Addiction* 1974, **69**, 343–348.
10. Bindemann S, Wells BWP, Schofield CBS. Drug misuse in a special clinic patient population in Glasgow. *Br J Venereal Diseases* 1974, **52**, 343–347.
11. Plumb MM, Holland J. Comparative studies of psychosocial function in patients with advanced cancer. Interviewer-rated current and past psychiatric symptoms. *Psychosomatic Med* 1981, **43**, 243–254.
12. Psychological Aspects of Breast Cancer Study Group. Psychological response to mastectomy: a prospective comparison study. *Cancer* 1987, **59**, 189–196.
13. Hughson AVM, Cooper AF, McArdle CS, Smith DC. Psychological effects of radiotherapy after mastectomy. *Br Med J* 1987, **294**, 1515–1518.
14. Cassileth BR, Knuiman NW, Abeloff ND, Falkson G, Ezdinli EZ, Menta CR. Anxiety levels in patients randomized to adjuvant therapy versus observation for early breast cancer. *J Clin Oncol* 1987, **4**, 972–974.
15. Zonderman AB, Costa PT McCrae RR. Depression as a risk for cancer morbidity and mortality in a nationally representative sample. *JAMA* 1989, **262**, 1191–1195.

Acknowledgement—This research was supported by a Cancer Research Campaign grant (CRC/XC1041/E4/2E40).

APPENDIX: ESI SCALE

20 symptoms of anxiety and depression are arranged on a self-report form, of which 8 specifically relate to anxiety state and 8 to depression. 4 remaining items are commonly associated with both anxiety and depression. The questionnaire asks patients whether they feel low in spirit, keyed up and unsettled, unable to concentrate, anxious and uptight, a burden to others, irritable and on edge, troubled by guilt, no pleasure in living, discontented and ill at ease, worried without cause, depressed, a sense of impending disaster, no enjoyment of life, emotionally tense, a strong sense of being punished, snappy and bad-tempered, sad and withdrawn, unable to relax, easily startled or out of control. The ESI scale aims to identify normal functioning (score 0–7), appropriately reactive response (8–13), and genuine psychopathology (14 and over). These ranges may change in the

light of wider clinical use. Since the perceived difference between these states is principally one of frequency and severity of specific symptoms, a frequency and severity response to all items is included. The categories "all or most of the time" and "severely present" are scored 2; "from time to time" and "mildly present" are scored 1; and "not at all" and "not present" are scored 0. The maximum anxiety and depression frequency and severity score is 24 in both cases. Measures of internal consistency/inconsistency and reliability/unreliability are also incorporated. The ESI scale uses one side of an A4 sheet and is completed and scored in minutes. Full details are available from S.B.

Eur J Cancer, Vol. 27, No. 2, pp. 174–178, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Pefloxacin and Vancomycin vs. Gentamicin, Colistin Sulphate and Vancomycin for Prevention of Infections in Granulocytopenic Patients: a Randomised Double-blind Study

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To test the value of pefloxacin for the prevention of infections in patients with chemotherapy-induced neutropenia, oral pefloxacin plus vancomycin (PV) (n=76) or gentamicin, colistin sulphate and vancomycin (GCV) (n=74) were administered in a randomised double-blind study. Infections were significantly less severe in the PV than in the GCV group. Patients receiving PV had significantly fewer episodes of bacteraemia and central venous line infections than patients treated with GCV. Gram-positive and gram-negative infections were significantly less frequent in patients receiving PV, because of fewer infections with *Staphylococcus* species and enterobacteriaceae. Stool culture detected significantly more gram-positive organisms in the PV group and more gram-negative organisms in the GCV group. Thus, PV was more efficacious than GCV for the prevention of gram-positive and gram-negative infections in the neutropenic patients, despite lower efficacy in eradicating gram-positive organisms from the lower intestinal tract.
Eur J Cancer, Vol. 27, No. 2, pp. 174–178, 1991.

INTRODUCTION

DESPITE EMPIRICAL broad-spectrum parenteral antibiotics, systemic bacterial infections remain a major cause of death during chemotherapy-induced neutropenia [1]. These infections predominantly originate from the gastrointestinal tract and are favoured by chemotherapy-induced damage of the mucosal barrier [1, 2].

New fluorinated quinolones have shown promise for gastrointestinal decontamination and infection prevention in the neutropenic patient because of their broad spectrum of activity on aerobic bacterial species (mainly gram-negative), their reduced tendency to induce rapid appearance of bacterial resistance, lower toxicity than the widely used cotrimoxazole and moderate toxicity for colonisation-protective anaerobic gastrointestinal flora [3–6]. Norfloxacin, which is poorly diffusible was first tested and was superior to placebo [7], non-absorbable antibiotics including polymyxin and vancomycin [8], and the well-absorbed cotrimoxazole [9, 10] for prevention of both colonisation and systemic infections, with excellent tolerance. The highly diffusable ciprofloxacin [11] and ofloxacin [12, 13] gave similar results to those of norfloxacin. However, none of these quinolones adequately prevented colonisation and systemic infections due to gram-positive organisms [7–13].

Pefloxacin has potential advantages over ciprofloxacin: an approximately two times longer half-life and five times higher trough steady-state level [14, 15], and the drug is more diffusible than ciprofloxacin in sputum, oropharyngeal mucosa, and skin [15, 16], which are potential ports of entry for gram-positive organisms. Furthermore, compared with ciprofloxacin, pefloxacin has equivalent minimal inhibitory concentrations (MIC) against gram-positive organisms and slightly higher MIC against gram-negative organisms [18].

We therefore decided to test pefloxacin for infection prevention in profoundly neutropenic patients. Because of the lack of efficacy of quinolones to prevent intestinal gram-positive colonisation [7–13] and the efficacy of vancomycin in achieving this goal [8, 19], vancomycin was added (PV). This regimen was compared with the best conventional decontamination regimen used in our department, namely gentamicin, colistin sulphate and vancomycin (GCV) [19], which gives equivalent results to cotrimoxazole [20]. To detect potentially small differences

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Revised 16 Nov. 1990; accepted 23 Nov. 1990.