The first international urokinase/warfarin trial in colorectal cancer

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Three hundred and forty-four patients with operable colorectal adenocarcinoma, Dukes' stage B or C, were entered into a randomized controlled trial of intraoperative and postoperative intravenous urokinase and/or long-term sodium warfarin therapy. The factorial design of the trial allowed evaluation of each therapy separately. Age, sex, Dukes' stage and cancer site were similar in the treatment groups. Using life-table methods, survival and recurrence/metastases free survival were estimated up to 6 years postoperatively. No significant effects of either therapy on these endpoints were found.

Introduction

In colorectal cancer, surgery has remained to date the mainstay of treatment, with adjuvant therapy contributing little to the outcome.

Since the 1950's interest has developed in the vascular spread of tumor cells and the formation of metastases mainly due to the groups led by Wood et al. [5] and Salsbury [10]. When circulating cancer cells are prevented from forming a fibrinogen/fibrin network they lose their ability to form metastases [11]. Animal studies and observations of patients treated with anticoagulants appeared to suggest that fibrinolytic agents and anticoagulants inhibited tumour growth and decreased the risk of cancer spread [4].

Following pilot studies with the fibrinolytic agent urokinase, which involved measuring fibrin degradation products (FDP) and euglobulin lysis times (ELT), it was found possible to induce fibrinolysis safely when urokinase was given immediately after removal of the tumour. No increase in postoperative blood loss was noted in these cases. For prolonged anticoagulation oral coumarin derivatives were used, as they were shown to be the most effective in inhibiting the tumour and preventing metastases [7].

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A multicentre randomized trial was therefore established in colorectal cancer Dukes' stage B and C using urokinase to induce fibrinolysis and warfarin as the oral anticoagulant.

**Materials and methods**

The trial was carried out in nine European centres with trial offices in London and Switzerland. Patients with operable colorectal adenocarcinoma were potentially eligible for inclusion in the study. Patients were excluded preoperatively if they had been previously treated with long-term anticoagulation, if there were contraindications to oral anticoagulation, or if regular outpatient control was impossible. Informed consent was also required. No attempt was made to standardize surgical techniques between the different centres except that all the macroscopic tumours should be removed. The final classification into Dukes' stages B and C was made by the pathologist.

All eligible patients were preoperatively randomized (by telephoning a trial office) to receive urokinase or not. Randomization was stratified by centre. Treatment with urokinase commenced immediately after removal of the tumour and continued after surgery with an intravenous infusion of 250,000 IU, given over 5 h. This achieved a modest increase in fibrinolytic activity with approximate doubling of FDP levels and halving of the ELT when measured in a sample of cases. Following pathological staging, patients with a tumour classified as Dukes' stage B or C (see table 1), and no concurrent malignancy were further randomized to receive or not to receive warfarin therapy for 2 years adjusted to achieve a doubling of prothrombin time. All other patients were excluded from the trial. Note that preoperative and postoperative use of prophylactic subcutaneous low-dose heparin or anticoagulant therapy for postoperative thrombotic complications did not exclude a patient.

The trial was based on a 2 x 2 factorial design with four treatment arms: (i) no urokinase/no warfarin, (ii) no urokinase/warfarin, (iii) urokinase/no warfarin and (iv) urokinase/warfarin. A sample size of 450 patients stage B or C with a total study duration of 5-25 years was determined adequate to detect a doubling of the median survival by either therapy with a power of 95 per cent and a significance level of 1 per cent [3, 8].

The trial commenced in March 1980, patient entry ceased 5 years later and follow-up to beyond July 1986 was required. A total of 503 potentially eligible patients was randomized to the urokinase or no urokinase groups. Three hundred and forty-four (68.4 per cent) of these were stage B or C and fulfilled the trial entry criteria. These patients form the basis of this report. This sample size is smaller than that originally planned, but has nearly the same statistical power due to the longer follow-up. Table 2 details the reasons for exclusion of the remaining 159 ineligible patients. Explicit reasons were not given to the trial office for all exclusions prior to

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