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# Adjuvant Oral Razoxane (ICRF-159) in Resectable Colorectal Cancer

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***Summary.*** *One hundred and seventy six patients (81 controls, 95 receiving treatment) have entered a prospective randomized trial of long-term oral adjuvant razoxane (ICRF-159) following removal of a colorectal cancer. The median follow-up is 34 months. The treated patients in Dukes' groups B and C have a significantly longer disease-free interval than the control patients (P = 0.01 'as randomized' and P = 0.004 'as treated'). The differences in survival for Dukes' groups B and C are not significant, although follow-up is short. In Dukes' groups B and C, however, 24 of 56 of the patients in the control group have died (43%), as against only 17 of 64 in the treatment group (27%). The treatment produces very few side-effects, is well tolerated by patients, and is taken orally.*

## Introduction

Survival of patients with resectable colorectal cancer (CRC) has not improved significantly in the last 20 years, and according to one report has begun to deteriorate [15]. The dominant prognostic factor remains Dukes' grouping, which is essentially a classification of the degree of local and lymphatic spread of the tumour [8]. Treatments adjuvant to surgery have so far failed to make a significant impact. Attempts to influence survival of patients with CRC by adjuvant chemotherapy are limited by the paucity of drugs that have shown activity in the advanced disease [16]. Of the few drugs that are active in the advanced disease only 5-fluorouracil (5-FU) and razoxane [(±)1,2-*di*(3,5-dioxopiperazin-l-yl) propane] (ICRF 159; NSC 129943; ICI 59118) are suitable for long-term adjuvant treatment. The nitrosoureas and mitomycin C are also active, but are generally considered too toxic for prolonged therapy. 5-FU has been widely and intensively studied [9, 12], but it is not unanimously accepted that it has even the marginal influence on survival in CRC that has been reported [4, 16].

Razoxane (Rz) has not previously been tried as adjuvant or maintenance treatment in CRC. It has, however, a number of biological activities that could make it useful in the treatment of residual or minimal tumours [1]. It specifically prevents tumour dissemination and metastases in some experimental tumours, and normalizes the neovasculature these tumours induce [11, 13, 20]. The drug is cytostatic rather than cytotoxic, and does not seem to affect non-dividing cells. Most cells capable of division have been affected by the drug. Even affected cells, however, are not necessarily destroyed; they may increase in size and become multinucleate [10]. It becomes difficult, therefore, when the criterion of response is tumour size, to assess how effective the drug has been. Affected cells cannot only enlarge, but may continue to multiply, though they may lose the ability to metastasize [19]. In the presence of subclinical residual disease and micrometastases Rz might therefore prevent the formation of further metastases and control or slow down the development of those that are already present.

Previous use of Rz in CRC has been in the advanced disease and at maximum tolerated doses [2, 14]. These early reports showed an effect of Rz in advanced CRC according to the criteria of objective remission, although a subsequent publication has failed to confirm this [17]. Maximum tolerated doses require that treatment courses should be very short, while treatment-free intervals have to be relatively

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long to allow drug-induced marrow suppression to recover. During this interval the tumour can also recover. In the present trial, Rz was given at the maximum dose that could be tolerated on a continuous basis, with the minimum treatment-free interval.

We report here the early results of a randomized prospective controlled clinical trial of long-term oral adjuvant Rz in which survival and time to first recurrence were the criteria of response.

## Patients and Methods

One hundred and seventy-six patients have entered the trial and have been followed up for a minimum of 5 months (81 controls and 95 receiving Rz). Eighty percent of the patients came from one hospital and the remainder from three other centres.

All patients had a CRC removed and survived to the first out-patient appointment (usually between 4 and 8 weeks after operation). At this time patients in the treatment group started treatment with Rz 125 mg twice daily by mouth for 5 days per week (Monday to Friday) indefinitely. Blood counts were performed weekly for the first month and then monthly, and the dose of Rz was reduced or stopped if the WBC fell below $3.0 \times 10^3/\mu l$. The drug was restarted when the blood counts permitted. Control patients were managed according to the usual practice of the participating centre. Radiotherapy was used for palliation of pain in some cases. Patients who were suspected of having relapsed were investigated and treated appropriately, with chemotherapy in some cases.

Patients were stratified according to Dukes' grouping [5], with the addition of a group D. Patients classed in group D were those found at operation, to have definite tumour that was not in continuity with the primary.

## Results

The median follow-up time is 34 months. The distribution of patients by Dukes' grouping is shown in Table 1, and shows an excess of treated patients in Dukes' groups B and D.

Ten patients randomized to the treatment group never received any Rz, and a further two did not receive it until after their tumour recurred. These patients have been retained in the treatment group of the 'as randomized' analyses. They have been considered with the control group, with whom their management was identical in the 'as treated' analyses. Of these ten patients, one was in Dukes' group A, two in group B, three in group C, and four in group D.

The trial has been assessed by both the recurrence-free interval and survival and has been analysed by the log-rank test as described by Peto et al. [18]. It is important to note that this test relates

**Table 1.** Dukes' grouping

| Dukes' group | Control | Treatment |
|---|---|---|
| A | 17 | 17 |
| B | 23 | 35 |
| C | 33 | 29 |
| D | 8 | 14 |
| Total | 81 | 95 |

**Table 2.** Criteria for recurrence in Dukes' A, B, and C patients

| | As randomized | | As treated | |
|---|---|---|---|---|
| | Control | Treatment | Control | Treatment |
| Laparotomy | 7 | 4 | 7 | 4 |
| Serial liver ultrasound | 4 | 2 | 4 | 2 |
| Radiological | 4 | 4 | 4 | 4 |
| Sigmoidoscopy | 3 | 3 | 4 | 2 |
| Other Histological | 1 | 2 | 2 | 1 |
| Palpable gross hepatomegaly | 2 | 4 | 4 | 2 |
| Abdominal mass | 1 | 0 | 1 | 0 |
| Neurological | 0 | 2 | 0 | 2 |
| Total | 22 | 21 | 26 | 17 |

**Table 3.** Statistical significance by the log-rank test[a]

| | As randomized | | As treated | |
|---|---|---|---|---|
| | Recurrence | Survival | Recurrence | Survival |
| All patients $p$ = (No stratification) | 0.19 | 0.97 | 0.02 | 0.18 |
| Dukes' B | 0.09 | 0.10 | 0.158 | 0.174 |
| Dukes' C | 0.06 | 0.82 | 0.012 | 0.193 |
| Dukes' B + C | 0.013 | 0.276 | 0.004 | 0.07 |

[a] All figures indicate the statistical significance of the advantage of the treated group in relation to the control group

**Table 4.** Age at operation in Dukes' groups B and C

| Age | Control | | Treated | |
|---|---|---|---|---|
| Dukes' | B | C | B | C |
| 30–40 | 0 | 1 | 0 | 1 |
| 41–50 | 1 | 4 | 2 | 3 |
| 51–60 | 8 | 7 | 9 | 6 |
| 61–70 | 5 | 11 | 9 | 4 |
| 71–80 | 6 | 8 | 11 | 13 |
| 81–90 | 3 | 2 | 4 | 2 |
| Total | 23 | 33 | 35 | 29 |

**Table 5.** Patient gender in Dukes' groups B and C

| | Control | | Treated | |
|---|---|---|---|---|
| Dukes' | B | C | B | C |
| Male | 11 | 21 | 17 | 15 |
| Female | 12 | 12 | 18 | 14 |
| Total | 23 | 33 | 35 | 29 |

**Table 6.** Site of tumour in Dukes' groups B and C

| Site | Control | | Treated | |
|---|---|---|---|---|
| Dukes' | B | C | B | C |
| Rectum | 5 | 13 | 10 | 11 |
| Rectosigmoid | 0 | 4 | 2 | 1 |
| Descending colon | 10 | 7 | 15 | 9 |
| Transverse and flexures | 4 | 2 | 6 | 3 |
| Ascending colon and caecum | 4 | 7 | 2 | 5 |
| Total | 23 | 33 | 35 | 29 |

patient events to time under observation. It measures the rate at which events occur, and the absolute number of events in each group is of secondary importance.

Recurrence was taken to be either the time at which definite recurrence was noted or death, if this occurred without prior evidence of recurrence. The methods by which recurrence was diagnosed are shown in Table 2, which indicates an equal distribution of objective and subjective criteria between the control and treatment groups. Dukes' group D is excluded by definition.

There are no statistically significant differences between treated and control patients in any of the Dukes' groups analysed individually, as randomized, but numbers of patients are small (Table 1). The graphs show a visual separation between control and treated patients for Dukes' groups B and C, but not for A and D. When Dukes' groups B and C are combined after stratification [18] statistically significant differences emerge. The differences are most clearly seen in the rate of recurrence (Table 3). When patients are considered as treated rather than as randomized, levels of significance are further increased. The matching for patients in Dukes' groups B and C for age, sex, and site of tumour are shown in Tables 4–6.

### *Disease-Free Interval and Recurrence*

The site of first recurrence for Dukes' B and C cases is shown in Table 7, and only those cases in which recurrence was diagnosed prior to death are included. Locoregional and hepatic metastases were most frequent. In the treated group three patients developed metastases in bones and two in the brain. The rate of recurrence has been greater in the control than in the treated patients (Table 3), and this is shown graphically in Fig. 1. The recurrences were seen primarily in the first year, as has been previously reported [3].

While we believe that Fig. 1 represents the results of greatest clinical importance, we are also including two further graphs. These are the graphs for the best and worst levels of significance from Table 3. Figure 2 shows survival strictly as randomized, without any stratification for Dukes' grouping or exclusions. Figure 3 shows the difference in recurrence-free interval for Dukes' groups B and C when considered after stratification and considered as treated.

### *Survival*

There was close surveillance of the patients in this trial, and good documentation of the mode of death in almost all cases. Eleven patients in all Dukes' groups (four controls, seven treated patients) are known to have died of intercurrent disease or without evidence of recurrent cancer at autopsy (Table 8). They have been considered as 'lost to follow-up' from the time of death for the statistical analyses of disease-free interval [18]. Patients in whom there was any doubt about the cause of death are considered as having died of cancer. No exclusions have been made from the survival figures, which therefore include the patients in Table 8. The actual numbers of deaths are shown in Table 9.

In Dukes' groups B and C considered as randomized, 24 of 56 patients have died in the control group (43%), as against 17 of 64 in the treatment group (27%). When considered as treated, 27 of 62 in the control group (44%) and 14 of 58 in the treated group (24%) have died.

### *Toxicity*

The doses of Rz used in this trial were exceptionally well tolerated and gave few side-effects. The white cell count fell in all Rz-treated patients, and to below $3.0 \times 10^3/\mu l$ in half of them. This was indirect evidence that the drug was being absorbed and that the dose of Rz given was the maximum permissible. A higher dose of Rz would not have been possible because of the leukopenia produced, and in half the patients the dose had to be reduced either perma-

**Table 7.** Site of first recurrence in Dukes' B and C stage tumours, 'as treated'

| Dukes' stage | | Patients | With recurrence | % | Loco-regional | Liver | Lung | Bone | Brain | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| B | No Rz | 25 | 4 | 16 | 4 | – | – | – | – | – |
| | Rz | 33 | 4 | 12 | 1 | 1 | – | 1 | – | 1 |
| C | No Rz | 37 | 19 | 51 | 7 | 10 | 2 | – | – | 1 |
| | Rz | 25 | 12 | 48 | 4 | 3 | 2 | 2 | 2 | – |

Note: Two patients had recurrences in two sites simultaneously

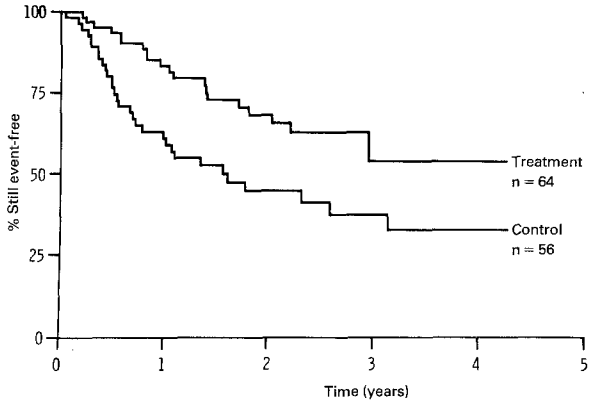


**Fig. 1.** Life table analysis showing recurrence-free interval 'as randomized' for Dukes' groups B and C. Log-rank analysis, $P = 0.013$

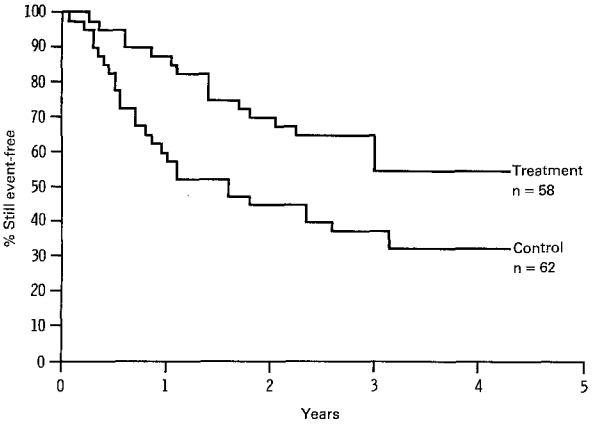


**Fig. 3.** Life table analysis showing recurrence-free interval for Dukes' groups B and C 'as treated'. Log-rank analysis, $P = 0.004$

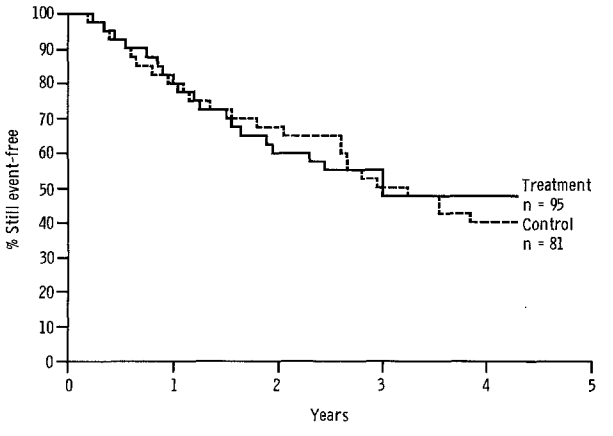


**Fig. 2.** Life table analysis showing survival for all Dukes' groups without stratification 'as randomized'. Log-rank analysis, $P = 0.97$

nently or temporarily. Other symptoms that occurred in the treatment group are shown in Table 10, although they were not all necessarily caused by Rz.

Ten patients discontinued Rz for one of the reasons stated in Table 10. Three patients stopped the drug after less than 3 weeks, six between 3 and 12 weeks, and one patient after 14 months. A further two patients stopped Rz for symptoms that continued after the treatment was stopped. All these patients, even though their treatment courses were severely attenuated, are retained in the treated group in all analyses.

In six patients (one control, five Rz), bronchopneumonia has been stated as the cause of death, without evidence of tumour recurrence. This was the finding at autopsy in two patients in the treated group, and two further patients in the treated group were known chronic bronchitics who suffered exacerbations of their disease. None of these patients was neutropenic but it is possible that there was a functional impairment of neutrophil activity, although there is no evidence on this point.

## Discussion

Early in the trial, the life table curves showed a separation of the treated and control groups, which has been maintained as the follow-up period has

**Table 8.** Non-cancer deaths

| | Number | Dukes' group | Comments |
|---|---|---|---|
| Controls | B56 | A | Died in hospital, bronchopneumonia, no sign of recurrence |
| | B59 | A | Died in hospital, congestive cardiac failure, no sign of recurrence |
| | B78 | A | Post mortem, myocardial infarction, no sign of recurrence |
| | B114 | B | Suicide, post mortem, no sign of recurrence |
| Treated group | A11 | B | Died at home following recent clinic appointment, bronchopneumonia, no sign of recurrence. Kyphoscoliosis. Known chronic bronchitic |
| | A20 | C | Died in hospital, bronchopneumonia, no sign of recurrence. Known chronic bronchitic |
| | A32 | A | Coronary thrombosis, no sign of recurrence |
| | A38 | C | Carcinoma of the breast, bone secondaries, no sign of recurrence |
| | A125 | B | Post mortem, bronchopneumonia, no sign of recurrence |
| | A129 | C | Bronchopneumonia, no sign of recurrence |
| | A130 | B | Post mortem, purulent bronchitis, no sign of recurrence |

**Table 9.** Deaths (excluding definite non-cancer deaths)

| | As randomized | | As treated | |
|---|---|---|---|---|
| | Control (%) | Treatment (%) | Control (%) | Treatment (%) |
| Total | 30/81 (37) | 31/95 (33) | 38/93 (41) | 23/83 (28) |
| Dukes' group | | | | |
| A | 2/17 (12) | 2/17 (12) | 3/19 (16) | 1/15 (7) |
| B | 8/23 (35) | 3/35 (9) | 8/25 (32) | 3/33 (9) |
| C | 16/33 (48) | 14/29 (48) | 19/37 (51) | 11/25 (44) |
| D | 4/8 (50) | 12/14 (86) | 8/12 (67) | 8/10 (80) |

**Table 10.** Toxicity and reported symptoms in treated patients ($n = 95$) in all Dukes' groups

| | | Stopped treatment |
|---|---|---|
| Leukopenia (WBC $3.0 \times 10^3/\mu l$) | 41 | 0 |
| Thrombocytopenia (platelets $< 100 \times 10^3/\mu l$) | 2 | 2 |
| Partial alopecia (no wigs) | 8 | 0 |
| Gastrointestinal | 5 | 5 |
| Vertigo | 1 | 1 |
| 'Pain in chest' | 1 | 1 |
| Skin rash | 1 | 1 |

extended. As patient accrual has progressed so the level of statistical significance has increased, so that we now have values that are generally considered significant. The advantage is apparent only for the Dukes' B and C cases, who are the patients with minimal residual tumour and who might be expected to benefit most from the cytostatic and anti-metastatic effect of Rz [10, 19]. It would be most difficult to show an effect in Dukes' A cases, as most of these are cured by surgery alone, while in Dukes' D cases metastases are already present and the tumour burden is probably overwhelming.

Although Rz was originally shown to be effective in advanced CRC [2, 14], we, in agreement with Paul et al. [17], have found no statistically significant difference in this group (Dukes' D), although numbers are small. In one patient with a single hepatic metastasis, the lesion was seen to regress on serial liver ultrasound examinations during treatment with Rz, and then subsequently enlarge.

The advantage to the Rz-treated groups B and C reaches statistical significance for recurrence-free interval when taken strictly as randomized (Table 3). In this analysis the treated group contains six patients who never received any Rz. When analysed as treated, the levels of significance improve further. In this analysis as treated, the treatment group still contains seven further patients who stopped Rz prematurely.

So far, only the differences for recurrence-free interval have reached statistical significance. In the study from Malmö [3], half of all recurrences were apparent within 1 year of operation and 92% within

4 years; the median follow-up time in the present trial is nearly 3 years, and it is therefore likely that most of the recurrences that are to be expected will already have been seen. Survival by definition exceeds recurrence-free interval, and longer follow-up is therefore needed to see whether the figures for survival become significant as the period of observation increases.

Examination of the pattern of first recurrence (Table 7) shows why Rz may have been effective. There appears to have been a diminution of liver metastases in the Dukes' C patients receiving treatment, with the appearance of metastases in bone and brain. These are uncommon sites for metastatic CRC, and were found only once each in the necropsy series of Willis [23]. Rz may have changed the pattern of metastases, delaying the appearance of metastases in one site and allowing time for others to present.

There are a large number of factors that influence survival in CRC, some of them to a greater degree than even the most optimistic aspirations of currently available therapies, and the effect that these might have had on this trial should be considered. Clinical and pathological criteria have been assessed in detail with regard to prognosis and quantified by Spratt and Spjut [21] and by Wood et al. [24]. The conclusion from their two studies on 1,137 and 1,326 patients, respectively, was that analysis on the lines of Dukes' grouping was still of paramount importance in the assessment of prognosis. Our analyses were therefore performed after such a stratification, with the addition of a Dukes' group D, which included those cases with the worst prognosis from within the other Dukes' groups. If the original Dukes' classification is used (without a Dukes' group D), prognostic subsets of statistical significance, such as lymphatic metastases in the highest excised node [6] and venous [22] and local invasion [25], may still be identified. With the numbers present in this trial it was not feasible to subdivide the Dukes' groups according to these criteria, but their influence should have been minimized by the addition of Dukes' group D.

The heterogeneous nature of CRC makes it preferable to include large numbers of patients in trials to accommodate all the prognostic variables, and this has resulted in the trend towards multicentre studies. Unfortunately, increasing the number of centres increases the number of variables in proportion, as the surgeon may be a most influential factor [7]. A smaller trial, such as this, may be more closely controlled than its multicentred counterpart, and this is an advantage to be weighed against the disadvantage of smaller numbers.

The results of this trial should be assessed in the context of the results of other adjuvant treatments in CRC. 5-FU is the most successful drug at present, but has produced results that only border on statistical significance when used as an adjuvant therapy [9, 12]. The benefit from 5-FU is achieved in conjunction with unpleasant symptoms in the patients and the problems of an intravenous therapy. Two of the outstanding advantages of Rz as used in this trial are its oral administration and the insignificance of side-effects. These properties make prolonged administration feasible, and this in itself may be a crucial factor in determining the effectiveness of the drug.

Therefore, we wish to emphasize that if there has been an improvement in prognosis of resectable CRC due to Rz, it has been achieved with minimal impairment of the quality of life. Any benefit produced does not have to be offset against the problems of toxicity and inconvenience that have brought a sobering reappraisal of so much of cancer chemotherapy.

Finally, we believe that at the very least we have shown that Rz may be given for a prolonged period of time with acceptable safety. Further studies of this drug, both as a single agent and in combination with other drugs, appear justified in the adjuvant treatment of CRC to define more precisely its therapeutic effect.

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