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Letter to the Editor

Adjuvant Oral Razoxane (ICRF 159) in Resectable Colo-Rectal Cancer

Dear Sir:

We have read with interest the article by Gilbert et al. [2].

The authors report a significantly prolonged recurrence-free interval (RFI) for patients treated with Razoxane when the patients with resected tumours classified as Duke's stages B and C were combined.

This is potentially a most important observation and the data therefore demand careful analysis. There are aspects of this study that are of serious concern.

There are marked differences in the number of patients in each of the Duke's categories. The data are analysed both 'as randomised' and 'as treated'. In the former analysis there were 50% more Duke's B patients in the treatment group, while in the as treated analysis there were 50% more Duke's C patients in the control group. Both these factors discriminate against the control group. It is well recognised that the outlook for both RFI and survival for Duke's B patients is superior to that for Duke's C patients [1, 3]. This degree of difference, in patients who have not received adjuvant therapy, is considerably greater than the difference shown between the Razoxane-treated patients and the controls in this study. Comparison of two groups of such differing composition and prognosis is misleading. Indeed, the prolonged RFI is hardly surprising when the treated patients comprise a prognostically favourable group whether analysed as randomised or as treated.

Gilbert and co-workers report no difference in survival or RFI when all patients are considered together or when Duke's B and C patients are analysed separately.

Separate analysis of prospectively stratified groups (e.g., Duke's A, B, and C) within adjuvant trials is valid because it is most likely that such therapy will benefit only a proportion of the total patients treated. If groups of differing natural histories are to be combined at a later date to provide sufficient numbers for statistical significance it is essential that the composition of each group is evenly balanced between treated and control patients. Unequivocal conclusions in trials of adjuvant therapy of common cancers are important if patients are to receive beneficial therapy and avoid useless and possibly harmful treatment. Sadly, the severe deficiencies in the reported study make it impossible to evaluate the role of Razoxane as adjuvant therapy in colo-rectal cancer.

Yours sincerely

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P. F. M. Wrigley
Consultant Physician

References

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2. Gilbert JM, Hellmann K, Evans M, Cassell PG, Stoodley B, Ellis H, Wastell C (1982) Adjuvant Razoxane (ICRF 159) in resectable colo-rectal cancer. Cancer Chemother Pharmacol 8: 293–299
3. Gill PG, Morris PJ (1978) The survival of patients with colo-rectal cancer treated in a regional hospital. Br J Surg 65: 17–20

Dear Sir:

Thank you for showing us the letter by Drs Slevin, Harvey and Wrigley and allowing us to comment.

We are pleased to report that their fears are groundless and arise from their incomplete appreciation of the application of the log rank test. The patients in our study were prospectively randomised to control and treatment groups and were subsequently stratified into Duke's groups A, B, C, and D. Individual groups were analysed separately and then the separate results for Duke's groups B and C were summated.

When the Duke's groups are analysed separately and the results are then added together no bias is introduced by the difference in numbers which has arisen from the stratification. If the Duke's groups B and C had been combined first and then analysed as a single group, then the bias which your correspondents erroneously attribute to us would indeed have been present. If one did make this error, then the already significant difference in favour of the treated patients would increase even further.

The analysis of sub-groups within a clinical trial is described in detail by Peto R. et al. [1]. Mr J. Peto is one of the authors of this paper, which describes the application of the log rank test in clinical trials and he kindly performed all the analysis presented in our paper. We are assured by him that his handling of the data has not introduced the bias suggested by your correspondents.

Yours sincerely

J. M. Gilbert
K. Hellmann
M. Evans
P. G. Cassell
B. Stoodley
H. Ellis
C. Wastell

References

1. Peto R, Pike MC, Armitage P et al. (1976) Design and analysis of randomised clinical trials requiring prolonged observation of each patient. Br J Cancer 34:585–612; (1977) Br J Cancer 35:1–39

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