Patterns of Failure Following Locoregional Radiotherapy in the Treatment of Limited Stage Small Cell Lung Cancer

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Summary of Trial

Coy et al reported on a multicentre trial looking at the timing of concurrent locoregional radiotherapy with chemotherapy for limited stage small cell lung cancer. This is a randomised trial conducted between February 1985 and December 1988. There were three hundred and thirty two patients entered into the study. The aim of the study was to determine if during the course of chemotherapy whether early concurrent radiotherapy (radiotherapy given with the first cycle of etoposide and cisplatin) was superior to late concurrent radiotherapy (radiotherapy given with the last cycle of etoposide and cisplatin) for progression free survival and overall survival.

The study found that the progression free survival and overall survival were superior in the early radiotherapy arm. The argument put forward in the paper was that by delaying radiotherapy till the last cycle of EP gave these chemotherapy resistant cells a chance to metastasize. The trial found that the delay in administering radiotherapy by 12 weeks had a significant impact on survival.

Design Features

The study was undertaken after a pilot study performed by British Colombia Cancer Agency showed that etoposide and cisplatin given concurrently with thoracic radiotherapy gave acceptable toxicity and promising results for limited stage small cell lung cancer.

The title of this paper is misleading. The title is "patterns of failure following locoregional radiotherapy in the treatment of limited stage small cell lung cancer". The aim of the trial however is whether early or late concurrent radiotherapy improves relapse free survival or overall survival. The paper does not really tackle the issue of failure patterns after treatment for limited stage cell lung cancer.

This study is designed as a randomised controlled trial. It provides the greatest for concluding causality and is subject to be least number of biases.

The patients were derived from 22 participating centers across Canada. The patient eligibility, study design, response criteria and staging investigations were reported in another publication (Journal of Clinical Oncology, Volume 11, No. 2 (February), 1993 : pp 336-344). The current published paper should state these in the methods. If however one makes the effort to review the previous publication then both the entry criteria and the exclusion criteria are clearly stated.

In regards to the treatment, firstly, there is no conclusive evidence that concurrent therapy is superior to sequential treatment. Therefore in this trial it would have been better to have three randomised arms. That is the trial should have included a sequential arm - chemotherapy followed by radiotherapy in those patients who had a complete response. Secondly, the dose prescribed for the thoracic irradiation is 40 Gy in 15 fractions given over a three week period. Recent studies suggest that for thoracic irradiation a minimum tumour dose of 50 Gy in standard fractionation is necessary for control of thoracic disease. It would have been better if the trial used standard fractionation rather than giving 2.67 Gy/fraction. This would have allowed a better comparison between trials since most have used standard fractionation.

Thirdly, the radiotherapy field and how the patient were treated were well described. The problems associated with the radiotherapy were that there was no correction for lung inhomogeneity and the spine was shielded from the posterior field for the entire course of treatment. The shielding of the spinal cord is discussed in the paper. The problem with this approach is that the disease itself may potentially be partially shielded. The authors argued that by treating without posterior shielding would increase the toxicity to the oesphagus and thereby decreased treatment tolerance.

Fourthly, the use of alternating chemotherapy regimes (cyclophosphamide, adriamycin and vincristine alternating with etoposide and cisplatin) has not been proven to the more effective than etoposide and cisplatin alone.

There was no power base assessment of the adequacy of the sample size in this paper. However if the statistical methods are reviewed in the previous publication then the trial was designed to provide a power of 80% to detect an improvement in the two year survival rate from 20% to 35% at a significance level of 0.05 (two - sided). The power of

the study is the capacity of the study to detect a true difference.

Conduct of Study

There were three hundred and thirty two patients entered into the study over a three year and ten month period from 22 Canadian centres. There was a good participation rate. The patients were stratified by centre prior to randomisation. The paper did not inform the reader the method used for randomisation. Prior to commencing a multicentre trial the randomisation can be done by a randomisation list for each hospital so that there are approximately equal numbers of patients assigned to each treatment arm at a particular institution.

There was no comment in this paper regarding consent for the trial which should be present. This was again covered in the previous publication. Informed consent was obtained according to the Medical Research Council of Canada. With informed consent, a document must be signed by the patient. As the informed consent was obtained prior to randomisation then the patient agrees to undertake the treatment they are allocated.

With a multicentre trial it is difficult to control the conduct of the study. There was an audit of the radiotherapy given. The audit was done by three radiation oncologists. There was no comment as to whether there was blinding of the radiation oncologists. In other words, whether the radiation oncologists were aware of the treatment that the patients were assigned. The diagnostic biopsy or cytology specimen was reviewed by a local reference pathologist at each participating centre, rather than centrally. There were 22 pathologists reviewing the material allowing for possible bias.

Statistical Analysis

There were three hundred and thirty two patients of which the trial considered 24 to be ineligible - 13 from the "early" arm and 11 from the "late" arm. These patients had been randomised prior to review. The conditions that were present prior to randomisation although not detected until the time of review are reasonable to deem ineligible. They are those patients that were diagnosed with :- extensive disease (5 patients), non small cell lung cancer (10 patients), and inadequate pulmonary function (4 patients). It is invalid to declare a patient ineligible based on a condition which was not present at randomisation but appeared subsequently - those unable to tolerate protocol treatment (4 patients) and those who had non measurable disease (2 patients). There was no specific exclusion for patients who had disease that could not be measured. These patients should have been included in the statistical analysis. The data should be analysed on an intention to treat basis.

Survival for analysis was defined in the paper as the time from the date of the first cycle of chemotherapy to the date of death or date of last report. Kaplan-Meier survival curves were shown (figure 1 in the paper). The graph was appropriately labelled. There are two commonly used methods to determine survival curves, life (actuarial) tables and the Kaplan-Meier procedure. The two methods are similar except with Kaplan-Meier the time since entry into the study is not divided into intervals for analysis. Survival is estimated each time a patient dies.

The survival curves were analyze using a log rank test, which is appropriate. The paper found in favor of the "early" treatment arm for survival with a significant p value.

Forward stepwise Cox regression was used to assess prognostic factors. Forward regression starts with one variable in the regression equation and additional variables are added, one at a time until all the statistically significant variables are included in the equation. If that variable is found to be statistically significant it will be included in the regression equation. From this study the important prognostic factors were - male gender and poor performance status.

The time to recurrence was defined in the paper as the time from the date of the first cycle of chemotherapy to the date of the first recurrence or date of last report. The Kaplan-Meier method was used to determine the recurrence free survival. The graph (Fig. 2 in this paper) was labelled correctly. The treatment arms were analysed using the log rank test with the "early" radiotherapy treatment arm showing a significant improvement ($p = 0.021$). The relative risk for the treatment arms was given (1.35) with a 95% confidence interval. Again a Cox regression model was used with male gender being the only significant prognostic factor.

There were 83% of patients who completed the prescribed 6 cycles of chemotherapy. There were equal numbers in both groups and there was no significant difference in chemotherapy toxicity. Patients in the "early" arm developed more cutaneous side effects and more oesphagitis.

There were 96% of patients treated with locoregional radiotherapy in the "early" arm but only 87% in the "late" arm. Approximately 2/3 of the 26 patients were from the "late" treatment arm who did not receive locoregional XRT. There was no comment as to whether the difference between the two arms was significant. Also the duration of radiotherapy was longer in the "late" arm. Only 8.7% of patients in the "early" arm had treatment for more than 23 days compared to 24.8% in the "late" arm. Again there was no indication as to whether the difference was significant.

After completion of 6 cycles of chemotherapy and thoracic irradiation, the patient underwent a cerebral CT scan. Those with no radiographic evidence of brain metastases were treated with PCI (25 Gy in 10 fractions via opposing lateral fields). 83% of the patients received PCI. There were small numbers in both groups who had developed radiological cerebral metastases upon completion of their chemotherapy and radiotherapy.

After PCI, there were 15.8% in the "early" arm and 23.8% in the "late" arm who developed cerebral metastases. This was not statistically significant using the Fishers' exact test. Fishers' effect test is used as an alternative to the chi-square test when the expected frequencies are small. The trial found that there was in total a greater number of brain failures in the "late" treatment arm (28% vs. 18%). This was statistically significant using the Fishers' exact test. The argument was that the "early" treatment arm reduced the number of brain failures. However by analyzing entire group with inclusion of the patients who did not receive thoracic radiotherapy or had prolongation of radiotherapy in the "late" treatment arm may mean that this difference is false.

Conclusion

The study found that the progression free survival and overall survival were superior in the "early" radiotherapy treatment arm. The trial found that by delaying the radiotherapy by 12 weeks had an impact on overall survival. The argument could forward by the paper was that by delaying radiotherapy gave the opportunity for chemotherapy resistant cells to metastasize.

A comparison with a third arm would have addressed the issue of whether concomitant or sequential radiotherapy was superior. This paper relied on a previous publication for the conduct of the study as well as the design features. These should have been included in this paper.

It is difficult to draw conclusions from this trial, since the radiotherapy fractionation and planning with no lung corrections and posterior shielding for the entire course of treatment are not standard practice. Also patients in the "late" radiotherapy treatment arm had more protracted treatment and a greater number did not received thoracic radiotherapy.