Patient accrual into chemotherapy trials in non-small cell lung cancer

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In this edition of *Thorax* Spiro and colleagues[1] report their perceived failure to recruit patients to the Big Lung trial (BLT). It is appropriate to consider why only 9% of eligible patients entered the trial and what impact this has on this important study.

BLT addresses the role of cisplatin-based combination chemotherapy in non-small cell lung cancer (NSCLC). This is not a trivial regime in a patient group with a median age of 67 years, many of whom will have major vascular co-morbidities. That fewer than one sixth of patients were deemed ineligible for these reasons is surprising. It is also noteworthy that 12% of patients had elective chemotherapy—presumably all with inoperable disease since there is no current evidence to justify routine postoperative adjuvant therapy. It is disappointing, but hardly surprising in the current UK research environment with its dependence on the pharmaceutical industry, that 13% of patients were treated in centres without the infrastructure for clinical research. It would be interesting to know how many of the 52 patients too late for consideration were postoperative referrals. It has been our experience, which is reflected in the poor accrual of subjects for LU22 (the MRC neoadjuvant chemotherapy trial), that it is extremely difficult to access patients fast tracked through surgery to discuss randomisation for chemotherapy trials.

Thus, the reality of this "failure" is that one quarter of eligible patients entered this study. How does this compare with other studies, particularly those with "no treatment" control arms? The authors compare their achievement unfavourably with the accrual of breast cancer patients to clinical trials in Scotland where 12% of all patients entered trials.[2] For lung cancer in Scotland in 1995 this figure was 3%.[3] In one hospital in Toronto between 1984 and 1989 18% of breast cancer patients entered studies[4]; in Edinburgh, in the same period, 27% of patients suitable for conservation therapy of breast cancer were randomised.[5]

The difference between BLT and breast cancer trials appears to be the high rate of patient refusal (74%) as the reason for non-entry. This has been reported in other studies to be as low as 4%[6] but was 46% and 37% in Toronto and Edinburgh, respectively. How can eligible patients be persuaded to enter studies? Patients have been reported to have difficulty with the uncertainty of randomisation, particularly with a no treatment arm, the inconvenience and expense of additional visits, and the complexity of informed consent documents.[7] A focus group study in Australia found that patients had a poor understanding of the need for and organisation of clinical trials, the role of randomisation, and saw research as a gamble to be taken when no other treatment option was available. No individual benefit was perceived from trial participation.[8] A systematic review confirmed these concerns. The authors recommended simple protocols and minimum demands on patients, dedicated research staff, and planning and piloting of recruitment.[9] Perhaps doctors need training in patient recruitment to clinical trials. Interestingly, an American study reported that patients were 13 times more likely to enter a study if advised to do so by their primary care practitioner.[10] A nursing study suggested that patients decide instantaneously about trial participation,[11] suggesting an element of "selling" clinical trials as well as ensuring adequate understanding of the process and issues.

The problem this accrual rate raises is the applicability of the resulting data to the whole population of patients with NSCLC. The question posed by the trial is changed from the intended "What is the role of chemotherapy in all patients with NSCLC?" to "What is the place of chemotherapy in those patients where I am unconvinced it has a proven role?" The benefits seen in this second group may be smaller than in those excluded because chemotherapy is perceived to offer a definite benefit. This will alter the statistical power of the study and may produce a negative result that will be erroneously applied to all patients with NSCLC rather than to the group actually randomised.

The authors raise a further very important question—whether doctors and patients agree on what justifies chemotherapy and constitutes a clinically significant benefit. An American study suggested that patients want a survival benefit of six months or longer from chemotherapy, but would accept chemotherapy for quality of life advantages without improved survival.[12] We have carried out a small pilot study addressing this in Edinburgh. Our data replicated the American experience but, while some patients would accept chemotherapy for a survival benefit of less than one month, others wanted over 18 months survival benefit to justify treatment.

Where does this leave chemotherapy in patients with NSCLC? In the context of surgery, the meta-analysis suggested that adjuvant postoperative chemotherapy might be at least as advantageous in NSCLC as in breast cancer.[13] Five studies testing this hypothesis (including BLT) have accrued over 3000 patients, and this question will be answered this decade. Accrual to these studies remains important. The fact of a survival benefit with chemotherapy before radical radiotherapy or in patients with advanced disease is not in doubt. This has been reinforced by further studies since the meta-analysis,[14 15] and BLT is not large enough to negate previous studies in future meta-analyses. What remains is a value judgement about the size of benefit, which properly should be left to patients. BLT may cloud rather than clarify this issue. The question of quality of life benefit remains critical. Three studies, two using single agent chemotherapy, one of which remains unpublished, have reported an improved quality of life with chemotherapy.[15 16] BLT is vital to confirm this benefit, to enable us to fully inform patients, and to allow them to decide their own treatment.

It is unfortunate that accrual in BLT has been slower than anticipated. Randomising patients in clinical trials is a difficult and time consuming art. Rather than being criticised for their poor accrual, Spiro and coworkers should be congratulated for their efforts in recruiting patients to this study, and they, along with the other participants, should be encouraged to complete the surgical and quality of life studies. We need to absorb the lessons of BLT to improve our accrual in future, both by improving the infrastructure for these studies and perhaps by con-

structing trials that fit more closely with patients' perception of usefulness.

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