Chemotherapy in non-small cell lung cancer: An update of an individual patient data-based meta-analysis

To the Editor:

In the September 2004 issue of the *Journal*, Sedrakyan and associates¹ reported a systematic review and meta-analysis of postoperative chemotherapy versus surgery alone in non-small cell lung cancer. This meta-analysis is based on abstracted data from 15 randomized controlled trials (RCTs). This included 7200 patients and builds on results of our individual patient data-based (IPD) meta-analysis,² published in 1995.

The Non-Small Cell Lung Cancer Collaborative Group, which was responsible for the IPD meta-analysis published in 1995, welcomes the meta-analysis provided by Sedrakyan and associates,¹ which added summary data from 7 trials and approximately 5000 patients to information from the 1995 meta-analysis. However, the interpretation of the results is limited by the absence of trial description and quality evaluation. Furthermore, the results of any systematic review performed with data extracted from publications of trials should be viewed with a degree of caution.³

IPD meta-analyses, which involve the central collection, validation, and analysis of the original trial data, are the gold standard of systematic review and have many advantages over literature-based approaches. They allow the reviewer to check the data, ensure the randomization process was adequate, investigate heterogeneity, and report longer follow-up, and can limit many biases.⁴ They also permit subgroup analysis of patient level characteristics such as age or tumor stage. Of course, it is also well documented that this type of review takes longer to carry out.

The 1995 meta-analysis included more than 9000 patients from 52 RCTs and assessed the effect of chemotherapy in 4 different settings.

An updated and extended IPD meta-analysis is currently under way, and data collection is ongoing. New agents and timings have been investigated in all settings. The update consists of adding trials published since the 1995 analyses and additional follow-up data from trials already included, and investigating additional outcomes in certain settings. Seven different

therapeutic questions will be addressed, and the total number of patients randomized has increased to approximately 23,000 patients. The corresponding protocols are available at the following websites: <http://www.ctu.mrc.ac.uk/download.asp> or http://www.igr.fr/php/index.php?ids_path=2.51.70.127.567.

In a setting equivalent to that described by Sedrakyan and associates,¹ we identified 22 new RCTs with more than 8000 new patients, bringing the total number of trials to 38. If we can include these patients, it would bring the total number of patients in this comparison alone to more than 10,500 patients or 23% more patients than are included in the review by Sedrakyan and associates.¹

Although the meta-analyses by Sedrakyan and associates¹ and a recent similar review by Hotta and associates⁵ are a valuable resource in the absence of other evidence, the results should be considered with caution until they can be compared with the updated IPD meta-analysis. We anticipate that the results of our IPD meta-analyses will be available in 2006.

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Reply to the Editor:

We support and applaud the efforts of Ms Burdett and her team in conducting an individual patient data-based (IPD) meta-analysis of postoperative chemotherapy trials. Although there are controversies regarding the conduct of IPD meta-analyses, such as the inclusion of data from unpublished studies and potential investigator bias in terms of data submitted,^{1,2} such studies may be particularly useful in conducting subgroup analyses to identify those patients most likely to benefit from therapy and the optimal treatment regimen to be used.

The non-IPD nature of our meta-analysis does not, however, take away from the validity of the findings that clearly demonstrate a survival advantage for patients treated with adjuvant chemotherapy over those treated with surgery alone.³ This is also underpinned by a recent presentation on adjuvant UFT (uracil and tegafur), the oral 5-fluorouracil derivative, at the 2004 annual meeting of the American Society of Clinical Oncology. In this work, individual patient data from 2003 patients recruited to 6 randomized controlled trials were systematically reviewed. The overall survival benefit for treated patients is 5.3% (hazard ratio = 0.77; $P = .011$) at 5 years and 7.7% (hazard ratio = 0.74; $P = .001$) at 7 years. This is similar to our reported survival benefit for UFT. In addition, continued divergence of the survival curves over time is similar to those commonly seen in breast cancer adjuvant trials.⁴

The authors are correct that since our publication, further randomized controlled trials have been presented. The 2 largest and principal new studies presented at the 2004 meeting of the American Society of Clinical Oncology for platinum-based chemotherapy, however, reported substantial benefits associated with adjuvant chemotherapy.^{5,6} Combining the results of these trials with the previous randomized controlled trials evaluating platinum-based regimens has demonstrated a further overall benefit for platinum-based postoperative chemotherapy (relative risk, 0.86; 95% confidence interval, 0.80-0.93). Moreover, sensitivity analyses determined that even if there were unreported or future studies enrolling more than 2000 patients that showed a statistically significant 20% higher