



EVIDENCE WATCH

A review and assessment of recent clinical trial data

This issue of *Oncology Exchange* provides overviews of important clinical trial data presented at the 40th Annual Meeting of the American Society of Clinical Oncology (ASCO), held in New Orleans, LA, June 5–9, 2004. Leading Canadian experts offer commentary and clinical interpretations.

Lung cancer

RANDOMIZED CLINICAL TRIAL OF ADJUVANT CHEMOTHERAPY WITH PACLITAXEL AND CARBOPLATIN FOLLOWING RESECTION IN STAGE 1B NON-SMALL CELL LUNG CANCER (NSCLC): REPORT OF CANCER AND LEUKEMIA GROUP B (CALGB) PROTOCOL 9633.

Investigators: Strauss GM et al.

The Cancer and Leukemia Group B (CALGB) Protocol 9633 was a Phase 3, randomized, multicentre trial designed to test the value of adjuvant chemotherapy in resected Stage 1B non-small cell lung cancer (NSCLC). Three groups — CALGB, The Radiation Therapy Oncology group (RTOG) and the North Central Cancer and Leukemia Group (NCCTG) — enrolled 344 patients (mean age 61; 64% men) 4 weeks after surgery to remove Stage 1B NSCLC tumours. Patients were randomized to either observation alone or to chemotherapy with paclitaxel and carboplatin. The 12-week regimen consisted of paclitaxel 200 mg/m² over 3 hours and carboplatin AUC 6, both on day 1, every 3 weeks for 4 cycles.

At 4 years patients in the chemotherapy group had a relative reduction

in risk of dying from lung cancer of 49%, and of 38% for death from all causes, compared to those in the observation group. Survival at 4 years was 71% in the chemotherapy group vs 59% in the observation group (Table 1). The adjuvant chemotherapy was well tolerated, with no therapy-

related deaths. Eighty-five percent of patients received all 4 courses of chemotherapy. At a planned interim study analysis, the Data and Safety Monitoring Board recommended that the study be suspended, due to the positive impact of chemotherapy on survival.

TABLE 1. Outcomes in patients with resected Stage 1B NSCLC followed by chemotherapy vs observation

| Outcome | Postsurgical treatment, 12-week course | | |
|-------------------------------|--|-------------|--------------|
| | Carboplatin + paclitaxel | Observation | P-value |
| Risk of lung cancer mortality | 15% | 26% | not reported |
| 4-year overall survival | 71% | 59% | 0.028 |

A PROSPECTIVE RANDOMIZED TRIAL OF ADJUVANT VINOURELBINE (VIN) AND CISPLATIN (CIS) IN COMPLETELY RESECTED STAGE 1B AND II NON-SMALL CELL LUNG CANCER (NSCLC) INTERGROUP JBR.10.

Investigators: Winton TL et al.

This prospective, randomized, multicentre Phase 3 trial aimed to determine whether, following surgical removal of an early-stage non-small

cell lung cancer (NSCLC) tumour, adjuvant chemotherapy with vinorelbine and cisplatin was more effective in prolonging survival than observa-

tion alone (the current standard of care). After surgery, 482 patients (mean age 61; 65% men) with completely resected Stage 1–2 NSCLC

were randomized to receive followup observation (n = 243 patients) or 16 weeks of chemotherapy (n = 239 patients) consisting of 4 cycles of vinorelbine (25 mg/m² weekly) and cisplatin (50 mg/m² days 1 and 8) given every 28 days.

At five years, survival was 15% greater in the group receiving postoperative vinorelbine + cisplatin chemotherapy than in the observation group (Table 2). Patients receiving chemotherapy had a prolonged time to recurrence. The most common side effects of the combination chemotherapy were fatigue (77%), nausea (76%),

anorexia (53%), vomiting (46%), sensory neuropathy (45%) and constipation

(44%). Treatment-related death occurred in < 1% of patients.

TABLE 2. Outcomes in patients with resected early-stage NSCLC tumours followed by chemotherapy vs observation

| Outcome | Postsurgical treatment, 16-week course | | |
|-------------------------|--|------------------|---------|
| | Cisplatin + vinorelbine | Observation only | P-value |
| Median survival | 94 months | 73 months | 0.012 |
| Mean time to recurrence | not reached in 5 years | 46.7 months | 0.0002 |
| 5-year overall survival | 69% | 54% | 0.002 |

COMMENTARY: Scott Laurie MD, FRCPC, Medical Oncologist, Ottawa Regional Cancer Centre; Assistant Professor, University of Ottawa

The NSCLC Collaborative Group Meta-analysis, published in 1995, suggested a small benefit for cisplatin-based adjuvant chemotherapy following surgical resection, with an absolute increase in 5-year overall survival of 5% (P = 0.08).¹ This benefit was insufficient to bring about the adoption of adjuvant chemotherapy as standard practice. Many of the trials in the meta-analysis were small, and used older chemotherapy regimens. In the 1990s several new agents such as vinorelbine and the taxanes were found to have activity in NSCLC, leading to the development of so-called “third-generation” platinum-containing doublets which appeared more active against metastatic disease than older regimens. Large, definitive trials of adjuvant therapy using these newer agents were launched in the mid-1990s to elucidate the role of chemotherapy in this setting.

Results of several of these trials have been reported in the last few years. The Adjuvant Lung Project Italy (ALPI) study, which randomized 1209 patients with Stage 1–3 NSCLC to observation or 3 cycles of chemotherapy with mitomycin + vindesine + cisplatin, failed to demonstrate an improvement in survival with the addition of chemotherapy.² In contrast, the International Adjuvant Lung Cancer Trial (IALT) Collaborative Group, which randomized 1868 patients with resected Stage 1–3 NSCLC to either observation or cisplatin-based chemotherapy with either etoposide (the majority of patients) or a vinca alkaloid, detected a 4% improvement in 5-year overall survival with the addition of chemotherapy (P < 0.03).³

At the 2004 ASCO meeting, the 2 important trials summarized above added to the evidence in favour of adjuvant chemotherapy. Both showed large (12% and 15%) absolute survival benefits with adjuvant chemotherapy. Toxicity was acceptable, with a very low (< 1%) incidence of treatment-related deaths. Transient decreases in quality of life are expected with adjuvant chemotherapy, but mostly resolve following completion of treatment. Several possible explanations for the strikingly positive results of these 2 trials are:

- Cisplatin + vinorelbine and carboplatin + taxol are modestly superior to regimens such as cisplatin + etoposide and mitomycin + vindesine + cisplatin in the metastatic setting; perhaps this difference is magnified in the adjuvant setting.
- Although the doses of chemotherapy (particularly cisplatin) planned for administration were similar in all trials, fewer dose reductions or omissions occurred in the North American Intergroup trials, resulting in increased drug delivery to those patients.
- Postoperative radiotherapy, known to be detrimental in Stage 1 and 2 NSCLC, was not administered in the NCIC and CALGB trials, but was common in the ALPI and IALT trials, possibly obscuring some of the benefit of chemotherapy.
- The benefit of adjuvant therapy could be greater in Stage 1 or 2 disease when the likelihood of chemoresistant, micrometastatic clones is lower, as opposed to Stage 3.

ONGOING ISSUES

Several questions regarding the role of systemic therapy in resectable NSCLC remain unanswered. What is the optimal number of cycles of therapy? Can some of the chemotherapy be delivered preoperatively, when patients tolerate chemotherapy better? Randomized trials comparing solely postoperative vs pre- and postoperative chemotherapy should be performed. What about patients who cannot tolerate platinum-based doublet therapy? Many patients with NSCLC are older, with multiple comorbid illnesses. A study of adjuvant single-agent vinorelbine compared to surgical resection alone has been performed, and the results of this are eagerly awaited. Finally, the role of targeted therapies will also need to be evaluated; a randomized North American Intergroup trial, led by the National Cancer Institute of Canada (NCIC), of adjuvant therapy with gefitinib (Iressa™) vs placebo is ongoing. A large, individual patient meta-analysis of these more recent adjuvant therapy trials is planned, and will help to define

LANDMARKS

the true magnitude of benefit conferred by postoperative chemotherapy.

IMPLICATIONS FOR PRACTICE

These 2 studies are remarkably similar and sufficiently striking to spark a change in the standard of care for patients with early-stage, resected NSCLC. Following surgery, an assessment of suitability for adjuvant chemotherapy should be made within 6 to 8 weeks of resection. A note of caution, however: all of these trials enrolled fit patients with median age in the early 60s, performance status mostly 0 or 1, normal end-organ function and no contraindication for platinum-based chemotherapy. Only patients who fulfill these criteria should receive this therapy, and then only after a full and frank discussion of the adverse events and

risks including the small, but real, risk of chemotherapy-related death. Nonetheless, for patients with early-stage, resected NSCLC, adjuvant platinum-based chemotherapy represents a significant step forward towards improving the possibility of cure for the number-one cause of cancer death.

References:

1. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995;311:899-909.
2. Scagliotti GV, Fossati R, Torri V et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003;95:1453-61.
3. Le Chevalier T for the IALT Investigators. Results of the Randomized International Adjuvant Lung Cancer Trial (IALT): cisplatin-based chemotherapy (CT) vs no CT in 1867 patients (pts) with resected non-small cell lung cancer (NSCLC) *Proc Am Soc Clin Oncol* 2003;22:2 (abstract 6).

Breast cancer

GLOBAL PHASE III STUDY OF GEMCITABINE PLUS PACLITAXEL (GT) VS PACLITAXEL (T) AS FRONT-LINE THERAPY FOR METASTATIC BREAST CANCER (MBC): FIRST REPORT OF OVERALL SURVIVAL.

Investigators: Albain KS et al.

In this international Phase 3 trial, 529 patients with unresectable, locally recurrent or metastatic breast cancer previously treated with anthracyclines were randomized to receive frontline therapy with either gemcitabine + paclitaxel or paclitaxel alone. Treatment was administered on a 21-day cycle with patients in the gemcitabine + paclitaxel group receiving a median of 6 cycles and those in the paclitaxel-only group, 5 cycles. As reported at last year's ASCO meeting, preliminary results showed that the gemcitabine + paclitaxel regimen resulted in significantly longer time to cancer progression and a higher overall response rate. This year's presentation on survival

outcomes reported that at mean followup of 15.6 months, gemcitabine + paclitaxel provided significant overall survival advantage over paclitaxel alone (Table 3). Median time to can-

cer progression was 5.2 months vs 2.9 months and overall response rate was 41% vs 22%, respectively, in favour of gemcitabine + paclitaxel. The combination regimen was well tolerated.

TABLE 3. Outcomes in patients with metastatic breast cancer previously treated with anthracyclines

| Outcome | Treatment, 21-day course | | |
|-------------------------|--------------------------|------------------|---------|
| | Gemcitabine + paclitaxel | Paclitaxel alone | P-value |
| Median overall survival | 18.5 months | 15.8 months | 0.018 |
| 1-year survival | 70.7% | 60.9% | 0.019 |

COMMENTARY: Kathleen I. Pritchard, MD, FRCPC, Head, Clinical Trials & Epidemiology, Toronto Sunnybrook Regional Cancer Centre; Professor, Departments of Medicine and Public Health Sciences, Faculty of Medicine, University of Toronto

The interesting ASCO presentation by Dr. Kathy Albain provides food for thought concerning our approach to the treatment of women with metastatic breast cancer. This is the second major trial in the last few years to show a significant disease-free and overall survival advantage for the use of a doublet of drugs, as opposed to an extremely active single agent alone in the treatment of metastatic breast cancer. The prior trial of Dr. Joyce O'Shaughnessy showed better

progression-free and overall survival with the combination of capecitabine and docetaxel compared to docetaxel alone.¹ In both studies, however, patients receiving the doublet had considerably increased toxicity, experienced more treatment delays and dose reductions, and suffered more serious side effects such as febrile neutropenia.

Continued on page 40


LANDMARKS

continued from page 18

It is useful for Canadian oncologists to consider whether they wish to increase the median time to cancer progression from 2.9 to of 5.2 months and improve the response rate from 22% to 41% at the cost of increased toxicity and consequent decrease in quality of life. The same question was asked following publication of Dr. O'Shaughnessy's results¹ and most Canadian oncologists answered with a resounding "no." It seems that, at least in the Canadian environment, treatment with sequential single agents remains favoured in order to provide maximum disease control with minimum toxicity and optimum quality of life.

Dr. Albain's trial, like that of Dr. O'Shaughnessy, shows that the second non-taxane drug used in the doublet may be a more interesting contender than we had previously believed. Until Dr. O'Shaughnessy's results were published, no major Phase 3 randomized trials compared capecitabine to any other major single-agent chemotherapy for breast cancer (i.e. an anthracycline or a taxane), and it remained a marginal player. The demonstration of superior disease-free and overall survival of the docetaxel + capecitabine doublet over docetaxel alone provided data suggesting that capecitabine may be a more active drug in breast cancer than many of us had previously suspected. Similarly, gemcitabine is now catching our attention: if it is sufficiently active to provide improved disease-free and overall survival in this setting, perhaps it would be more useful as a single agent in metastatic disease and/or more of a candidate for

use in adjuvant therapy than had been previously thought.

Although full publication of Dr. Albain's results are pending, many of us will be considering gemcitabine more frequently as third- and fourth-line therapy for patients with metastatic disease, and as a major drug in the clinical trials setting. For example, a proposed National Surgical Adjuvant Breast and Bowel Project (NSABP) study will soon examine the doublet of gemcitabine and docetaxel in the adjuvant setting, and we will await these results with great interest. 

Reference:

1. O'Shaughnessy J, Miles D, Vukelja S et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;20:2812-23.

PROTOCOLS & PRACTICES

Perrin & Bernstein, continued from page 31

17. Souhami L, Scott C, Brachman D et al. Randomized prospective comparison of stereotactic radiosurgery (SRS) followed by conventional radiotherapy (RT) with BCNU to RT with BCNU alone for selected patients with supratentorial glioblastoma multiforme (GBM): Report of RTOG 93-05 protocol (abstract). *Int J Radiat Oncol Biol Phys* 2002;54:94-95.
18. Prados MD, Scott C, Sandler H et al. A phase 3 randomized study of radiotherapy plus procarbazine, CCNU, and vincristine (PCV) with or without BUdR for the treatment of anaplastic astrocytoma: a preliminary report of RTOG 9404. *Int J Radiat Oncol Biol Phys* 1999;45: 1109-15.
19. Capala J, Stenstrom BH, Skold K et al. Boron neutron capture therapy for glioblastoma multiforme: clinical studies in Sweden. *J Neurooncol* 2003;62:135-44.
20. Laperriere N, Perry J, Zuraw L et al. Radiotherapy for Newly Diagnosed Malignant Glioma in Adults Practice Guideline Report #9-3. Program in evidence-based care: Neuro-Oncology Cancer Disease Site Group Report: January 2004. Available at www.cancercare.on.ca/pdf/pebc9-3f.pdf
21. Bampoe J, Bernstein M. Advances in radiotherapy of brain tumors: radiobiology versus reality. *J Clin Neurosci* 1998;5:5-14.
22. Fine HA, Dear KB, Loeffler JS et al. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993;71:2585-97.
23. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002;359:1011-18.
24. Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. *J Clin Oncol* 2001; 19:509-18.
25. Friedman HS, McLendon RE, Kerby T et al. DNA mismatch repair and O⁶-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. *J Clin Oncol* 1998; 16:3851-57.
26. Chibbaro S, Benvenuti L, Caprio A et al. Temozolomide as first-line agent in treating high-grade gliomas: phase II study. *J Neurooncol* 2004;67:77-81.
27. Hirose Y, Berger MS, Pieper RO. p53 effects both the duration of G₂/M arrest and the fate of temozolomide-treated human glioblastoma cells. *Cancer Res* 2001;61:1957-63.
28. Stupp R, Mason WP, Van den Bent MJ et al. Concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM). Conclusive results of a randomized phase III trial by the EORTC Brain & RT Groups and NCIC Clinical Trials Group. Proceedings of the 40th Annual Meeting of the American Society of Clinical Oncology, 2004.
29. Cairncross JG, Macdonald DR. Successful chemotherapy for recurrent malignant oligodendroglioma. *Ann Neurol* 1988;23:360-64.
30. Cairncross JG, Ueki K, Zlatescu MC et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst* 1998; 90:1473-79.

