Updated survival analysis of JBR.10: A randomized phase III trial of vinorelbine/cisplatin versus observation in completely resected stage IB and II non-small cell lung cancer (NSCLC)


Presenter’s Affiliation: London Regional Cancer Program, London, ON, Canada

Type of Session: Scientific

Background
- Non-small cell lung cancer (NSCLC) is the current leading cause of cancer mortality in both men and women.
- Patients are at substantial risk for recurrence even following complete surgical resection. Half of stage 1B and nearly two-thirds of stage II patients will eventually relapse.
- Adjuvant chemotherapy for early-stage NSCLC has been a focus of effort to attempt to reduce the risk of recurrence following resection since most failures occur distantly following resection with curative intent.
- Trials conducted in the 1970s and 1980s did not provide consistent evidence of benefit, although a meta-analysis published in 1995 rekindled interest after subset analysis demonstrated that cisplatin-based chemotherapeutic regimens conferred a survival benefit, although the result was not statistically significant. Interestingly, patients randomized to non-cisplatin based regimens had a higher risk of death (15%) than those not receiving adjuvant chemotherapy.
- Multiple large trials have been subsequently performed to assess for a potential survival benefit for early-stage NSCLCs treated with cisplatin-based chemotherapeutic regimens. These include the: Adjuvant Lung Cancer Project Italy (LPI), Adjuvant Navelbine International Trialist Association (ANITA), International Adjuvant Lung Trial (IALT), the Big Lung Trial (BLT) and JBR.10, the latter of which was a phase III trial that established adjuvant cisplatin-based chemotherapy as a recommended treatment in early-stage completely resected NSCLC.
- The most extensive follow-up data prior to this JBR.10 update came from the International Adjuvant Lung Cancer Trial (IALT), in which 1,867 patients with resected stage I, II, or III NSCLC were randomly assigned to cisplatin-based chemotherapy or to observation. Updated results presented at ASCO 2008 (LeChavalier, abstract #7507) demonstrated a beneficial effect of adjuvant chemotherapy on overall survival (HR: 0.91; 95% CI: 0.81-1.02, p = 0.10) and on disease-free survival (HR: 0.88; 95% CI: 0.78-0.98, p = 0.02). However, there was a significant difference between the results of overall survival before and after 5 years (HR: 0.86; CI: 0.76-0.97, p = 0.01 versus HR: 1.45; CI: 1.02-2.07, p = 0.04). The difference in results between fewer than and more than 5 years of follow-up suggested the need for longer follow-up on other large adjuvant trials.
- This report describes the updated survival data for JBR.10 with more than 9 years of median follow up.

Materials and Methods
- This study is a multicenter, randomized controlled trial with a data cut-off for this update of July 2008. A total of 532 patients were registered and 482 were randomized into observation (n = 240) or chemotherapy (n = 242).
- Eligible patients included those with completely resected stage IB (T2N0) or II (T1 - 2N1) NSCLC who were randomized to receive 4 cycles of vinorelbine/cisplatin or observation within 6 weeks of surgery.
- Baseline characteristics were well balanced with respect to age (median age 61 in both groups), sex, ECOG performance status, histological subtype (53% adenocarcinomas in both arms), ras status, and stage.
- The primary endpoint was overall survival (OS), and secondary end points included relapse-free survival (RFS), toxicity and quality of life (QOL).
Results

- Kaplan-Meier curves were generated for OS and DFS.
- A log-rank test was used to compare survival distribution and to test cause specific hazard.
- For the competing risk analysis, the Gray test was used to test the difference in cause specific incidences.
- All efficacy analyses were done on an intention-to-treat (ITT) basis.

**Median follow-up in this update is 9.3 years (range 3.2 - 13.8 years).**

- 12 patients were lost to follow up, a median of 4.9 years following randomization (range: 1.5 - 12 years).
- Overall, 271 total deaths occurred, 73% due to lung cancer or its treatment. 143 patients died in the observation arm (105 from their lung cancer) and 128 in the chemotherapy arm (88 from their cancer). Two patients died as a result of their chemotherapy.
- Examination of secondary malignancies in both groups demonstrated fewer cancers in the chemotherapy arm. There were a total of 9 secondary malignancies in the observation arm and 6 in the chemotherapy arm. 8.8% of patients in the observation arm and 7.9% of patients in the chemotherapy arm developed new cancers thought unrelated to their primary. There were 4 head and neck cancers in the observation group (0 in the treatment group) and 3 new non-small cell lung cancers (0 in the treatment group).
- In the updated results, the survival analysis continues to show a benefit for chemotherapy: HR 0.78 (CI 0.61 - 0.99, p = 0.04). Kaplan-Meier curves separate at 2 years and remain separate over time.
- The benefit appears to be confined to N1 patients when looking at updated survival by stage. In stage II disease, the median OS was 6.8 years in the chemotherapy arm versus 3.6 years in the observation arm, HR 0.68 (CI 0.5 - 0.92, p = 0.01).
- N0 patients did not appear to benefit: in IB patients, the median OS was 11.0 years in the chemotherapy arm versus 9.8 years in the observation arm, HR 1.03 (CI 0.7 - 1.52, p = 0.87). When IB patients were divided into patients with tumors less than or greater than 4 cm, patients with larger tumors were seen to derive benefit not seen in IB disease with primaries less than 4 cm, although this trend was not statistically significant (HR 0.66, p = 0.14).
- Overall, chemotherapy significantly prolonged DSS, HR 0.73 (CI 0.55 - 0.97, p = 0.03).
- Competing risk analysis showed observation to be associated with significantly higher risk of death from lung cancer (p = 0.02) with no difference in incidences of death from other causes between arms (p = 0.62).

**Author's Conclusions**

- Prolonged follow-up of patients in the JBR.10 trial continues to demonstrate a benefit in survival for patients receiving adjuvant chemotherapy.
- There is no appreciable difference in late toxicity, non-disease related deaths or rates of secondary malignancies (although the chemotherapy arm did have fewer second cancers).
- OS advantage at 5 years was 11% (p = 0.04), exceeding the marginal benefit of 5% in the British Medical Research meta-analysis and the 4.1% survival advantage seen in the IALT trial at 5 years (p < 0.03).
- This benefit appears to be confined to N1 patients, although IB patients with tumors greater than 4 cm demonstrate a trend (although not statistically significant) towards improved OS.
- The observed survival benefit persists in some patients for greater than 12 years consistent with cure.

**Clinical/Scientific Implications**

- The LPI, ANITA, IALT and BLT trials all included patients with stage IIIA disease in whom there is not an insignificant likelihood of occult extrathoracic disease and who are qualitatively different from stage I and II lung cancer patients with respect to performance status, overall disease burden, and tolerance of chemotherapy.
- The LACE meta-analysis, which pooled the 5 largest trials (ALPI, ANITA, BLT, IALT and JBR10) involving 4,584 patients demonstrated a benefit varying according to stage with HR of 1.40 for IA (95% CI 0.95 to 2.06); HR for stage IB 0.93, (95% CI 0.78 to 1.10), HR for stage II 0.83 (95% CI 0.73 to 0.95); and HR for stage III 0.83 (95% CI, 0.72 to 0.94). Based on these results, the benefit of adjuvant chemotherapy in IB patients was still unclear.
- The updated JBR.10 results help to clarify the benefit of chemotherapy in completely resected stage IB and II cancers and demonstrates a persistent benefit with the addition of chemotherapy for node positive patients.
- Adjuvant chemotherapy does not seem to increase the risks of late toxicities, including non-disease related deaths or...
rates of second cancers.

- Bottom line: cisplatin-based chemotherapy should be offered to all node positive patients in the adjuvant setting and should be considered for patients that are node negative but have tumors larger than 4 cm, a group in which further study is indicated.

See Patient Summary

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