

Adjuvant vinorelbine plus cisplatin extended survival longer than observation in resected non–small-cell lung cancer

Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non–small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol*. 2006;7:719-27.

Clinical impact ratings: Oncology ★★★★★☆ Pulmonology ★★★★★☆

QUESTION

In patients with completely resected stage IB to IIIa non–small-cell lung cancer (NSCLC), is adjuvant vinorelbine plus cisplatin better than observation?

METHODS

Design: Randomized controlled trial (Adjuvant Navelbine International Trialist Association [ANITA]).

Allocation: {Concealed}†.*

Blinding: Unblinded.*

Follow-up period: Median 76 months.

Setting: 101 centers in 14 countries.

Patients: 840 patients 18 to 75 years of age (median age 59 y, 86% men) who had stage I (T2N0 only), stage II, or stage IIIa NSCLC according to 1986 TNM classification; complete resection of the primary tumor; World Health Organization performance status ≤ 2 ; and adequate biological function. Exclusion criteria were concurrent malignant disease (except adequately treated nonmelanoma skin cancer or in situ cervical cancer) or other previous primary tumors.

Intervention: Chemotherapy ($n = 407$) or observation ($n = 433$). Chemotherapy consisted of vinorelbine, 30 mg/m² (Navelbine, Pierre Fabre Medicament Production, Pau, France), on days 1, 8, 15, and 22 (cycles repeated every 4 wk) for a maximum of 16 doses; and cisplatin, 100 mg/m² (Cisplatyl, Sanofi Paris, France), on days 1, 29, 57, and

85. Postoperative radiotherapy was implemented at the discretion of the individual center (dose ranging from 45 to 60 Gy, 2 Gy/fraction, 5 fractions/wk) but was eventually recommended in patients with node-positive disease to start 2 weeks after chemotherapy or within 2 weeks after randomization in the observation group.

Outcomes: Overall survival. Secondary outcomes were disease-free survival and safety.

Patient follow-up: 100% (intention-to-treat analysis).

MAIN RESULTS

Median survival was longer in the chemotherapy group than in the observation group (66 vs 44 mo; hazard ratio [HR] 0.80, 95% CI 0.66 to 0.96, $P = 0.017$). The absolute overall survival benefit increased 2.8% (number needed to treat [NNT] 36) at 1 year, 4.7% (NNT 22) at 2 years, 8.6% (NNT 12) at 5 years, and 8.4% (NNT 12) at 7 years. Median disease-free survival was also longer in the chemotherapy group (36 vs 21 mo; HR 0.76, CI 0.64 to 0.91, $P = 0.002$). The

absolute disease-free survival benefit increased 9% (NNT 12) at 6 months, 9.5% (NNT 11) at 1 year, 9.6% (NNT 11) at 2 years, 8.7% (NNT 12) at 5 years, and 5.5% (NNT 19) at 7 years. 202 patients (50%) in the chemotherapy group completed the 4 cycles. Fewer patients in the chemotherapy group had lung relapse and bone metastasis (Table). The most frequent side effects of chemotherapy were neutropenia, anemia, and febrile neutropenia; other common side effects included asthenia, nausea or vomiting, anorexia, and infection.

CONCLUSION

In patients with completely resected stage IB to IIIa non–small-cell lung cancer, adjuvant vinorelbine plus cisplatin extended survival longer than did observation.

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*See Glossary.

†Information provided by author.

Adjuvant vinorelbine plus cisplatin vs observation in completely resected stage IB to IIIa non–small-cell lung cancer at median 76 months‡

Outcomes	Vinorelbine plus cisplatin	Observation	RRR (95% CI)	NNT (CI)
Lung relapse	22%	28%	21% (0.6 to 38)	17 (9 to 672)
Bone metastasis	3.7%	11%	65% (39 to 80)	15 (10 to 29)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

The study by Douillard and colleagues confirms the findings from a recent randomized trial (1) showing that adjuvant chemotherapy improves survival for completely resected NSCLC. This treatment should now be considered the standard of care.

However, this trial raises questions about which patients should receive adjuvant chemotherapy. The improvement in 5-year survival seemed to be limited to patients with stages II (52% vs 39%) and IIIa (42% vs 26%) NSCLC. These findings are supported by a meta-analysis of 5 trials of adjuvant chemotherapy involving 4584 patients that showed no significant survival improvement from adjuvant chemotherapy in patients with stage IB NSCLC (HR 0.93, CI 0.78 to 1.10) (2).

Recent research suggests that molecular markers may help in determining which patients benefit from adjuvant chemotherapy. An analysis of pathology specimens from a recent study suggests that the benefit from adjuvant chemotherapy is limited to patients whose tumors did not express excision repair cross-complementation group 1 protein (3). However, the finding requires validation.

In the study by Douillard and colleagues, the data concerning post-operative radiation therapy (PORT) are conflicting. Patients with N1 nodal disease randomized to chemotherapy had worse 5-year survival if they received PORT, but patients with N2 nodal disease had improved 5-year survival if they received PORT. However, the intervention of PORT was not randomized, and therefore these findings require confirmation and should not change current practice.

In summary, adjuvant chemotherapy should be offered to patients with completely resected stages II and IIIa NSCLC. The role of adjuvant chemotherapy in stage IB disease remains controversial.

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References

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