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The role of adjuvant chemotherapy in early-stage and locally advanced non–small cell lung cancer

ABSTRACT

Adjuvant chemotherapy benefits only a small proportion of patients in the setting of resected early-stage non–small cell lung cancer, and in unselected patients, any benefit is modest. Analysis of clinical trials of adjuvant chemotherapy revealed that differential expression of DNA repair proteins and a 15-gene expression profile affected outcomes with treatment. Biomarkers and gene expression profiles are now being studied in prospective clinical trials to gauge their value in selection of adjuvant therapy and individualization of therapy.

Despite surgery, 40% to 75% of patients with stage I to IIIA non–small cell lung cancer (NSCLC) will die within 5 years. After multiple trials showed no survival advantage to chemotherapy in the adjuvant setting for the treatment of locally advanced NSCLC, the first hint of benefit came in 1995 with the publication of a meta-analysis of 14 clinical trials, which showed a nonsignificant 5% improvement in 5-year survival with chemotherapy after surgery.[1]

A second meta-analysis, this one conducted by the Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group, demonstrated a hazard ratio (HR) of 0.89 (P = .005) on the end point of overall survival with the use of postoperative cisplatin-based chemotherapy in patients with NSCLC; this translates to a 5-year absolute improvement of 5.4% from chemotherapy.[2] The survival benefit was confined to patients with stage II and stage III disease.

Post hoc exploratory subgroup analyses of the Cancer and Leukemia Group B (CALGB) 9633[3] and Adjuvant Navelbine International Trialist Association (ANITA)[4] trials revealed a significant survival benefit to four cycles of cisplatin-based adjuvant chemotherapy in patients with stage Ib disease who had tumors 4 cm or larger.

BIOMARKERS

Prognostic and predictive biomarkers beyond cancer stage are needed, as only 10% to 15% of patients with resected NSCLC who receive chemotherapy derive a benefit. Predictive markers can be used to guide therapeutic decision-making, and prognostic markers permit estimation of patient outcome independent of treatment modality.

Excision repair cross-complementation group 1 (ERCC1) is a rate-limiting protein in the excision repair complex of nucleotide excision repair of damaged DNA.[5] Nucleotide excision repair removes platinum-DNA adducts from tumor DNA, thus repairing DNA damage caused by systemic chemotherapy. In NSCLC, patients with tumors expressing low levels of ERCC1 show worse nucleotide excision repair capability and a worse overall prognosis in the absence of treatment compared with patients with higher expression of ERCC1. ERCC1 positivity is therefore a favorable prognostic biomarker. In a major retrospective biomarker analysis of the International Adjuvant Lung Cancer Trial (IALT), patients with low levels of ERCC1 activity had statistically superior survival after adjuvant chemotherapy compared with observation after surgery, whereas patients with ERCC1-positive tumors who have intact nucleotide excision repair had no benefit from adjuvant chemotherapy compared with patients who have surgery alone **(Figure 1)**.[6]

As with ERCC1, expression of the DNA mismatch repair protein mutS homolog 2 (MSH2)[7] is both prognostic and predictive after surgery. In

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a separate biomarker analysis from the IALT study, approximately two-thirds of patients with NSCLC had MSH2-negative tumors by immunohistochemistry, indicating lack of expression of MSH2 in tumors. Patients with expression of MSH2, who have intact mismatch repair, had a better prognosis and benefitted less from systemic chemotherapy than those with an absence of MSH2 expression.[8]

Individually, ERCC1 and MSH2 have similar power in predicting benefit from adjuvant chemotherapy in NSCLC; the HR for death was similar in patients with low expression of either gene.[8] The two biomarkers combined, however, were more powerful than either alone in their ability to predict a survival advantage with chemotherapy.[8] In an evaluation of 658 patients with NSCLC for whom both biomarkers were available, patients who expressed low tumor levels of both ERCC1 and MSH2 had an HR for death that was 35% lower with adjuvant chemotherapy compared with surgery alone after median follow-up of 7.5 years; the presence of two positive biomarkers was associated with an increase in the HR for death by 32%. Validation of these findings in a phase 3 setting will be necessary before these biomarkers can be used in the clinical setting.

The Southwest Oncology Group (SWOG) is conducting a trial (SWOG 0720) in patients with stage I NSCLC to determine whether a subset based on ERCC1 and ribonucleotide reductase M1 (RRM1) status will derive benefit from adjuvant therapy with gemcitabine together with cisplatin. Ribonucleotide reductase subunit 1 is the regulatory subunit of ribonuclease reductase, which is an enzyme that catalyzes the deoxynucleotide production required for DNA repair.

Two other clinical trials, under way but not completed, testing various forms of chemotherapy and targeted therapy based on *ERCC1* and epidermal growth factor receptor (*EGFR*) mutation status are the Tailored Post-Surgical Therapy in Early Stage NSCLC (TASTE) and the International Tailored Chemotherapy Adjuvant (ITACA) trials. The TASTE trial is comparing standard chemotherapy (cisplatin plus pemetrexed) with customized adjuvant treatment based on EGFR and ERCC1 status in patients with stage II or IIIa nonsquamous NSCLC. The ITACA trial is a phase 3 study of pemetrexed, cisplatin, and radiotherapy determined by thymidylate synthase (TS) and ERCC1 gene expression levels in patients with stage II to III completely resected NSCLC. TS is an enzyme responsible for maintaining intracellular levels of thymidine, important for DNA synthesis and repair, and may serve as a predictor of response to pemetrexed.

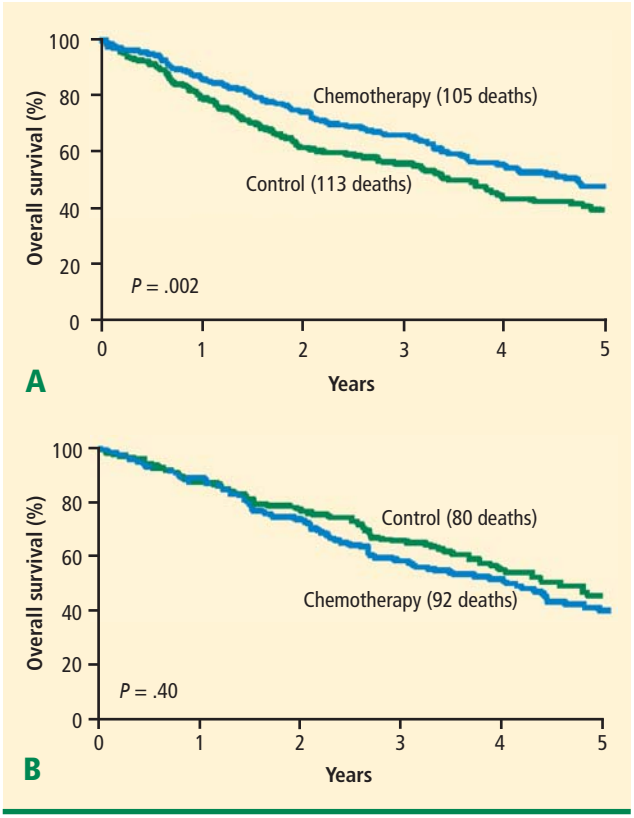

FIGURE 1. In the International Adjuvant Lung Cancer Trial, the hazard ratio (HR) for overall survival in patients with excision repair cross-complementation group 1 (ERCC1)–negative tumors who were assigned to chemotherapy was 0.65 **(A)** compared with controls, whereas the adjusted HR for survival with chemotherapy in patients with ERCC1-positive tumors was 1.14 **(B)**.

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GENE EXPRESSION PROFILING

Gene expression profiles, already used to predict benefit from chemotherapy in early-stage breast cancer, may inform treatment decisions in lung cancer as well. A15-gene signature that could predict risk of recurrence and death after surgery alone for stage Ib or II NSCLC was identified using fresh frozen tissue of patients from the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) JBR.10 trial of vinorelbine/cisplatin.[9] The risk profile was subsequently validated with reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) in the same cases and in four independent sets of patients.[9]

This 15-gene expression profile was unique in that it could also predict response to systemic chemotherapy, whereas most other gene profiles have served

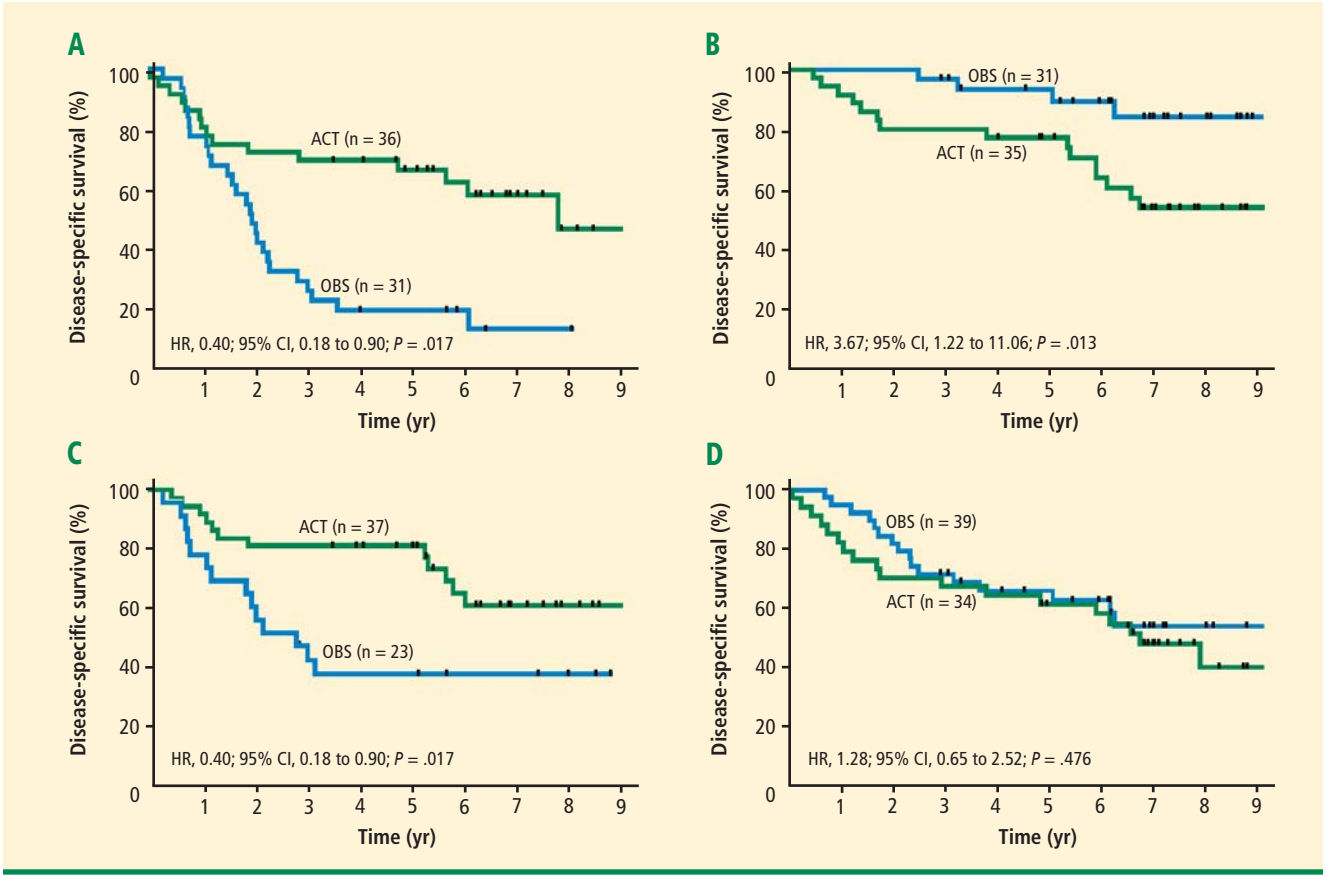

FIGURE 2. The predictive effect of a 15-gene profile with adjuvant chemotherapy in the JBR.10 trial. Only high-risk groups by microarray or reverse transcriptase-quantitative polymerase chain reaction benefited from adjuvant chemotherapy (panels **A** and **C**). ACT = adjuvant cisplatin-based chemotherapy; OBS = observation

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only as prognostic markers following surgery. Adjuvant chemotherapy significantly reduced the risk of death among patients identified as high risk using the 15-gene signature, with an HR of 0.40 in those deemed high risk by RT-qPCR and 0.33 by microarray technique, compared with observation **(Figure 2)**. This benefit with chemotherapy was absent among the low-risk individuals.[9]

Among those patients with stage Ib disease, the gene expression profile was both prognostic (HR of 13.22 for disease-specific survival in the high- vs low-risk population) and predictive (HR of 0.44 for the use of adjuvant chemotherapy in the high-risk patients but no survival benefit observed with chemotherapy in low-risk patients).[9]

USE OF BIOMARKERS TO SELECT TREATMENT

As alluded to earlier, the use of biomarker expression to guide treatment selection is an area of intense investigation. In the metastatic setting, therapy targeted to the *EGFR* mutation has proven to be remarkably beneficial in patients with *EGFR*-activating mutations. In the adjuvant setting, the NCIC CTG BR.19 trial enrolled an unselected population of patients with completely resected stage Ib to IIIa NSCLC; the patients were randomized to 2 years of treatment with the tyrosine kinase inhibitor gefitinib, which targets EGFR, or placebo. Tissue samples from trial participants were collected and revealed *KRAS* mutation in 27%, a high *EGFR* gene copy number by fluorescence in situ hybridization (FISH) in 41%, and an activating *EGFR* mutation in 21%.

The NCIC CTG BR.19 trial was greatly underpowered because enrollment was stopped at 503 patients when, in 2008, the SWOG 0023 investigators reported a worse overall median survival with maintenance gefitinib after definitive chemoradiation in patients with stage III NSCLC.[10] As a result of the early termination of patient accrual, the median duration of adjuvant gefitinib in NCIC CTG BR.19 was

less than 5 months. Further, only 20% were exposed to chemotherapy and only 21% of the final study population had an *EGFR* mutation. In the overall study population, the HR for overall survival among gefitinib recipients was 1.23, indicating harm, and there was a trend in favor of placebo on the end point of disease-free survival. Neither *KRAS* nor *EGFR* copy number was predictive or prognostic, and *EGFR* mutation status was not prognostic.[11] Patients with wild-type *EGFR* had a trend toward detriment with maintenance gefitinib that was similar to that of the overall population, and those with *EGFR* mutation experienced no benefit with maintenance gefitinib.

In the Randomized Double-Blind Trial in Adjuvant NSCLC with Tarceva (RADIANT), patients with resected stage I to IIIa NSCLC, with the option for postoperative chemotherapy, were assessed for EGFR expression by immunohistochemistry or FISH and then randomized to erlotinib or placebo for 2 years. The trial completed accrual in 2010 and results are expected in 4 to 5 years.

Cleveland Clinic is currently accruing patients for a phase 2 trial of patients with resected stage I to IIIa NSCLC. All patients will have their tumors screened for activating *EGFR* mutations; those with activating mutations will receive adjuvant erlotinib for 2 years . starting within 6 months of surgery.

SUMMARY

Although adjuvant chemotherapy has been well established for patients with early-stage NSCLC, stage alone is not an ideal biomarker to predict the utility of chemotherapy, as the vast majority of patients derive no benefit from chemotherapy.

Biomarkers have been poorly validated and therefore are inappropriate for clinical use at this time. Validation of gene arrays has been disappointingly slow in lung cancer because of the absence of large tumor banks that are available in breast cancer and colon cancer.

It remains unclear whether targeted therapies improve outcomes over traditional chemotherapy in the adjuvant setting in NSCLC, as tumors in the metastatic and adjuvant settings are not the same.

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