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The Forum for Early Diagnosis and Treatment of Lung Cancer

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The purpose of ***Lung Cancer Frontiers*** is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.

Gene Therapy for Malignant Pleural Mesothelioma

By Edmund K. Moon, MD and Steven M. Albelda, MD

Malignant mesothelioma originates from the mesothelial surface of the pleural and peritoneal cavities, the tunica vaginalis, and pericardium. Malignant pleural mesothelioma (MPM) accounts for 80% of mesothelioma cases and usually presents in the fifth to seventh decade of life with dyspnea, pleural effusion, and non-pleuritic chest pain in the context of a history of asbestos exposure.[1,2] With a disease course affected only minimally by current treatments,[1,3] MPM has a poor prognosis (6-18 months median survival) unless it can be completely resected (a rare occurrence). This article will focus on novel gene therapy approaches for MPM that have the potential to improve outcomes for this devastating disease.

MPM as a target for gene therapy

Malignant pleural mesothelioma is potentially a good disease target for gene therapy because the thin layer of mesothelial and malignant cells offers a large surface area for efficient, rapid, and diffuse gene transfer, and the pleural space is easily accessible and amenable to biopsy, delivery of study vector/gene, and fluid sampling to confirm successful gene transfer. Pleural cavity access has been enhanced by the availability of an indwelling, tunneled pleural catheter system.[4] Accordingly, our group, and others, have used a variety of gene therapy approaches (***Table 1***) in an attempt to improve MPM treatment.

Suicide gene therapy

One of the first gene therapy approaches for mesothelioma was the use of "suicide gene therapy." Tumor cells were transduced with a cDNA encoding the herpes simplex virus-1 thymidine kinase (HSV*tk*) gene, which made transduced cells sensitive to the normally non-toxic nucleoside analog gancyclovir (GCV).[5] HSV*tk's* effect in the presence of GCV is enhanced by a "bystander effect" resulting from the passage of toxic GCV metabolites from transduced to non-transduced cells through gap junctions and/or apoptotic vesicles,

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Table 1. Gene Therapy Approaches for Malignant Pleural Disease

Approach	Examples
Suicide gene therapy	Herpes simplex thymidine kinase gene plus ganciclovir Cytosine deaminase gene plus 5-fluorocytosine
Cytokine gene therapy	Interleukin-2, interleukin-12, Type 1 and Type 2 interferons GM-CSF
Gene modified T-cells	Modified T-cells with tumor antigen-specific chimeric T-cell receptors
Non-specific induction of innate and acquired immunity	Liposome/DNA complexes, anti-CD40 ligand Mycobacterial heat shock protein gene (HSP-65)
Tumor-selective replicating viruses	Herpes virus, vaccinia virus, adenovirus, measles virus
Induction of apoptosis	p53, $p16^{INK4A}$, p14(ARF), Bak, anti-sense SV40-T antigen REIC/Dkk-3
Anti-angiogenesis	Soluble form of the VEGF receptor (Flt-1) Anti-angiogenic pigment epithelium-derived factor

causing the death of non-transduced "bystander" cells. Additional bystander effects are caused by an anti-tumor immune response induced by cell death and accompanied by endogenous "danger signals" (such as heat shock proteins and protein high mobility group box 1 protein) and tumor-associated antigen release that activates both the adaptive and innate immune systems.[6,7]

One can also take advantage of the bystander effect seen in HSV*tk*/GCV therapy by using other cell types as vectors, instead of viruses. For example, a Phase 1 trial using irradiated ovarian carcinoma cells (vector cells) transfected ex-vivo with HSV*tk* (PA1-STK cells) injected into the pleural space of patients with MPM was conducted by Schwarzenberger et al. with the aim to not only kill the transduced "vector cells", but also the neighboring MPM cells via the bystander effect subsequent to GCV administration.[8] Minimal side effects were seen and ^{99}Tc-radiolabeled PA1-STK cells demonstrated preferential adhesion to tumor lining the chest wall. There

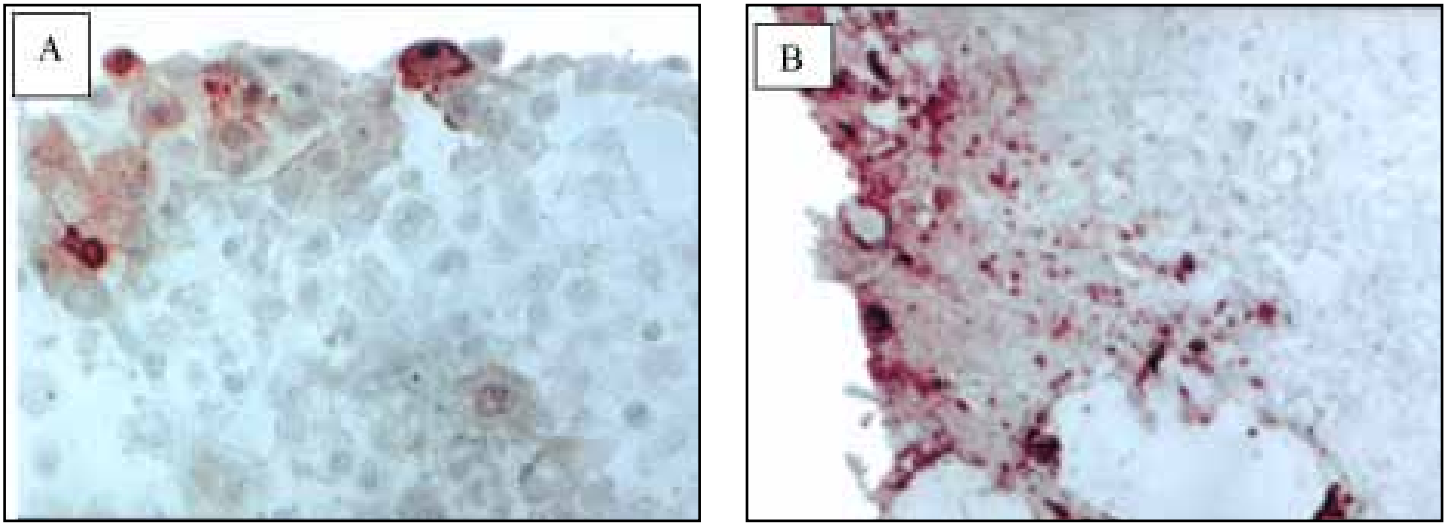

Figure 1. HSV*tk* protein expression determined by immunohistochemistry in pleural biopsies from a patient with MPM 72 hours after instillation of Ad.HSV*tk*. Red staining represents HSV*tk* expression. While pre-treatment samples showed no staining, nuclear and cytoplasmic staining is seen on the tumor surface (Panel A, 40x) and in deeper tumor layers (Panel B, 20x).

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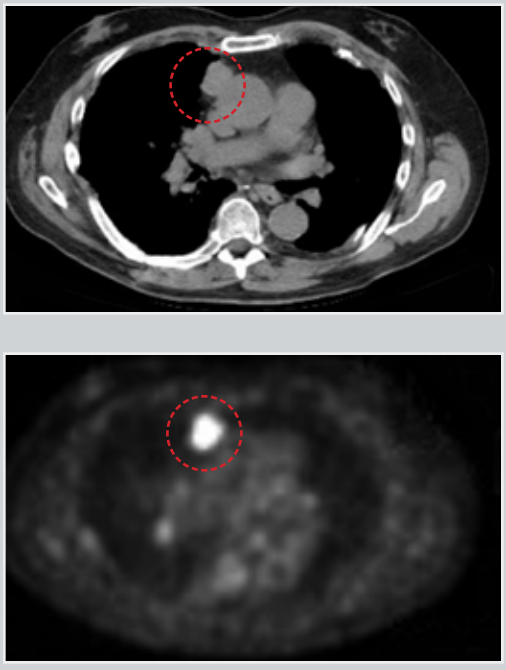
were also some post-treatment increases in the percentage of CD8+ T-lymphocytes in the pleural fluid. However, no significant clinical responses were seen.[8-10]

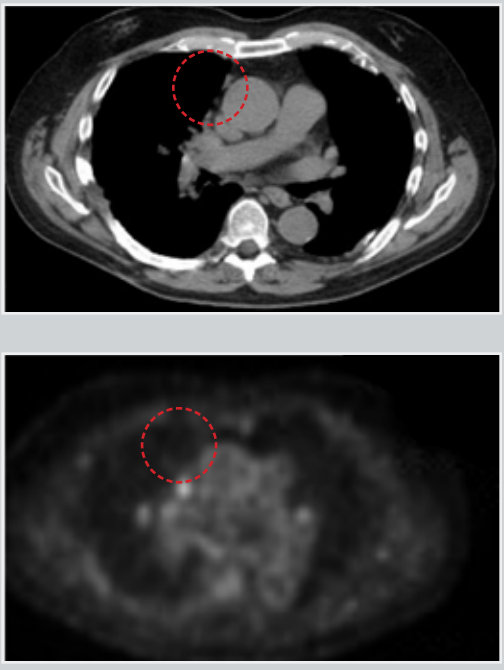
Based on pre-clinical murine model data, Sterman and colleagues initiated a series of Phase 1 clinical trials of replication-incompetent adenovirus expressing HSV*tk* (Ad. HSV*tk*/GCV) in patients with advanced MPM. After a single administration of intrapleural Ad.HSV*tk* vector, GCV was given intraveneously twice daily for two weeks.[11,12] Dose-related intratumoral HSV*tk* gene transfer was demonstrated by immunohistochemistry in all patients above a threshold dose of ≥ 3.2 x 10^{11} particle forming units, although expression was rather superficial (***Figure 1***). Overall, the therapy was well tolerated with minimal side effects and dose-limiting toxicity was not reached. Anti-tumor antibodies and anti-adenoviral immune responses, including high titers of anti-adenoviral neutralizing antibody (AANAb), were generated in both serum and pleural fluid. No one in the trial had baseline AANAb, and because AANAb formation happens after the therapy is given and gene transfer occurs, it is unlikely that there was any effect on anti-tumor activity. These immune responses did not seem to be affected by the administration of intravenous corticosteroids at the time of vector instillation.[13] A number of clinical responses (including survival of more than 3 years) were seen at the higher dose levels,[14] including two patients with stage I epithelioid MPM who survived for long periods (7 and 9 years). Because regression occurred over several months, the effect could not be entirely explained by the initial toxic effects on transfected cells. It was thought that the effect was primarily due to the induction of the immune bystander effect by Ad.HSV*tk*/GCV. This suggested that primary induction of an anti-tumor immune response through use of cytokines might be useful.

Figure 2. Regression of mediastinal tumor in a patient with MPM before and after treatment with intrapleural Ad.IFN-α as measured by PET/CT

Before Ad.IFN-α



6 months after Ad.IFN-α



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Cytokine gene therapy

Several Phase 1 and Phase 2 clinical trials have been published documenting anti-tumor responses in MPM after intrapleural infusion of interleukin-2 (IL-2), interferon-β (IFN-β), and interferon-γ (IFN-γ) proteins.[15-20] Although intriguing responses have been noted, these approaches have been limited by toxicity and the need for repeated intrapleural administration of the soluble agent to maintain efficacy.

In Australia, Robinson and colleagues conducted the first clinical trial of intratumoral cytokine gene delivery in MPM patients using a recombinant, partially replication-restricted vaccinia virus (VV) that expressed the human IL-2 gene. Serial VV-IL-2 vector injections over a period of 12 weeks into chest wall lesions of six patients with advanced MPM resulted in minimal toxicity with no demonstrable evidence of vector spread to patient contacts. Though no significant regression of tumor was seen, modest intratumoral T-cell infiltration was detected on post-treatment biopsy specimens.[21]

Based on pre-clinical data by Odaka and colleagues,[22,23] a Phase 1 clinical trial using a non-replicating adenovirus to express IFN-β (Ad.IFN-β) was conducted in MPM (seven patients) and metastatic pleural malignancies (three patients) at the University of Pennsylvania.[24,25] Gene transfer was detected in seven of the 10 patients as assessed by measurement of pleural fluid IFN-β mRNA or protein. Anti-tumor immune responses, including humoral responses to known tumor antigens (e.g., SV40 Virus Tag, mesothelin) and unknown tumor antigens, were elicited in seven of 10 patients. Four patients demonstrated meaningful clinical responses, defined as disease stability and/or regression on ^{18}FDG-PET and CT imaging 60 days after vector administration. Two patients are still alive, surviving for longer than three years after intrapleural Ad.IFN-β gene therapy.

Based on pre-clinical studies showing enhanced effects after two doses of vector, a second Phase 1 trial involving two intrapleural administrations of Ad.IFN-β separated by one to two weeks was conducted in 17 patients (10 with MPM and seven with malignant pleural effusions.) Again, overall treatment was well tolerated and anti-tumor humoral immune responses similar to those seen in the initial trials were induced. Several patients had meaningful clinical responses (mixed and/or partial responses) as determined by pre- and post-vector delivery PET/CT scans. However, high AANAb titers were detected after either a one or two week period, inhibiting effective gene transfer of the second dose.

Subsequently, a third Phase 1 trial of Ad.IFN (using IFN-α instead of IFN-β, solely as a result of changes in corporate sponsorship) for patients with progressive MPM was recently conducted with a modified protocol with the hope of enhancing second dose gene transfer. Thus, two Ad.IFN-α vector doses were administered three days apart and patients were screened for the presence of AANAb. Interestingly, a number of patients had AANAb titers of greater than 1:1000 at baseline, likely from prior adenovirus exposure (e.g., upper respiratory tract infections), and they were excluded from the study. The first cohort of three patients received two doses of 1×10^{12} vp (viral particles) intrapleurally. However, because of higher than expected gene transfer levels and side effects related to cytokine release, subsequent patients received two doses of 3×10^{11} vp. Patient safety and tolerability were again confirmed. Pre- vs. post-treatment peripheral blood mononuclear cell comparisons revealed natural killer cell activation and the generation of anti-tumor antibodies. For the first time, successful gene transfer from the second dose was demonstrated, likely due to the fact that neutralizing antibodies were not induced within a three day time frame. Approximately half the subjects had stable disease/mixed response by modified RECIST criteria[26,27] at 60 day follow up, and PET/CT imaging revealed promising clinical responses (***Figure 2***).

Gene modified T-cells

One especially promising new area in gene therapy is the use of lentiviral or retroviral vectors to transduce T-cells with modified T-cell receptors engineered to attack specific tumor antigens.[28] This approach has shown success in patients with melanoma[29-31] and our group and others have strong pre-clinical data to support using T-cells targeted to attack mesothelin-expressing tumor.[32,33] A clinical trial with mesothelin-targeted T-cells is planned at the University of Pennsylvania within the next year.

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The future of gene therapy for MPM

Gene therapy for the treatment of MPM holds great promise, but it is in its infancy. Like any other cancer treatment strategy, its anti-tumor effects must be maximized while minimizing toxicity.

Currently, most of the efforts in MPM gene therapy are focused on immunogene therapy – delivery of inflammatory cytokines or gene-modified T-cells. Immunotherapies tend to work best in patients with smaller tumor burdens. However, like most new therapies, immunogene therapies will first be evaluated for safety in patients with refractory disease, despite this being a less than ideal population for assessment of tumor response. Once safety is established, however, the approaches can be tried in patients with earlier-stage disease and in combination with standard-of-care therapies. Any new approach will need to be integrated with current care. This is the strategy we have taken in studies using Ad.IFN therapy. Safety, with some efficacy data, was established in heavily pre-treated patients, many with large amounts of tumor. With this data in hand, we can now take advantage of pre-clinical studies showing synergy between Ad.IFN and systemic chemotherapy,[34] and we have begun to administer the Ad.IFN vector in combination with front-line chemotherapy (pemetrexed/cisplatin) or second line chemotherapy (gemcitabine/carboplatin) for MPM patients with earlier and smaller disease burdens. Additionally, in light of pre-clinical studies demonstrating a benefit of debulking surgery in combination with immunotherapy,[35] a neoadjuvant surgery trial involving vector administration to MPM patients followed by maximal cytoreduction and adjuvant chemo-radiotherapy is also planned. Thus, we will soon have trials available for surgical candidates, chemotherapy candidates, and patients with refractory disease. We hope to take the same approach with adoptive T-cell transfer.

At this point in time, gene therapy for mesothelioma remains experimental and restricted to a few referral centers. However, the practicing clinician can move this approach forward by discussing the option of participating in clinical trials with patients. The most important criteria for participation would be a good performance status and a willingness to participate in a clinical trial. Our group, and others, have developed financial resources to help support patient travel and expenses. As successes with early trials accumulate, larger randomized trials at multiple tertiary care centers around the country will be conducted, providing more options for participation. Ultimately, it is hoped that these therapies will be available for all patients.

Conclusion

Malignant pleural mesothelioma continues to be a deadly disease because of ineffective treatment options. Over the past two decades, however, novel gene therapy strategies that target tumor cells and augment the immune response against MPM have shown promise in both the pre-clinical and clinical arenas. Moving forward, a multi-modality approach incorporating surgery, chemoradiotherapy, and gene therapy has the potential to further enhance treatment options for this devastating disease.

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Steven M. Albelda, MD*, is the William Maul Measey Professor of Medicine, Associate Director of the Pulmonary Division, and Director of Lung Research at the University of Pennsylvania Medical Center. His research focuses on developing novel treatments for malignant mesothelioma, with special emphasis on gene and immunotherapy. A major area of recent interest is augmentation of anti-tumor immune effects using surgery, COX-2 inhibitors, antibodies against MCP-1, and chemotherapeutic drugs. His laboratory is also characterizing the importance of tumor-associated macrophages and neutrophils. His clinical interests are primarily in thoracic oncology.*

Disclosures

The authors have reported to *Lung Cancer Frontiers* that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Lung Cancer Meetings and Symposia

Thomas L. Petty Aspen Lung Conference
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July 3-7, 2011
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Selections from the Peer-Reviewed Literature

By Laurie L. Carr, MD

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Early palliative care for patients with metastatic non-small-cell lung cancer

Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ; Massachusetts General Hospital, Boston, MA. *N Engl J Med* 2010; 363:733-742

BACKGROUND: Patients with metastatic non-small-cell lung cancer have a substantial symptom burden and may receive aggressive care at the end of life. We examined the effect of introducing palliative care early after diagnosis on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease.

METHODS: We randomly assigned patients with newly diagnosed metastatic non-small-cell lung cancer to receive either early palliative care integrated with standard oncologic care or standard oncologic care alone. Quality of life and mood were assessed at baseline and at 12 weeks with the use of the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale and the Hospital Anxiety and Depression Scale, respectively. The primary outcome was the change in the quality of life at 12 weeks. Data on end-of-life care were collected from electronic medical records.

RESULTS: Of the 151 patients who underwent randomization, 27 died by 12 weeks and 107 (86% of the remaining patients) completed assessments. Patients assigned to early palliative care had a better quality of life than did patients assigned to standard care (mean score on the FACT-L scale [in which scores range from 0 to 136, with higher scores indicating better quality of life], 98.0 vs. 91.5; P=0.03). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs. 38%, P=0.01). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs. 54%, P=0.05), median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, P=0.02).

CONCLUSIONS: Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival. (Funded by an American Society of Clinical Oncology Career Development Award and philanthropic gifts; ClinicalTrials.gov number, NCT01038271.)

EDITORIAL COMMENT: This study is one of the first randomized trials of palliative care given concurrently with chemotherapy for advanced lung cancer patients. Palliative care is treatment given to relieve disease symptoms rather than to halt disease progression. This approach is different from hospice care, which focuses on symptom palliation at the end of life. Patients with newly diagnosed, advanced non-small-cell lung cancer (NSCLC) were randomized in a non-blinded fashion to either standard care or standard care with early referral to a palliative care program. The endpoints were improvement in quality of life (QOL) and mood at 12 weeks, the number of patients who received "aggressive care", and overall survival. Formal evaluation and clinic visits to a designated palliative care team, using a standardized evaluation protocol, were associated with improvements in mood, QOL, and overall survival. The median survival for those randomized to the early palliative care group was 11.6 months vs. 8.9 months

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for the control group. This improvement was statistically significant and comparable to survival increases reported in therapeutic trials that have led to changes in the standard of care for NSCLC.

It is not clear how palliative care visits improved survival, but there are several possibilities. Past studies have shown that improvements in QOL and mood can prolong survival, and this study is consistent with those findings. The authors also speculate that more time spent with palliative care support may stabilize symptoms after cancer treatment and prolong survival. Finally, there was no control for the extra amount of time that patients randomized to the treatment arm spent with clinicians (median of four extra visits). Perhaps spending extra time with medical providers without a palliative care focus would also produce similar improvements, and future studies should account for this variable. A comparison of the costs of caring for patients with advanced lung cancer with early palliative care vs. standard care would have made this trial even more compelling.

This study is important because it stresses the value of palliative care during ongoing oncologic therapy, such as chemotherapy. Treatment for cancer and palliation of the physical and emotional burden of a terminal disease are not mutually exclusive. Indeed, this study shows that patients live longer and better lives when palliative care and oncologic therapy are given together. Often, clinicians, patients, and family members mistakenly believe there must be a choice between palliative care and cancer therapy. This study provides valuable information for physicians and patients regarding palliative care, both during cancer therapy and at the end of life.

Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study

Crinò L, Dansin E, Garrido P, Griesinger F, Laskin J, Pavlakis N, Stroiakovski D, Thatcher N, Tsai CM, Wu YL, Zhou C; Department of Oncology, Hospital Santa Maria della Misericordia, Sant Andrea delle Fratte, Perugia, Italy.
Lancet Oncol 2010; 11:733-740

BACKGROUND: Results of two phase 3 trials have shown first-line bevacizumab in combination with chemotherapy improves clinical outcomes in patients with advanced or recurrent non-squamous non-small-cell lung cancer (NSCLC). The SAiL (MO19390) study was undertaken to assess the safety and efficacy of first-line bevacizumab combined with standard chemotherapy regimens in clinical practice.

METHODS: Between August, 2006, and June, 2008, patients with untreated locally advanced, metastatic, or recurrent non-squamous NSCLC were recruited to this open-label, single group, phase 4 study from centres in 40 countries. Eligible patients had histologically or cytologically documented inoperable, locally advanced, metastatic, or recurrent disease (stage IIIB-IV); an Eastern Cooperative Oncology Group performance status of 0-2; and adequate haematological, hepatic, and renal function. Patients received bevacizumab (7.5 or 15 mg/kg every 3 weeks) plus standard chemotherapy for up to six cycles, followed by single-agent bevacizumab until disease progression. The primary endpoint was safety; analysis was by intention to treat (ITT). This study is registered with ClinicalTrials.gov, number NCT00451906.

FINDINGS: At the final data cutoff (July 24, 2009), an ITT population of 2212 patients was assessed. The incidence of clinically significant (grade > or = 3) adverse events of special interest was generally low; thromboembolism occurred in 172 (8%) patients, hypertension in 125 (6%), bleeding in 80 (4%), proteinuria in 67 (3%), and pulmonary haemorrhage in 15 (1%). 57 (3%) patients died because of these adverse events, with thromboembolism (26 patients, 1%) and bleeding (17, 1%) as the most common causes. The most common grade 3 or higher serious adverse events deemed by investigators to be associated with bevacizumab were pulmonary embolism (28 patients; 1%) and epistaxis, neutropenia, febrile neutropenia, and deep vein thrombosis (all of which occurred in 13 patients [1%]). Bevacizumab was temporarily interrupted after 28 (2%) of 1347 bleeding events and 72 (7%) of 1025 hypertension events, and permanently discontinued after 110 (8%) bleeding events and 40 (4%) hypertension events. No new safety signals were reported.

INTERPRETATION: Our results confirm the manageable safety profile of first-line bevacizumab in combination with various standard chemotherapy regimens for treatment of advanced non-squamous NSCLC. (Funding: F Hoffmann-La Roche Ltd.)

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EDITORIAL COMMENT: This phase 4 study investigated the incidence of adverse events when bevacizumab was combined with first-line cytotoxic chemotherapy in community oncology practices. Over 2,000 patients undergoing therapy for NSCLC were assessed and received a median of seven doses of bevacizumab. In total, 13% of patients had a grade ≥ 3 adverse event that was attributed to bevacizumab. The most common serious events were pulmonary embolism, neutropenia and deep venous thrombosis. Fifteen patients (1%) had grade ≥ 3 pulmonary hemorrhage, defined as hemorrhage of sufficient severity to require transfusion or procedural intervention, or resulting in death. Of these 15 patients, 8 died, a percentage consistent with previous phase 3 studies. Although most adverse events resolved, a total of 57 deaths (3%) were attributed to bevacizumab toxicity. The adverse events seen with bevacizumab were consistent across several different chemotherapy regimens, mostly cisplatin or carboplatin based doublets.

A previous retrospective, subgroup analysis of the E4599 trial, a phase 3 study of first-line chemotherapy with bevacizumab, reported increased toxicity among patients older than 70 years (Ramalingam S et al. *J Clin Oncol* 2008; 26:60-65). Toxicities included bleeding and neutropenia, and there was no improvement in survival of elderly patients randomized to the bevacizumab arm of therapy. Although only a retrospective, subgroup analysis, the E4599 trial results have dissuaded some oncologists from using bevacizumab for elderly patients. The patient population in SAiL was younger than the average age of an advanced NSCLC patient, but elderly patients were enrolled (subject ages ranged from 24-86 years). However, the SAiL study investigators do not describe how many patients were older than 70 years or if the number of adverse events in this population was greater than in younger patients, leaving this important safely issue unresolved.

In the SAiL study, there was a high level of disease response and a median survival of 14.1 months, which is reassuring in a broad patient population in a community setting. It was also reassuring that no new or unexpected adverse events were seen with bevacizumab. However, life-threatening adverse events associated with bevacizumab have now been well documented in multiple lung cancer studies and must be carefully considered and discussed with patients prior to its use.

Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR

Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T; North-East Japan Study Group. *N Engl J Med* 2010; 362:2380-2388

BACKGROUND: Non-small-cell lung cancer with sensitive mutations of the epidermal growth factor receptor (EGFR) is highly responsive to EGFR tyrosine kinase inhibitors such as gefitinib, but little is known about how its efficacy and safety profile compares with that of standard chemotherapy.

METHODS: We randomly assigned 230 patients with metastatic, non-small-cell lung cancer and EGFR mutations who had not previously received chemotherapy to receive gefitinib or carboplatin-paclitaxel. The primary end point was progression-free survival; secondary end points included overall survival, response rate, and toxic effects.

RESULTS: In the planned interim analysis of data for the first 200 patients, progression-free survival was significantly longer in the gefitinib group than in the standard-chemotherapy group (hazard ratio for death or disease progression with gefitinib, 0.36; P<0.001), resulting in early termination of the study. The gefitinib group had a significantly longer median progression-free survival (10.8 months, vs. 5.4 months in the chemotherapy group; hazard ratio, 0.30; 95% confidence interval, 0.22 to 0.41; P<0.001), as well as a higher response rate (73.7% vs. 30.7%, P<0.001). The median overall survival was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (P=0.31). The most common adverse events in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%). One patient receiving gefitinib died from interstitial lung disease.

CONCLUSIONS: First-line gefitinib for patients with advanced non-small-cell lung cancer who were selected on the basis of EGFR mutations improved progression-free survival, with acceptable toxicity, as compared with standard chemotherapy. (UMIN-CTR number, C000000376.)

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EDITORIAL COMMENT: This was a phase 3 study of patients with advanced NSCLC randomized to receive either first-line gefitinib or traditional cytotoxic chemotherapy with carboplatin and paclitaxel. This study was conducted within a Japanese patient population with known EGFR mutations that predict sensitivity to tyrosine kinase inhibitors (TKIs) including gefitinib. The investigators in this study excluded patients who harbored a mutation within EGFR that leads to TKI resistance (T790M) to further enrich the population. Testing for KRAS mutations was not performed. Although KRAS mutations predict primary resistance to gefitinib, these mutations are rarely found in patients with EGFR mutations. Therefore, screening for and excluding patients with KRAS mutations would probably not have significantly influenced the results.

First-line gefitinib was associated with significant improvement in progression-free survival and response rate. Although there was a trend towards improvement in overall survival with first-line gefitinib (30.5 vs. 23.6 months), this did not reach statistical significance. When evaluating overall survival, the treatment that patients received in second and subsequent lines of therapy becomes important. In this study, although there was no protocol-specific second-line therapy given, the study recommended crossover to the other arm of therapy upon progression, and indeed nearly 95% of patients who first received carboplatin and paclitaxel received gefitinib in the second line. Thus, almost all of the patients enrolled were treated with gefitinib, which most likely accounts for the close outcomes in overall survival. The authors retrospectively analyzed the response to gefitinib in the second line. Patients who received gefitinib in the second line had a slightly inferior response rate of 58.5%, compared to 73% in the first line. The difference in response rate, in addition to the trend towards improved survival with first-line therapy, suggest the importance of using a TKI prior to cytotoxic chemotherapy.

Erlotinib and gefitinib are both small molecules that bind the catalytic cleft of the EGFR intracellular kinase domain to inhibit phosphorylation and downstream signaling. They share a similar toxicity profile (rash, diarrhea, fatigue and interstitial lung disease). After demonstrating an overall response rate of 10.6% in a phase 2 study of NSCLC patients who had received prior chemotherapy (Kris MG, et al. *JAMA* 2003; 290:2149-2158), gefitinib received accelerated FDA approval for use in this population. However, in a post-marketing, phase 3 study, the ISEL trial (Thatcher N, et al. *Lancet* 2005; 366:1527-1537), improvement in overall survival with gefitinib therapy was not confirmed. Based on these results, the FDA revised the label for gefitinib, restricting its use to patients currently enrolled in clinical trials or those who had already demonstrated benefit from its use. ISEL did not require EGFR mutation testing for enrollment, which probably accounted for the negative results. However, BR.21, a phase 3 trial of erlotinib in previously treated NSCLC patients, also did not require EGFR mutation testing for enrollment, yet it did demonstrate a survival benefit. Based on these results, erlotinib was FDA-approved for this indication (Shepherd FA, et al. *N Engl J Med* 2005; 353:123–132). Although subsequent studies have demonstrated improved efficacy in patients with EGFR mutations, gefitinib has not undergone further FDA label revision and erlotinib remains the TKI used for NSCLC in the US. Because these drugs share the same mechanism of action and side effect profile, clinical trial data collected using gefitinib is often used to determine treatment guidelines for the use of erlotinib.

Although this study analyzed an Asian population of patients treated with gefitinib (a chemotherapeutic agent not available in the US), it adds growing evidence to support testing for EGFR mutations and using a TKI in first-line therapy for patients with activating mutations. Improvements in median survival of NSCLC patients with TKI-sensitive mutations treated with TKIs have been observed in other studies, as well, which is encouraging. A median survival of 30.5 months in metastatic lung cancer is inspiring and further emphasizes the importance of directed therapy in this disease.

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Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study

Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, Juhász E, Esteban E, Molinier O, Brugger W, Melezínek I, Klingelschmitt G, Klughammer B, Giaccone G; SATURN investigators; Department of Medical Oncology, Ospedale Civile di Livorno, Livorno, Italy. *Lancet Oncol* 2010; 11:521-529

BACKGROUND: First-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) is usually limited to four to six cycles. Maintenance therapy can delay progression and prolong survival. The oral epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib has proven efficacy and tolerability in second-line NSCLC. We designed the phase 3, placebo-controlled Sequential Tarceva in Unresectable NSCLC (SATURN; BO18192) study to assess use of erlotinib as maintenance therapy in patients with non-progressive disease following first-line platinum-doublet chemotherapy.

METHODS: Between December, 2005, and May, 2008, 1949 patients were included in the run-in phase (four cycles of platinum-based chemotherapy). At the end of the run-in phase, 889 patients who did not have progressive disease were entered into the main study, and were randomly allocated using a 1:1 adaptive randomisation method through a third-party interactive voice response system to receive erlotinib (150 mg/day; n=438) or placebo (n=451) until progression or unacceptable toxicity. Patients were stratified by EGFR immunohistochemistry status, stage, Eastern Cooperative Oncology Group performance status, chemotherapy regimen, smoking history, and region. Co-primary endpoints were progression-free survival (PFS) in all analysable patients irrespective of EGFR status, and PFS in patients whose tumours had EGFR protein overexpression, as determined by immunohistochemistry. This study is registered with www.ClinicalTrials.gov, number NCT00556712.

FINDINGS: 884 patients were analysable for PFS; 437 in the erlotinib group and 447 in the placebo group. After a median follow-up of 11.4 months for the erlotinib group and 11.5 months for the placebo group, median PFS was significantly longer with erlotinib than with placebo: 12.3 weeks for patients in the erlotinib group versus 11.1 weeks for those in the placebo group (HR 0.71, 95% CI 0.62-0.82; p<0.0001). PFS was also significantly longer in patients with EGFR-positive immunohistochemistry who were treated with erlotinib (n=307) compared with EGFR-positive patients given placebo (n=311; median PFS 12.3 weeks in the erlotinib group vs 11.1 weeks in the placebo group; HR 0.69, 0.58-0.82; p<0.0001). The most common grade 3 or higher adverse events were rash (37 [9%] of 443 patients in the erlotinib group vs none of 445 in the placebo group) and diarrhoea (seven [2%] of 443 patients vs none of 445). Serious adverse events were reported in 47 patients (11%) on erlotinib compared with 34 patients (8%) on placebo. The most common serious adverse event was pneumonia (seven cases [2%] with erlotinib and four [<1%] with placebo).

INTERPRETATION: Maintenance therapy with erlotinib for patients with NSCLC is well tolerated and significantly prolongs PFS compared with placebo. First-line maintenance with erlotinib could be considered in patients who do not progress after four cycles of chemotherapy. (Funding: F Hoffmann-La Roche Ltd.)

EDITORIAL COMMENT: The recent availability of new agents with minimal cumulative toxicity, such as pemetrexed and erlotinib, has renewed interest in maintenance therapy for NSCLC. In this study, patients with advanced NSCLC of any histology underwent first-line chemotherapy with a platinum based doublet. Those patients who did not have disease progression following four cycles of therapy, and who maintained an ECOG performance status of 0 or 1, were randomized to erlotinib or placebo as maintenance until documented disease progression. Of the 1,949 patients who were screened and underwent first-line chemotherapy, only 878 patients (45%) were eligible for randomization. Although testing for EGFR mutations was performed, patients were stratified by EGFR immunohistochemistry. Median PFS was significantly longer for patients in the erlotinib group (12.3 weeks) than for those in the placebo group (11.1 weeks) (HR 0.71, 95% CI 0.62-0.82; p<0.0001). Although statistically significant, a one week improvement in PFS is of little clinical significance.

This study demonstrated an impressive difference in progression-free survival in patients with activating EGFR mutations (HR 0.10, CI 0.04-0.25; p<0.0001) who received erlotinib maintenance therapy. However, the emerging

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standard of care is for TKIs to be used in the first-line setting for this subpopulation of patients. Certainly, in patients with EGFR mutations who did not receive a TKI in the first line, this study demonstrated erlotinib should be given as maintenance therapy.

In patients with non-squamous cell lung cancer, including adenocarcinoma with wild-type EGFR, there is a documented improvement in overall survival of five months when pemetrexed is used as maintenance therapy, compared to placebo (Ciuleanu T, et al. *Lancet* 2009; 374:1432-1440). Because it is well tolerated and associated with a robust improvement in survival, pemetrexed has quickly become a useful drug for maintenance therapy in this group. Thus, in patients with non-squamous cell carcinoma, the role of erlotinib as maintenance therapy is limited, either because erlotinib has been used in the first line or because pemetrexed is chosen as maintenance therapy. This leaves a population of patients with squamous cell carcinoma who have wild-type EGFR and stable disease after first-line chemotherapy. Subgroup analysis in this study of patients with squamous cell carcinoma did show an improvement in PFS (HR 0.76, CI 0.60-0.95), but not in overall survival (HR 0.86, CI 0.68-1.10). Maintenance erlotinib is reasonable to use and now FDA-approved for this indication. However, because of all of these limitations, this study has had only a modest impact on treatment of NSCLC .

Disclosures

Dr. Carr served on the speakers bureau for CareFusion Corporation.

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