BRIEF REPORT

Best of the Month
A Roundup of Articles Published in Recent Months

Daniel Morgenszt ern, MD,*† and Ramaswamy Govindan, MD*†

Abstract: The nine papers selected for the “best of the month” cover a broad range of topics including adjuvant therapy, targeted therapy with epidermal growth factor or vascular endothelial growth factor inhibitors, surgical approaches to lung cancer, and use of genomic profiles.

Key Words: NSCLC, Lung cancer, Best papers.

1. LONG TERM FOLLOW-UP DATA FROM NON-SMALL CELL LUNG CANCER ADJUVANT CHEMOTHERAPY TRIALS

Mixed Message!

Administration of postoperative chemotherapy for patients with resected non-small cell lung cancer (NSCLC) has been in vogue only for the past few years and driven largely by three recent prospective studies. Long-term follow-up data from these adjuvant therapy studies are of great interest to the lung cancer community. It is quite reassuring that even after a median follow-up of 9.3 months, the JBR-10 study continues to show a persistent 5-year survival benefit for adjuvant chemotherapy compared with observation (67 versus 56%). However, this survival benefit was restricted to patients with stage II. The updated International Adjuvant Lung Cancer Trial, in contrast, showed a decreasing benefit from adjuvant chemotherapy after the first 5 years of follow-up, with the absolute benefit in 5-year overall survival (OS) reduced from 5.4 to 3.9%, now no longer statistically significant. No survival benefit for adjuvant chemotherapy was observed in either stage II (hazard ratio [HR] = 0.92; 95% confidence interval = 0.73–1.15) or stage III disease (HR = 0.85; 95% confidence interval = 0.72–1.01). Possible explanations for this discrepancy after the first 5 years of follow-up include use of older generation of chemotherapy agents such as vindesine or etoposide, administration of postoperative radiotherapy in a significant proportion of patients, and an increased non-lung cancer–related mortality in the International Adjuvant Lung Cancer Trial.

2. CETUXIMAB IN NSCLC

....In Need of a Predicted Biomarker!

Two large phase III trials recently evaluated the use of first-line cetuximab in combination with platinum-based chemotherapy in patients with advanced stage NSCLC. In the first-line erbitux (FLEX) trial was published in 2009 and showed a significant improvement in survival for the combination of cisplatin, vinorelbine, and cetuximab compared with the same chemotherapy alone. The primary endpoint, progression-free survival (PFS) according to the independent radiologic review committee was not met (4.40 months for the cetuximab arm and 4.24 months for the chemotherapy only arm). Among the secondary endpoints, cetuximab was associated with a significant improvement in overall response rate (25.7 versus 17.2%, \( p = 0.006 \)) but not in OS (9.69 versus 8.38 months, \( p = 0.16 \)). The only clinical factor correlated with survival benefit in the cetuximab arm was the presence of acneiform rash of any grade by day 21 (median survival of 10.4 months versus 8.9 months in patients with rash versus no rash). The correlative part of Bristol-Myers Squibb 099 study was performed in tumor samples from 225 randomly assigned patients. None of the markers tested, including K-Ras mutation status, epidermal growth factor receptor (EGFR) mutation status, EGFR protein expression by immunohistochemistry, and EGFR gene copy number by fluorescent in situ hybridization, were predictive for response to cetuximab. With two studies showing opposite results and no valid predictive marker, it is quite unlikely that cetuximab would be used widely in the treatment of metastatic NSCLC.

3. HYPERTENSION IN PATIENTS RECEIVING BEVACIZUMAB

Poor Man’s Biomarker

Bevacizumab is associated with a variety of severe toxicities including gastrointestinal perforation, bleeding,
thrombosis, would healing complications, and heart failure. Hypertension is a relatively common toxicity, with approximately 15% of the patients requiring antihypertensive therapy. With the hypothesis that hypertension may indicate the successful blockade of the vascular endothelial growth factor pathway, a retrospective study was conducted on the patients treated in the phase III trial ECOG 4599, which compared the efficacy of carboplatin and paclitaxel with bevacizumab (PCB) or paclitaxel with chemotherapy alone. Among the 741 eligible patients, there were no differences in baseline blood pressure (BP) measurements between patients according to the treatment arm. Hypertension, defined as BP more than 150/100 mmHg at baseline or at the end of cycle 1 or an increase more than 20 mmHg between day 1 and 21, was associated with a significant improvement in OS among patients treated with PCB (15.9 versus 11.5 months). However, this difference in OS was not seen in patients treated with chemotherapy alone. The survival benefit for patients treated with PCB who developed high BP by the end of cycle 1 remained significant in a multivariate Cox model adjusting for performance status, age, histology, sex, weight loss, and metastatic pattern (HR = 0.68, p 0.001). Survival benefit for PCB remained significant compared with paclitaxel with chemotherapy alone, even in patients who did not develop high BP. Therefore, although hypertension during bevacizumab treatment may require intervention to prevent cardiovascular complications, this toxicity may be viewed as an equivalent to the skin rash in patients treated with EGFR inhibitors, an inconvenience that may be beneficial.

**4. BEVACIZUMAB IN PATIENTS WITH CENTRAL NERVOUS SYSTEM METASTASES**

**Acceptable Risk**

Since the initial report of a patient with hepatocellular carcinoma who died of cerebral bleeding from a previously undiagnosed brain metastasis during a phase I trial, patients with central nervous system metastases have been excluded from bevacizumab trials. In a recent study, Besse et al. evaluated the risk of cerebral hemorrhage in patients enrolled in 13 randomized clinical trials, two single-arm safety trials, and two prospective studies including patients with treated brain metastases. Among the 8443 patients enrolled in the randomized trials for NSCLC, breast cancer, pancreatic cancer, and colon cancer, there were 187 patients (2.2%) with brain metastases, including 91 in patients treated with bevacizumab and 96 in patients receiving the control chemotherapy. The rate of cerebral hemorrhage in this population was 3.3% in the bevacizumab arms and 1.0% in the control groups. The incidence of cerebral hemorrhage in the two open-label, single-arm studies, Safety of Avastin in Lung (SAIL) (squamous cell lung cancer) and ATHENA (breast cancer), which excluded patients with brain metastases at presentation, was 0.9% (3 of 321 patients). Among 131 evaluable patients with NSCLC known treated brain metastases and enrolled in the two prospective studies (PASSPORT and ATLAS), one patient (0.8%) developed cerebral hemorrhage. Despite the limitations of a retrospective analysis comparing selected populations across trials, bevacizumab does not seem to be associated with a disproportional increase in the risk of bleeding in patients with solid tumors and brain metastases.

**5. GEFITINIB VERSUS CHEMOTHERAPY IN PATIENTS WITH EGFR TK MUTATED NSCLC**

**Ideal Drug for Patients with EGFR TK Mutated NSCLC**

In the landmark Iressa Pan-Asia Study (IPASS) study, Mok et al. reported a significant improvement in the PFS for gefitinib compared with chemotherapy with carboplatin and paclitaxel in the subset of patients with lung adenocarcinoma and EGFR mutation, while chemotherapy was superior in those without the mutation. The West Japan Thoracic Oncology Group (WJTOG) 3405 study was a randomized multicenter phase III trial comparing gefitinib versus cisplatin plus docetaxel in patients with previously untreated advanced NSCLC. Unlike the IPASS study, only patients with the EGFR TK mutations were enrolled in this study. Among the 172 equally distributed patients included in the survival analysis, the PFS was significantly longer in patients treated with gefitinib (9.2 versus 6.3 months, p < 0.0001). There were no differences in survival according to the mutation type (exon 19 deletions or L858R). The West Japan Thoracic Oncology Group 3405 supports the results of the subset analysis of survival from the IPASS based on EGFR mutation and provided stronger support for the use of first-line gefitinib in this selected patient population.

**6. THORACOSCOPIC LOBECTOMY ON THE RISE**

**Is Video-Assisted Thoracoscopic Surgery Becoming More Popular?**

There have been multiple reports showing that video-assisted thoracoscopic surgery (VATS) is associated with fewer postoperative complications compared with open thoracotomy. Because there are no randomized phase III trials comparing the two approaches, Subroto et al. searched the Society of Thoracic Surgeons General Thoracic Database from 2002 to 2007 to allow a more comprehensive evaluation. From an initial cohort of 6323 patients, 1281 patients in each group were selected through propensity matching. During the study period, the percentage of patients undergoing VATS increased from 10 to 27%. Although there were no differences in operative mortality between the two groups, the percentage of patients who had no surgical complications in patients treated with VATS or open lobectomy were 73.8 and 65.3%, respectively (p < 0.001). VATS was specifically associated with a significantly lower incidence of arrhythmias (7.3 versus 11.5%), pulmonary complications (7.5 versus 12.1%), and shorter length of stay (4 versus 6 days). This database study provided further evidence that VATS is associated with a lower incidence of complications, and its use has steadily increased during the past 6 years.
7. IS THERE A REASON FOR THE IMPROVED OUTCOMES FOR NSCLC ACCORDING TO AGE AND SEX?

A Genomic Look at the Demographic Variables

Despite clinical evidence for improved survival in patients with younger age and female gender, there is limited information on the biologic differences that could explain this variability in outcome. Mostertz et al.14 evaluated 787 NSCLC patient tumor samples, with corresponding clinical data from four independent data sets. Patients with stages I to IIIA were subdivided into four different subgroups according to age and gender into younger than 70 years, 70 years or older, men, and women. The relapse-free survival was significantly better in younger patients (p = 0.006) and women (p = 0.008). In both age groups and genders, there was a significant survival difference between the high-risk and low-risk clusters. Younger patients with high-risk for relapse had increased probability of activation of the Src and TNF gene signatures compared with the low-risk counterpart, whereas older patients in the high-risk category had increased activation of gene signatures for wound healing and invasiveness. Although men had an increased probability of activation in the chromosomal instability, epigenetic stem cell, invasiveness, and Myc and wound healing pathways, the E2F1 pathway was most commonly activated in women. Pathways activated more commonly in high-risk women included invasiveness and STAT3, whereas high-risk men had increased activation of STAT3, TNF, wound healing, and EGFR. Although these findings still require validation, this study represents a step forward in the understanding of biologic differences among demographic variables, with likely implications for individualized therapy.

REFERENCES


