Cisplatin Versus Carboplatin for Patients With Metastatic Non–Small-Cell Lung Cancer—An Old Rivalry Renewed

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Oncologists in the United States have embraced carboplatin as their favorite platinum drug for the first-line treatment of patients with metastatic non–small-cell lung cancer (NSCLC). Two North American phase III trials have compared carboplatin plus paclitaxel with cisplatin-based combinations and demonstrated similar efficacy but lower rates of nausea, leukopenia, and nephrotoxicity with the use of carboplatin (1,2). Carboplatin and either paclitaxel, docetaxel, or gemcitabine have since become the three most commonly used drug regimens in the United States for NSCLC. Furthermore, carboplatin plus paclitaxel was chosen as the standard treatment arm for the Eastern Cooperative Oncology Group (ECOG) study 4599, the randomized trial that demonstrated a statistically significant improvement in response rate and survival when bevacizumab was added to the doublet as first-line treatment of patients with nonsquamous NSCLC (3).

In this issue of the Journal, Ardizzoni et al. (4) report their individual patient data meta-analysis, which calls into question the common American approach. In their analysis of 2968 patients entered in nine randomized trials, treatment with cisplatin was superior to that with carboplatin in terms of radiologic response rate (30% versus 24%; odds ratio [OR] = 1.37, 95% confidence interval [CI] = 1.16 to 1.61; $P<.001$) when used as part of combination chemotherapy for the first-line treatment of patients with advanced NSCLC (4). Although the improvement in response rate did not translate into a statistically significant improvement in overall survival, the trend favored the use of cisplatin (hazard ratio [HR] = 1.07, 95% CI = 0.99 to 1.15; $P = .100$), and subset analyses demonstrated a statistically significant improvement in survival when cisplatin was used for patients with nonsquamous histology (HR = 1.12, 95% CI = 1.01 to 1.23) or when the cisplatin was used in combination with paclitaxel, docetaxel, or gemcitabine (HR = 1.11, 95% CI = 1.01 to 1.21). This comprehensive individual-patient meta-analysis confirms the conclusions of three prior meta-analyses dating back to 2004, which were based on essentially the same clinical trials but which used only published data (5–7).

Treatment-related toxic effects were also assessed in the meta-analysis. More thrombocytopenia was seen with carboplatin than with cisplatin (12% versus 6%, OR = 2.27; 95% CI = 1.71 to 3.01; $P<.001$), while cisplatin caused more nausea and vomiting (8% versus 18%, OR = 0.42; 95% CI = 0.33 to 0.53; $P<.001$) and renal toxicity (0.5% versus 1.5%, OR = 0.37; 95% CI = 0.15 to 0.88; $P = .018$). The authors conclude that treatment with cisplatin was not associated with a substantial increase in the overall risk of severe toxic effects. Although this conclusion is consistent with the data presented, the vomiting is arguably more troubling to patients than thrombocytopenia, which is largely asymptomatic, and few would argue that carboplatin is logistically much easier to administer.

The landscape for the competition between cisplatin and carboplatin has changed over the years. The concern for vomiting has become less with the use of improved antinausea medications (8). The use of lower doses of cisplatin—75–80 mg/m^2 every 3 weeks instead of the historical 100 mg/m^2 or more—also lowers the risk of emesis without compromising efficacy (9). Issues regarding cost are less relevant as carboplatin is now off patent, with less expensive generic versions on the horizon (10).

However, this rivalry has been renewed by two major developments in the treatment of NSCLC. The first is the now established role of adjuvant chemotherapy for patients with completely resected stage IB–III disease. The second is the data supporting the integration of bevacizumab for the treatment of stage IV disease.

With regard to adjuvant chemotherapy, there have been three prospective randomized trials that demonstrate that postoperative cisplatin-based chemotherapy improves survival over surgery alone for patients with early-stage disease (11–13). The only trial testing carboplatin, Cancer and Leukemia Group B trial 9633, did not demonstrate a survival benefit (14). Therefore, based on the available data, cisplatin combinations, primarily cisplatin plus vinorelbine, are the standard for adjuvant therapy. Carboplatin should not be routinely recommended as part of an adjuvant regimen. When a patient is offered adjuvant carboplatin-based chemotherapy, the decision is based on an extrapolation, unsupported by any phase III data. Similarly, the decade-old paradigm that suggests that neoadjuvant cisplatin is to be used for resectable stage IIIA (N2) disease is bolstered by the results of Ardizzoni et al. (4) showing that cisplatin is more likely to result in radiologic response and hopefully downstaging. As such, cisplatin is favored in any neoadjuvant regimen given the paucity of data demonstrating the efficacy of carboplatin in this setting (15,16).

In short, when you are hoping to cure NSCLC, cisplatin combinations are recommended.

In contrast, for patients with stage IV NSCLC in whom the goal is not cure but symptom and disease control, avoiding toxicity becomes more important, especially when there is little difference in survival when using a less toxic regimen. Even in this setting, however, for otherwise fit patients with severe cancer-related symptoms—such as cough, shortness of breath, or pain—that cannot be relieved by a local intervention, the potential

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DOI: 10.1093/jnci/djk222

increased response rate offered by cisplatin over carboplatin results in a better chance at tumor shrinkage and related symptom improvement.

Cisplatin versus carboplatin aside, the most important new drug to consider for the first-line treatment of stage IIIB or IV nonsquamous NSCLC is bevacizumab. The addition of bevacizumab to carboplatin plus paclitaxel in ECOG 4599 (3) more than doubled the radiologic response rate and decreased the overall risk of death (HR = 0.79; $P = .003$), albeit at the expense of an increased risk of toxic death (0.5% versus 3.5%, $P = .001$) from bevacizumab-related bleeding or neutropenia. Patients with squamous carcinoma were excluded from phase III clinical trials of bevacizumab because patients with squamous carcinoma had a higher risk of life-threatening hemoptysis in phase II testing of carboplatin plus paclitaxel with bevacizumab (17).

It deserves emphasis that the survival benefit of cisplatin over carboplatin in the Ardizzoni et al. analysis (4) was most apparent in the nonsquamous subgroup. Thus, although we should be mindful of the limitations of subgroup analyses, cisplatin appears to be more effective in exactly those patients who should be offered bevacizumab. The bevacizumab story will unfold further as data from the European trial BO17704 ("AVAiL"), which combines bevacizumab with cisplatin plus gemcitabine for the treatment of nonsquamous NSCLC, is released.

As stated by Ardizzoni et al. (4), progress in systemic therapy for NSCLC over the last 20 years has occurred in small increments. We are hopeful that less toxic drugs targeted at the unique molecular mechanisms that drive NSCLC to grow will lead to larger incremental improvements in the future. Until then, the apparent superiority of cisplatin over carboplatin demonstrated in this issue should not be taken lightly, particularly in patients being treated with curative intent. Equally inadvisable would be the overzealous use of cisplatin in patients with metastatic NSCLC in whom the drug may be poorly tolerated, such as those with substantial baseline renal impairment, hearing loss, peripheral neuropathy, or other serious medical comorbidities. We should also be reminded of the fact that no chemotherapy has been shown to improve survival in patients with a poor performance status (ECOG/Zubrod ≥ 2, Karnofsky $< 70\%$), a population especially vulnerable to the ill effects of cisplatin.

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Notes

Dr C. G. Azzoli has received research support from Sanofi-Aventis, Genentech, and Allos Therapeutics. Dr D. G. Pfister has received research support from Eli-Lilly, Genentech, and AstraZeneca and serves on an independent safety monitoring board for Sanofi-Aventis. Dr M. G. Kris has served as a consultant to Bristol-Myers Squibb.