

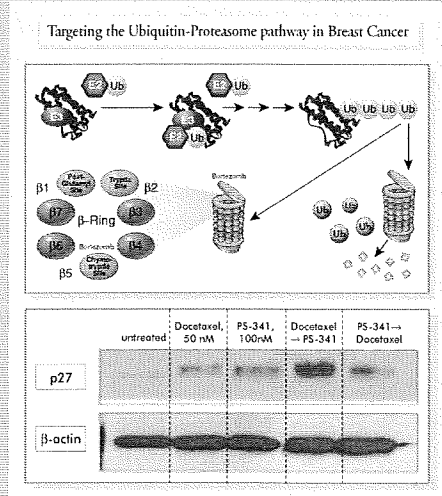
Clinical Breast Cancer

Volume 5, Number 2 June 2004

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The Once and Future Role of the Platinum Agents in Advanced Breast Cancer

Robert Nagourney

Reprinted from *Clinical Breast Cancer*, Vol. 5, No. 2, 123-124, 2000



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The Once and Future Role of the Platinum Agents in Advanced Breast Cancer

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Cis-dichlorodiammineplatinum(II) and the chemically related compounds carboplatin and oxaliplatin are among the most active chemotherapy drugs for the management of epithelial neoplasms. With established curative potential in the treatment of testicular neoplasms and small-cell lung cancer, these agents have also found an important role in non-small-cell lung cancer (NSCLC), and in ovarian, gastrointestinal, genitourinary, and upper aerodigestive cancers. Despite this impressive track record in a broad array of tumors, the platins have shown little traction in the management of advanced breast cancer.

One reason for the comparatively low use of the platins in breast cancer may be that early phase II trials were conducted in heavily pretreated patients. A broad array of DNA excision repair enzymes, including ERCC1, ERCC2, and XPA, are responsible for resistance to heavy metal intoxication. Conserved for millions of years, these protective mechanisms confer resistance to the platin derivatives in human tissues. Upregulation of these and related DNA repair enzymes following prior cytotoxic drug exposures may in part explain the degree of resistance to the platins observed in these early clinical trials. The zero response rate originally reported for cisplatin in patients with relapsed breast cancer¹ compared with the 47% response rate subsequently reported in chemotherapy-naïve patients with breast cancer² is exemplary of the rapid acquisition of resistance to related cytotoxins.

We are now witnessing a resurgence of interest in the application of the

platins in breast cancer management. In this issue of *Clinical Breast Cancer*, Nasr et al report the combination of gemcitabine plus carboplatin as second-line therapy for relapsed breast cancer.³ These investigators administered carboplatin to an area under the curve of 4.5 on day 1, combined with gemcitabine 1000 mg/m² on days 1 and 8 of a 21-day schedule. Most patients had received adjuvant chemotherapy and all received systemic therapy at relapse. The objective response rate of 33% (all partial responses with moderately severe though manageable toxicity) represents a good but not stellar result in this patient population. Several questions arise as we examine these results in the context of related regimens.

First, are cisplatin and carboplatin equivalent in the treatment of advanced breast cancer? Carboplatin, the cyclobutane-dicarboxylate derivative of cisplatin, has gained popularity in a number of malignancies because of its markedly diminished otologic, neurologic, and gastrointestinal toxicity. However, its equivalence to cisplatin remains an open question. Although relative equivalence has been shown in the management of ovarian cancer, the drug has not replaced cisplatin in testicular cancer treatment and may not provide equivalent benefit in NSCLC, in which it has largely replaced cisplatin. The head-to-head comparison of etoposide combined with carboplatin versus cisplatin in NSCLC,⁴ often quoted as evidence of equivalence, actually provided response rates of 27% for the cisplatin arm versus 16% for the carboplatin arm ($P = 0.07$). Had this trial included more than 162 patients, the results might have been different. In addition, carboplatin's advantage comes at the expense of greater myelosuppression. The 50% incidence of grade 3/4 neutropenia (20% with febrile neutrope-

nia), 26% incidence of grade 3/4 anemia, and 30% incidence of grade 3/4 thrombocytopenia reflect the hazards associated with combining gemcitabine, a drug with myelosuppression as its principal toxicity, with this more myelosuppressive platinum agent.

Second, what constitutes the optimal administration schedule for a platinum agent plus gemcitabine in breast cancer? The schedule applied by Nasr et al used carboplatin on day 1 combined with gemcitabine on days 1 and 8. Although this has gained popularity in advanced NSCLC, it may diminish the combinative benefit by eliminating platin exposure on day 8. The combination of gemcitabine with platinum derivatives represents the single most synergistic drug doublet ever examined in the laboratory. With more than 2000 analyses completed in human primary tumor cultures to date, gemcitabine has consistently revealed true synergy with platinum agents in > 70% of tumors, with comparable degrees of synergy for carboplatin, cisplatin, and oxaliplatin.^{5,6} By way of comparison, true synergy between paclitaxel and the platinum agents falls in the range of 20%-25%, depending on tumor type. In this context, the use of sequential doublets (ie, the platinum agent and gemcitabine administered with each scheduled dose on days 1 and 8 or days 1 and 15) may hold theoretical and practical advantage. A comparison of the regimen used by Nasr et al with 2 cisplatin/gemcitabine doublet regimens,^{7,8} both of which included patients with ≥ 2 previous treatments for advanced disease, reveals overall response rates of 39%-50%, with tolerable toxicities. The relative contributions of schedule versus the specific platinum salt used in the combination will require further study.

As the platinum agents gain popularity in the management of breast cancer, this important class of drugs has the

potential to improve outcomes for one of the most common human malignancies. The introduction of carboplatin or cisplatin with docetaxel and trastuzumab, currently under investigation by the Breast Cancer International Research Group (BCIRG) in the BCIRG 006 trial, represents one of many novel directions that such combinations are pursuing. Introducing gemcitabine combinations may offer even more exciting opportunities in the future.

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