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Perspectives and Commentaries

Is Cisplatin Useful for Breast Cancer?

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(A COMMENT ON: Cocconi G, Tonato M, Di Costanzo F, Bisagni G, Belsanti V, Buzzi F and Ceci G. Platinum and etoposide in chemotherapy refractory metastatic breast cancer. *Eur J Cancer Clin Oncol* 1986, **22**, 761–764.)

Cis-DIAMINEDICHLOROPLATINUM or cisplatin has shown marked antitumor activity in malignant tumors of the testis, carcinoma of the ovaries, uterine cervix, head and neck, bladder, lungs, and osteogenic sarcoma [1]. Less dramatic antitumor activity has also been described against other tumors. Although available for clinical trials for over 15 years, cisplatin has not been extensively evaluated in many tumor types due to its toxicity profile that includes severe nausea and vomiting, bone marrow suppression, nephrotoxicity, peripheral neuropathy and high frequency hearing loss. Renal tubular damage with urinary losses of amino acids, calcium, magnesium, and bicarbonate occurs regularly [2].

Breast carcinoma belongs to the group of moderately sensitive malignant tumors. Hormonal therapy is an effective palliative treatment in up to a third of patients with metastatic breast cancer and combination chemotherapy that includes cyclophosphamide, methotrexate, fluorouracil, and doxorubicin results in objective responses in 50–80% of patients. Hormonal therapy, and, to a lesser extent, combination chemotherapy, are reasonably well tolerated by most patients. If a new drug causes more frequent and severe toxicity than established treatment, a greater antitumor activity is required from it to be acceptable as a useful clinical alternative.

Hints of antitumor activity in patients with metastatic breast cancer were described in the earliest phase I and broad phase II trials of cisplatin [3, 4]. However, those early responses were either subjective in nature, or were poor partial responses of short duration. Subsequent phase II trials of cisplatin in metastatic breast carcinoma, performed on patients who had received extensive prior chemotherapy, showed conflicting results. In some centers cisplatin failed to show any antitumor activity [5] while in others a modest response rate (12–20%) could be demonstrated [6, 7, 8]. Published reports suggest that cisplatin is inactive against breast cancer at doses lower than 100 mg/m^2 every 3 weeks, while 12–20% of patients achieve an objective remission at doses of 100 mg/m^2 or greater [7, 8]. A recent report showed a 54% overall remission rate among 35 patients with metastatic breast cancer and no previous cytotoxic therapy, treated with 30 mg/m^2 of cisplatin daily for 4 days (120 mg/m^2 cycle) [9]. There were 13 complete (37%) and six partial remissions (17%). This overall response rate is similar to the best single agent activity of drugs like doxorubicin. However, close scrutiny of the paper suggests that the patient population had very favorable prognostic characteristics and most responses occurred in patients with soft tissue metastases. Nevertheless, such antitumor activity is impressive and despite the toxicity of the agent it suggests that cisplatin needs further evaluation in metastatic breast cancer.

The track record of cisplatin combinations in metastatic breast cancer is less encouraging. Experience with cisplatin and continuous infusion of fluorouracil [10], or with mitomycin and hexamethylmelamine [11], or with vindesine [12] showed response rates from 20–36%. The response rates and response durations achieved in these

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studies are consistent with single agent chemotherapy with either mitomycin, fluorouracil or vindesine in previously treated patients and do not suggest additive or synergistic activity.

Recently a prospective randomized trial of two combinations in patients with metastatic breast cancer and no prior chemotherapy was described [13]. Among 61 patients treated with cyclophosphamide, adriamycin and cisplatin (PAC) a 72% response rate was seen with a median duration of 14 months. Sixty-two patients treated with cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone (CMFVP) achieved a 42% response rate with a median response duration of 9 months. The differences in response were highly significant. In addition, 36% of patients treated with PAC achieved a complete remission vs. 16% of patients treated with CMFVP. Thirty-eight patients originally treated with CMFVP were crossed over to PAC after developing progressive disease; 53% of them achieved an objective remission.

The Mayo Clinic group could not reproduce these results [14]. It must be pointed out that the dose of cisplatin utilized by the Mayo Clinic group was 40 mg/m^2, less than half the dose used by Kolaric (30 mg/m^2/d × 3 days), and a dose shown to be ineffective in previous studies [7, 8]. In addition, the Mayo Clinic study employed only 4 cycles of PAC, whereas Kolaric administered up to 9 cycles to responding patients. Therefore the Mayo Clinic study could not be expected to reproduce the Yugoslavian results.

Do these preliminary results demonstrate that PAC chemotherapy is superior to any of the previously available combinations? Certainly not. Objective rates up to 80% are commonly obtained with various doxorubicin-containing combinations [15]. Complete remission rates are usually between 15 and 24%, although in very good prognostic subgroups up to 35% may achieve complete remission with fluorouracil, doxorubicin and cyclophosphamide (FAC) [16]. The complete response rate attributed to CAP is in the ball park of the complete response figures achieved with FAC. Doxorubicin-containing regimens are slightly better than non-doxorubicin-containing regimens as measured by overall response rate, complete response rate, duration of response, and length of survival [15]. Consequently, it is no surprise that CAP is superior to CMFVP. The appropriate comparison would be between CAP and other doxorubicin-containing combinations such as fluorouracil, doxorubicin and cytoxan (FAC). If CAP is proven to provide clearly superior results to FAC then it may be worth the added acute and long-term toxicity. However, until a substantial survival advantage for this combination is shown, CAP cannot be recommended for standard use and should not replace more tested regimens.

Elsewhere Cocconi *et al.* [17] report the results of a phase II trial with cisplatin and etoposide in refractory metastatic breast cancer. Four of 24 (17%) patients achieved a partial remission (median duration = 17 weeks). Etoposide alone can achieve similar results [18], which are marginal at best, considering the toxicity of the regimen. Similar results have been obtained with cisplatin and vindesine combinations [19], and those results are not superior to those achieved with vindesine alone [20]. Without a clear demonstration of improved efficacy it seems that cisplatin only adds toxicity to the combination. It appears that cisplatin is an active agent in the treatment of breast cancer. However, the magnitude of its clinical efficacy remains to be be established. Confirmatory phase II studies, with doses in excess of 100 mg/m^2, are needed to establish the single agent activity of cisplatin in patients with breast cancer. Furthermore, its role in combination chemotherapy of breast cancer and its role in the overall treatment strategy of breast cancer have not been established and need to be elucidated.

The use of appropriate hydration with careful electrolyte replacement, the use of mannitol, or hypertonic saline has decreased considerably the nephrotoxicity of cisplatin. Aggressive combination antiemetic programs can decrease and minimize nausea and vomiting related to cisplatin-containing combinations. Nevertheless, the acute toxicity of cisplatin is considerably higher than that observed with either cyclophosphamide, methotrexate, doxorubicin or fluorouracil and the safe use of cisplatin is more complex and requires considerably higher skills than the other agents. Currently the use of cisplatin in the treatment of breast cancer is clearly experimental, and while additional controlled clinical trials are warranted its routine use cannot be recommended.

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