CORRESPONDENCE

Segregation Analysis of Breast Cancer: Histopathologic Data

In a recent issue of the Journal, Goldstein and Amos (1) reported a segregation analysis of women with different types of breast cancer. They stated that the histologic diagnoses of the breast cancers were not reviewed, since it was believed that "the level of accuracy obtained by using local pathologists (reported to be at least 80%) was sufficient for the present analysis."

Unfortunately, the reference given to support this approach is to a paper that states that only the diagnosis of breast cancer itself and the diagnosis of "ductal type" are of such credibility (2). There is no mention of the other three subcategories used by Goldstein and Amos. In fact, one of their categories, "adenocarcinoma," is a term applied to most breast carcinomas and has never been regarded as a subcategory. Yes, the diagnostic separation of "cancer yes vs cancer no" can be acknowledged as 90% credible, but the same cannot be said about breast cancer types or subtypes, as is well known to those of us who deal with this body of information. It is a shame that histopathologic data should be thought of little use from papers such as this in which histopathology is used badly.

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References

Protection of Central Nervous System Metastases From Systemic Chemotherapy by Adrenal Corticosteroids

Although systemic chemotherapies in general do not cross the normal blood brain barrier, the neovasculature that invests central nervous system (CNS) metastases is abnormal and is permeable to chemotherapies (1). Since adrenal corticosteroids (steroids) decrease capillary permeability, their use in treating patients with CNS metastases may reestablish an effective blood brain barrier, thus protecting CNS tumors from systemic chemotherapy.

The blood brain barrier is a mechanical structure that protects the CNS from systemic toxic substances. The capillary endothelial cells, which form the normal blood brain barrier, are joined together at tight junctions, thus prohibiting the vast majority of water-soluble cancer chemotherapies from entering the CNS (2). However, the neovasculature that supplies blood to CNS metastatic disease is abnormal, comprised of loose capillary endothelial junctions and numerous fenestrations (3). In the Walker 256 rat carcinomatous meningitis model, intravenous cyclophosphamide, a water-soluble agent, crosses the abnormal blood brain barrier, producing a significant (49%) cure rate (4). From a clinical point of view, CNS lymphoma has been successfully treated with systemic chemotherapy (5,6), as have CNS metastases from adenocarcinomas of the breast (7) and lung (8), small-cell anaplastic carcinoma of the lung (9,10), and germ cell tumors (11).

Systemic steroid therapy is the standard first-line treatment for vasogenic cerebral edema induced by CNS metastases; steroids decrease the permeability of the neovasculature, thus reducing edema (12). Systemic steroid treatment significantly reduces, by at least 40%, capillary permeability in the viable portion of tumor in the Walker 256 brain metastasis model (13); clinically, steroids decrease contrast enhancement of brain metastases on computerized axial tomography scans and tumor blush on radionuclide brain scans (14).

Based on these data, it is reasonable to hypothesize that systemic steroid treatment decreases the capillary permeability of neovascularure, thus protecting CNS tumor deposits from systemic chemotherapy.

Combination systemic chemotherapy for the treatment of patients with non-Hodgkin's lymphoma is delivered with curative intent. Medical oncologists agonize over CNS prophylaxis for high-grade tumors and intermediate-grade tumors with bone marrow or testicular involvement. Since all curative chemotherapeutic regimens include steroids, it is likely that such therapy protects established subclinical CNS tumor deposits. Because steroids are not essential for the induction of complete remission (Bellet RE: unpublished data), deletion of these agents from combination chemotherapy programs may reduce CNS relapse and consequently improve cure rates.

With the advent of highly effective, yet emetogenic, systemic chemotherapies, many oncologists use systemic steroids to prevent and treat nausea and vomiting. Such an approach may protect CNS tumor deposits and thereby promote CNS relapse. Therefore, perhaps the use of steroids as antiemetics should be discouraged in patients receiving neoadjuvant or postoperative adjuvant systemic chemotherapy.

In the palliative treatment of patients with established CNS metastases, systemic chemotherapy can play an important role. This is especially so for patients with chemosensitive tumors, eg, lymphoma, breast, small-cell anaplastic, or germ cell, which have not been exposed to standard treatment. Since the chemosensitivity profile of CNS tumors should be identical to that of peripheral deposits (15), response of CNS metastases to systemic chemotherapy ought to be dependent on the capillary permeability of the neovasculature (drug delivery). Because steroids decrease capillary permeability, systemic steroid administration in these patients probably should be limited.

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In conclusion, the hypothesis that steroids protect CNS metastatic deposits from chemotherapy must be tested in large-scale clinical trials. The National Cancer Institute and cooperative groups are hereby challenged to test the "null" hypothesis in a randomized, prospective fashion, because ultimate rejection of the "null" hypothesis would have great impact on the practice of medical oncology.

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References


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