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Perspectives and Commentaries

Chemotherapy of Brain Metastases

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(A COMMENT ON: Giaccone, G, Donadio M, Bonardi GM, Testore F, Calciati A. Tenoposide (VM26): an effective treatment for brain metastases of small cell carcinoma of the lung. *Eur J Cancer Clin Oncol* 1988, **24**, 629–631.

BRAIN METASTASES (BM) are the most common of life-threatening neurological complications in cancer patients. In the absence of any treatment the median survival is dismal: about 6 weeks. Their precise frequency remains unknown, but some figures indicate that as many as one patient out of five who dies from a generalized cancer has BM at autopsy.

Brain secondaries may originate from almost any primary tumor and may occur at any stage of the neoplastic disease. However, the bulk of BM are seen in lung cancer (about 50%), breast carcinoma and melanoma (about 10–15% each), and the majority become clinically evident during the late stages of the disease. As will be seen later, these characteristics have major implications when planning treatment for patients with BM.

About 15% of BM are of unknown origin, thus occurring in the early stages of the neoplastic disease. It is assumed that most of them are due to lung cancers of small size.

Essentially three treatment modalities are used against BM: surgery, radiation therapy and chemotherapy.

Surgery

In patients with single metastases originating from an unidentified neoplasm, surgery is usually performed and leads to the diagnosis. But even when the primary tumor is known, selected patients will benefit from surgery [1]. Exceptionally long survivals, and even 10-year cures, have been reported in such cases.

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Radiation therapy

Cranial irradiation is the mainstay in the treatment of BM. The doses have not been standardized, but 3000 rads in 10 fractions are commonly delivered. The neurological status of at least 50% of patients will improve after irradiation and most of them remain improved for the rest of their lives [2]. In some cases a sterilization of cerebral metastases by radiation therapy has been revealed in autopsy [3]. Yet the benefit of this treatment remains limited in terms of median survival, to about 3 months, because death is often due to extraneural lesions. Conversely, patients who do not respond to cranial irradiation die within few weeks mostly from neurological dysfunction.

Chemotherapy

Both surgery and radiation therapy are local treatments, and since about half of the patients with BM will die from extraneural lesions a systemic treatment, such as chemotherapy, is highly desirable for further progress. Currently available chemotherapy, however, has some important theoretical limitations. Most of the solid tumors such as melanoma, non-small cell bronchogenic carcinoma or digestive carcinoma are fairly resistent to currently available chemotherapy combinations. BM tend to occur during the late stages of the neoplastic disease, thus in patients in whom several drugs have already failed and who, in addition, are less likely to tolerate an intensive chemotherapy. Despite the fact that the blood–brain barrier is altered in tumors, including BM, water-soluble anticancer drugs are still theoretically less likely to achieve cytotoxic concentrations in brain neoplasias.

Another essential point to realize before considering the results achieved by chemotherapy in BM is that the criteria used for treatment evaluation may not be adequate. As previously seen, survival in patients with BM is not related *only* to progression of brain lesions. Neither the regression of BM size, as documented by CT or MRI scans, nor the improvement of the neurological status are satisfactory criteria if corticosteroids and/or radiotherapy are given concomitantly with chemotherapy.

Despite these limitations chemotherapy has been shown to be effective against several types of BM. The most extensive study includes 100 patients with breast carcinoma of which 10 showed a complete, and 40 a partial regression of BM. The survival was 10+ months for complete, and 7 months for partial remissions, and only 1.5 months for non-responders [4]. The patients were treated with four different drug combinations including several drugs such as cyclophosphamide, methotrexate, vincristine or doxorubicin which cross poorly the blood–brain barrier [5]. These results confirm our experience with the vincristine and methotrexate combination in a limited number of patients with breast carcinoma BM [6]. In our study, BM complicating lung cancer (the majority of which were non-small cell carcinoma) did not respond. In small cell lung carcinoma, the assessment of systemic chemotherapy in the treatment of BM is made difficult by the use of concomitant prophylactic brain irradiation [7]. It is the merit of the paper by Giaccone *et al.*, published in a recent issue of the Journal [8], that it shows that VM-26 given alone is effective against BM of small cell lung carcinoma. Again, the drug used does not appear to cross readily the normal brain–blood barrier, and as in breast carcinoma BM, the survival of the responders was prolonged. Other examples of successful treatment of BM originating from much rarer, potentially chemosensitive, tumors have been also reported [9, 10].

Because local treatment consisting of radiation therapy and/or surgery are able to control BM growth in about 50% of patients, and because the control of the systemic disease is crucial in patients with BM, the use of intracarotid or intrathecal chemotherapy is less promising for the majority of patients with BM. In addition, the fact that BM are often multiple and bilateral further limits the use of intracarotid treatment. On the other hand, the diffusion of drugs from the CSF into solid tumors is poor. Therefore, intrathecal chemotherapy should be restricted at present to the treatment of meningeal carcinomatosis.

In summary

Although cranial radiation therapy and, in selected patients, surgery remain the mainstones for the control of BM growth, their effect on the median survival of patients with BM is limited because at least half of the patients so treated will die from extraneural lesions. Thus the need for an efficacious systemic chemotherapy is obvious.

Approximately 50% of BM originating from potentially chemosensitive primary tumors such as breast or lung small cell carcinomas and other less common neoplasias respond to systemic chemotherapy; a fact that is probably often underestimated when planning treatment of such cases. It should be recognized that drugs which do not readily cross the normal blood–brain barrier may be effective against BM.

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