Role of Chemotherapy on Brain Metastasis

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Abstract

Cytotoxic chemotherapy has been considered ineffective for brain metastasis, traditionally because of poor penetration across the blood-brain barrier. However, cytotoxic chemotherapy could be effective in some specific situation, e.g. macroscopic brain metastasis of chemosensitive disease, such as small cell lung cancer, germ cell tumor and breast cancer. Recently, tyrosine kinase inhibitors targeting epidermal growth factor receptor (EGFR) (gefitinib and erlotinib) or human epidermal growth factor receptor 2 (HER2) (lapatinib) have a promising activity to brain metastasis of lung cancer with activating EGFR mutations or breast cancer with HER2 overexpression. More molecular targeting agents will also be used against brain metastasis with the advance of understanding of molecular mechanism of cancer.

Cytotoxic chemotherapy has been considered to have a limited role for brain metastasis [1, 2]. Two reasons have been suggested to explain why cytotoxic chemotherapy did not achieve the control of brain metastasis. First, chemotherapeutic agents cannot penetrate effectively into brain tissue because of the blood-brain barrier. Current evidence including contrast enhancement of brain metastases showed that there is no blood-brain barrier functionally at least if the metastatic lesion is macroscopic [3, 4]. Second, the tumor which metastasized to the brain could have a resistance to chemotherapeutic agents. More complex genetic make-up of tumor cells within brain metastasis than extracranial metastasis could confer the resistance of brain metastasis to cytotoxic agents. But this hypothesis was not proven properly, and nowadays it is not accepted.

With increasing number of cancer patients who survive longer than previously and concomitant increasing incidence of brain metastasis, the need of salvage treatment modality has also increased after irradiation, and chronic toxicity of radiation has become clinicians’ concern. It provokes clinicians to try anticancer drugs against
brain metastasis to avoid irradiation or reduce radiation dose, or use drugs after irradiation.

Cytotoxics in Chemosensitive Disease

De novo chemosensitivity of the tumor is considered as the most important factor to determine the effect of chemotherapeutic agents against brain metastasis.

Small-cell lung cancer (SCLC) and germ cell tumor are well-known chemosensitive diseases, and showed a good, intracranial response to cytotoxics [5–8]. A randomized trial of SCLC included 19 patients with symptomatic brain metastasis at presentation, who were treated initially with cytotoxic chemotherapy, cyclophosphamide, vincristine and etoposide. A post-chemotherapy brain image was obtained in 14 patients, 8 of whom showed a partial response and one a complete response. The response rate was 64% (9/14) [5]. Rustin et al. [9] repeated that 13 (72%) of 18 patients with brain metastasis of choriocarcinoma were in a disease-free state after combination cytotoxic chemotherapy. Another chemosensitive disease, breast cancer, also showed a benefit from chemotherapy for brain metastasis [10, 11]. Etoposide and cisplatin combination showed 55% (12/22) of response rate, including five complete responses and seven partial responses [10]. A prospective study also showed the response rate of 38% (21/56) when etoposide and cisplatin were used as a front-line chemotherapy for the brain metastasis from breast cancer. The high response rate of the brain metastasis of chemosensitive disease confirmed the concept that de novo chemosensitivity is the most important factor determining the effect of chemotherapy against brain metastasis.

Cytotoxics in Non-Small Cell Lung Cancer

Because non-small cell lung cancer (NSCLC), breast cancer and melanoma comprise the most frequent primary sites of brain metastasis, these tumors have been frequently studied for chemotherapy against brain metastasis.

Based on good penetration through the blood-brain barrier and good tolerability, temozolomide was widely tested in brain metastasis. Temozolomide, in combination with radiotherapy, improved intracranial response [12] and progression-free survival [13] in various tumors including NSCLC with brain metastasis, but did not show single-agent, anticancer effect for NSCLC patients with brain metastasis [14]. Some reports showed a promising response rate of chemotherapy for NSCLC [11, 15]. A prospective study of etoposide and cisplatin as a first-line treatment showed a response rate of 37% [11] and another first-line treatment of vinorelbine, gemcitabine and carboplatin showed a response rate of 45% [15]. Despite some promising results of chemotherapy, the overall result of NSCLC was not consistent and inferior to that of chemosensitive disease.
Cytotoxics in Melanoma

The brain metastasis from melanoma is notorious because the brain lesion usually relates to the mortality of the patients, and at least 20% of stage IV melanoma patients develop brain metastasis, sometimes hemorrhagic metastasis [16].

Because temozolomide has a modest activity against extracranial, metastatic melanoma and a unique ability to penetrate the blood-brain barrier, this drug has been tested for brain metastasis from melanoma. A phase II study of temozolomide 200 mg/m²/day for 5 days every 28 days showed only 7% of objective response rate among 117 patients who were previously untreated [17]. Another study also showed a disappointing time to progression (median, 2 months) of temozolomide as a primary treatment [18]. Concurrent chemoradiation with temozolomide had a 10% response rate (3/31) and a median progression-free survival of 2 months [19]. Despite of attractive rationale of temozolomide for brain metastasis from melanoma, the clinical efficacy was disappointing, and this drug cannot be considered as a routine clinical practice.

Tyrosine Kinase Inhibitors

Many new classes of anticancer agents have been developed thanks to understanding the molecular basis of cancer. Small molecule inhibitors targeting epidermal growth factor receptor (EGFR) showed good antitumor activity against brain metastasis in the treatment of a special type of NSCLC. Extracranial lesions of NSCLC with some types of activating EGFR mutations respond very well to EGFR tyrosine kinase inhibitors (TKIs), gefitinib or erlotinib [20, 21]. EGFR TKIs have been tried for brain metastasis in the patients who had NSCLC with activating EGFR mutation. Brain lesions also responded well to EGFR TKIs without other treatment [22, 23]. Additionally, leptomeningeal carcinomatosis from NSCLC with activating EGFR mutations responded well to EGFR TKIs [24–26].

Lapatinib, another TKI targeting human epidermal growth factor receptor 2 (HER2), had a promising efficacy to brain metastasis from HER2 overexpressing breast cancer [27]. Similarly to EGFR TKIs, lapatinib was proven to have a clinical activity at first for extracranial metastasis of breast cancer which overexpressed HER2 [28]. Subsequently, lapatinib showed a promising efficacy to brain metastasis with HER2 expression.

Conclusion

Chemotherapy can be used in the specific subset of cancer for the management of brain metastasis. Cytotoxic chemotherapy had a substantial activity for the chemo-sensitive disease such as SCLC, breast cancer and germ cell tumor, and EGFR TKI