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Editorial

Carmustine Wafers and Intraoperative Pathological Diagnosis of Malignant Gliomas: Viewpoint of a Neurosurgeon

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Editorial

Carmustine, 3-bis (2-chloroethyl 1)-1-nitrosourea (BCNU), is a nitrosourea anti-tumor agent that has been used most frequently against malignant gliomas intravenously in the US and Europe. The clinical efficacy of carmustine has been limited due to its short half-life (about 20 minutes), the small fraction of the systemically administered dose that reaches the tumor at an effective concentration, and its associated systemic toxicities. To avoid these disadvantages, carmustine wafers (Gliadel) were developed. Carmustine wafers are biodegradable polymers that release 7.7 mg of carmustine over a few weeks directly into the tumor resection cavity in the brain. Following a phase I/II study in 1987, a phase III study in recurrent glioblastoma was performed in the US in 1989. This study showed that carmustine wafers were well tolerated and associated with a survival advantage; carmustine wafers were approved as local chemotherapy for recurrent glioblastoma in the US in 1996. Then, after a large, phase III, multicenter study, which showed that local chemotherapy with carmustine wafers offered a survival benefit to patients with newly diagnosed malignant gliomas, carmustine wafers were additionally approved for newly diagnosed malignant gliomas in the US in 2003 [1]. In Japan, carmustine wafers were also approved as local chemotherapy for newly diagnosed and recurrent malignant gliomas in September 2012, and since then have been widely used in neurosurgical clinics.

So far, Intraoperative Pathological Diagnosis (IOPD) has been recognized to play an important role as an intraoperative neuro-pathological procedure in brain tumor surgery in many hospitals. IOPD is useful not only for diagnosis of histological tumor type and malignancy grade, but also for making decisions regarding the extent of tumor resection. When carmustine wafers are used, IOPD is mandatory to confirm that the tumor is a malignant glioma, so the role of IOPD is becoming increasingly more important. Previously, the diagnostic accuracy of IOPD has been reported to be 94.0% to 95.6% for all brain tumor cases [2,3]. Ishikawa et al. [4] recently reported that the diagnostic accuracy of IOPD for histological tumor type was 98.5% in all glioma cases and 98.0% in non-glioma brain tumors. These researchers also reported that with regard to the diagnostic accuracy of malignancy grade, more than 98% of tumors diagnosed as WHO grade III/IV during IOPD were subsequently diagnosed as WHO grade III/IV at permanent diagnosis using paraffin sections; however, only 54.5% of tumors diagnosed as WHO grade II during IOPD were diagnosed as WHO grade III/IV at permanent diagnosis using paraffin sections [4]. These results show that attention should be paid to the underestimation of malignancy grade when utilizing IOPD. At the time of carmustine wafer placement, the greatest concern during IOPD is confirming that the tumor is a WHO grade III/IV malignant glioma. Differential diagnosis for malignant lymphoma, metastatic brain tumors, radiation necrosis, and acute inflammatory demyelination, including tumefactive demyelinating lesion, which mimics malignant gliomas neuroradiological, is always essential. In cases without typical histological features of glioblastoma, anaplastic astrocytoma, and anaplastic oligodendroglioma in small surgical specimens, it is difficult to histologically distinguish WHO grade II tumors from WHO grade III/IV tumors. The recent adoption of positron emission tomography and advanced magnetic resonance imaging modalities, including diffusion-weighted imaging, apparent diffusion coefficient mapping, and magnetic resonance spectroscopy, makes it feasible to better understand the biological characteristics of brain tumors, and these neuro imaging techniques should not only lead to precise histological tumor type detection, but also provide information regarding malignancy grade prior to surgery. As mentioned above, it is difficult even for expert pathologists to correctly diagnose histological type and malignancy grade of brain tumors during IOPD using small, frozen surgical specimens. Taking this viewpoint into account, neurosurgeons should consider providing surgical specimens that are as large as possible for IOPD, which are obtained from surgical fields with a high probability of tumors, and information from preoperative neuro imaging of the tumors should be given to pathologists to ensure a correct pathological diagnosis.

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