Clinical study

The application of 5-bromodeoxyuridine in the management of CNS tumors

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Summary

A variety of clinical reports have described the application of the bromodeoxyuridine labeling index as an adjunct to conventional pathological examination of CNS tumors. This index has proven useful in predicting the clinical outcome associated with many such tumors. Furthermore, because of its efficacy as a radiosensitizing agent, bromodeoxyuridine (and the closely related iododeoxyuridine) has been used in combination with radiation therapy for malignant glial neoplasms, with some encouraging results. Although most studies suggest that bromodeoxyuridine is safe, there is evidence that this compound does have potential side-effects, including the observation that it is a mutagen and carcinogen in some experimental systems. A number of new alternative approaches for predicting the clinical outcome of CNS tumors has been developed based on an increased understanding of their molecular biology. However, until such approaches are better characterized, the clinical application of bromodeoxyuridine will continue to play an important role in predicting the clinical behavior of many CNS tumors.

Introduction

To better predict the biological behavior and clinical outcome of CNS tumors, a number of methods have been developed as adjuncts to pathological examination of tissue specimens. Of these methods, perhaps the most studied and accepted at this time is the bromodeoxyuridine (B UdR) labeling index, having replaced the application of tritiated thymidine labeling studies. Based on the neurological literature alone, thousands of patients have had studies performed using preoperative administration of B UdR and subsequent analysis of the B UdR labeling index. Bromodeoxyuridine is a DNA base analog, replacing the methyl group of thymidine with the bromide ion. Because of its structural similarity to thymidine, it is incorporated into DNA during replication, and thus its labeling of cells is proportional to DNA synthesis during the S phase of the cell cycle. In turn, tissues with a high mitotic and replication rate have a high labeling index.

A breakthrough occurred in 1982 when a monoclonal antibody directed against 5-bromodeoxyuridine was developed by H.G. Gratzner, allowing immunohistochemical staining of cells which have incorporated this compound into their DNA during replication. Based on this technique, accurate measurement of the labeling index in pathological tissue samples may be made. Thus, over the past decade, many studies have focused on the basic science and clinical research applications of this technology for a variety of CNS tumors. Furthermore, the significant photosensitivity and radiosensitivity of B UdR incorporated within DNA has led to its application in postoperative radiation therapy and intraoperative ultraviolet tumor bed phototherapy.

In neurosurgical practice, the virtual abandonment of tritiated thymidine labeling in favor of the
application of BUdR is based on a number of reasons. As a radionuclide, use of tritiated thymidine is fraught with hazard [3], not the least of which is significant patient resistance to receiving a radioactive compound. It is expensive and cumbersome, requiring strict adherence to complicated protocols. Studies suggest the accuracy and reproducibility of results with tritiated thymidine are inferior to those seen with BUdR [1-3, 12, 44, 45]. BUdR has been reported by many authors to be safe, with minimal side effects at the doses used, and efficacious, with a significant predictive value for the biological behavior of tumors.

Unfortunately, there exist a number of concerns about BUdR; perhaps the most relevant is that bromodeoxyuridine is a mutagen and a carcinogen [4, 5, 46-64]. As new alternative approaches towards defining the index of cells undergoing division in pathological specimens continue to develop, they may supplant the BUdR based method in certain patients. Furthermore, additional approaches directed towards identifying genetic fingerprints of tumors may reveal their biological behavior better than the mitotic index alone.

**Approaches for BUdR labeling indices**

Two approaches have been developed for BUdR labeling indices. The first is to simply evaluate BUdR uptake in vitro, in tissue sections derived from operative tumor specimens. However, most studies have used the second approach, based on directly introducing the compound into the blood of a patient for a limited preoperative time period, ranging from at the outset of the case to three days of injections every eight hours preoperatively. The doses range from 200 to 600 mg/m²; studies suggest that with these doses, the systemic venous concentrations are less than 1.25 μM [3, 6, 20, 24, 65, 66]. The route of administration of BUdR is somewhat controversial, being either intravenous or intrarterial (via the internal carotid artery). Although the majority of clinical studies have used intravenous administration, arguments exist in support of the intra-arterial route [3, 66]. Included among these are the observation that up to 80% of BUdR is debrominated and further metabolized by the liver with the intravenous route [9], rendering its intracranial concentration less effective; the intraarterial approach led to a 11–16 fold higher concentration than with the same dose infused intravenously and reduced the systemic exposure to the compound [3, 60]. A critical argument against the intrarterial route is the observation of increased side effects, including ocular problems such as conjunctivitis and keratitis, probably due to the effective increase in concentration [33, 67].

Once the tumor is excised or a biopsy is obtained in the operating room, the tissue is fixed, dehydrated in chilled 70% ethanol, embedded in paraffin, cut into microsections, and then deparaffinized. Using immunohistochemical techniques with the anti-BUdR antibody, in representative microscopic fields, the ratio of cells with immunostaining to total cells scored is tabulated and termed the ‘labeling index’.

**Clinical application of BUdR labeling index**

The BUdR-labeling index has proven useful in a number of clinical trials. In a variety of CNS tumors, histological and ultrastructural analysis of tissue samples frequently provides suboptimal information about the biological behavior of the tumor, and hence its clinical outcome [68]. This is particularly true of meningiomas and gliomas, and the bulk of clinical trials using bromodeoxyuridine have focused on these two tumor types. In one study, twelve patients with meningiomas had preoperative BUdR labeling; six of the resected tumors were recurrent meningiomas. Of these, four had labeling indices greater than 1.5%, whereas all six of the nonrecurrent tumors had labeling indices less than 1% [14]. In an early study of 20 patients, 6 out of the 9 tumors with a labeling index greater than 1 were recurrent meningiomas. Of these, four had labeling indices greater than 1.5%, whereas all six of the nonrecurrent tumors had labeling indices less than 1% [14]. In an early study of 20 patients, 6 out of the 9 tumors with a labeling index greater than 1 were recurrent tumors [16]. In another series of 96 patients, meningiomas were resected and analyzed. In all of the patients whose tumors had a labeling index greater than 5%, the meningiomas recurred. Yet only 44% of the tumors recurred when the index was 1% to 5%, and only 6% recurred when the index was less than 1% [21]. Another reported se-