Treatment of Metastatic Brain Tumors with the Combination of 1-Methyl-1-Nitrosourea (MNU) and Cyclophosphamide

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Die Behandlung von Hirnmetastasen mit einer Kombination von MNU und Cyclophosphamid


Schlüsselwörter: Hirnmetastasen – MNU – Cyclophosphamid

Summary. The combination of MNU and cyclophosphamide was applied in 29 consecutive previously untreated patients with metastatic brain tumors. An objective regression of the metastatic process in the brain, with seven complete and seven partial remission, was observed in 14 out of 29 patients (48%). In three patients the disease was stable, and in 12 it progressed in spite of treatment. The objective parameters used in monitoring the effect of therapy included brain scintiscan, computerized brain tomography and neurological clinical status. Median remission duration was 11.2 months in complete responders, and 5.6 months in partial responders. Median survival was also the longest in complete responders (15.7 months). The median survival of non-responding patients was only 3.1 months.

Key words: Metastatic brain tumors – MNU – Cyclophosphamide
Metastatic brain tumors are often due to tumor dissemination, particularly in cases of primary breast and lung cancer, and melanoma and hypernephroma. Surgical therapy is occasionally applied in cases of solitary brain metastases; more often, however, such patients are irradiated. Considering that solitary metastases in the brain are relatively rare, the metastatic process being multifocal in most cases, a recent treatment mode involves chemotherapy. It is known that tumorigenic processes in the brain are mainly affected by nitrosourea derivatives (BCNU, CCNU, MeCCNU, MNU), i.e., liposoluble substances which cross the blood-brain barrier. Except for these cytostatic agents, only Procarbazine has been shown to have an antitumor effect in expansive malignant processes in the brain (Grunberg 1970; Gutin 1975).

When applied to experimentally induced animal tumors, 1-methyl-1-nitrosourea (MNU) has shown pronounced organotropy to the CNS, manifested by a marked antitumor activity in lower doses (Ivankovic 1974; Bossi 1975) and by a cancerogenic effect in very high doses (Druckrey 1965; Jänisch 1967; Schmäihl 1978). Moreover, recent studies reported by Ivankovic (1974) have shown the MNU-cyclophosphamide combination to be very successful in the treatment of L-5222 in rats, with an almost total cure rate. This is important because this type of experimentally induced leukemia in rats is localized not only in the bone marrow and other organs but mainly in the CNS. When we have performed Phase II clinical trial with this cytostatic drug combination in metastatic solid tumors (1977), and later in metastatic melanoma, we have also observed a marked antitumorigenic effect on brain metastases. This led us to undertake a special trial with the MNU-cyclophosphamide combination in patients with metastatic brain tumors, the results of which are presented below.

Patients and Methods

All the patients with a clinically proved diagnosis of brain metastases of a malignant tumor, who had not previously been treated with cytostatic agents or irradiation, were consecutively entered in the trial. In all patients the primary malignant process was verified pathohistologically. In all patients a clinical neurological examination, brain scintiscan, and EEG were applied as a diagnostic procedure; a computerized brain tomography was also performed in more than half of the patients. Examinations of the fundus oculi were also mandatory; another diagnostic method applied in about two-thirds of the patients was cerebral angiography. The same examinations were also used as objective parameters in monitoring the antitumorigenic effect of the MNU-cyclophosphamide combination. Because of this some examinations were repeated every 3 months (CT), and the brain scintiscan, neurological examinations and EEG were mandatorily repeated every 6 weeks.

Thirty-two patients with brain metastases, 12 women, and 20 men aged 19-68 (average 47 years), were entered in the trial. Treatment results were evaluated in 29 patients because three patients were lost for follow-up. The primary tumors included nine carcinomas of the breast, 10 melanomas, seven lung carcinomas (microcellular type), one seminoma, one carcinoma of the esophagus, and one adenocarcinoma of the parotid gland.

The chemotherapy schedule (Table 1) consisted of 6-day cycles, with i.v. administration of 4 mg/kg of MNU1 on the 1st, 3rd, and 5th day, and i.m. or i.v. administration of 6 mg/kg of cyclophosphamide on the 2nd, 4th, and 6th day. A 3-week rest period was applied between cycles. In the case of leukocyte (L) <2,500 and thrombocyte (Tr) <100,000 the next cycle was postponed until blood count normalization. All toxic side effects were regularly monitored during therapy. Only patients who received at least two chemotherapy cycles were evaluated. Therapy was continued as long as patients showed signs of tumor regression or stable disease signs. No corticosteroids were administered during chemotherapy.

1 MNU was supplied by Deutsches Krebsforschungszentrum – Heidelberg