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Lecture: fotemustine in brain tumors

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Abstract Fotemustine (FTMS) is a third-generation nitrosourea, in preclinical studies, FTMS compared favorably with carmustine (BCNU) and lomustine (CCNU) against several human tumor cell lines. In conventional schedule, FTMS is administered at a dose of 100 mg/sqm/week for three consecutive weeks as induction (I) treatment, followed by 100 mg/sqm every three weeks, after a 5-week rest, as maintenance (M). Several Italian groups reported the results using FTMS in malignant glioma patients recurring after temozolomide standard treatment. In these papers, the 6-progression free survival are ranging from 20 to 52%. With the schedule (I + M) myelosuppression is observed in more than 30% of patients, and thrombocytopenia and leukopenia are more frequent and significant in Temozolomide pretreated patients. On the bases of the hematological toxicities several authors experimented new schedules of FTMS administrated at low doses. Recently, some authors reported the interesting results of a multicenter study on recurrent glioblastoma multiforme patients combining FTMS with new antiangiogentic agent bevacizumab.

Keywords Fotemustine · Nitrosourea · Alkilating agents · Glioblastoma recurrent

Fotemustine (FTMS) is a third-generation nitrosourea characterized by a phosphoalanine carrier group grafted onto the nitrosourea radical. This structure improves penetration through the cell membrane and blood–brain barrier by using the amino acid transport system. In preclinical studies, FTMS was compared favorably with carmustine (BCNU) and lomustine (CCNU) against several human tumor cell lines [1].

Adult Phase I clinical studies showed that the maximum tolerated dose (MTD) was 100 mg/sqm/week with a dose-limiting toxicity (DLT) of thrombocytopenia [2]. In conventional schedule FTMS is administered at a dose of 100 mg/sqm/week for three consecutive weeks as induction (I) treatment, followed by 100 mg/sqm every 3 weeks, after a 5-week rest, as maintenance (M). The schedule was studied in 38 adults with recurrent malignant gliomas [3]. An objective response rate of 26% was achieved and 47% of patients had stabilization of disease. In another Phase II study involving 22 patients with high-grade cerebral glioma, [4] an 18% objective response rate was achieved and 32% of patients had stable disease (SD).

More recently several Italian groups studied the use of FTMS in malignant glioma patients recurring after temozolomide standard treatment. In these papers, more homogeneous as tumor histology and first line treatments, the 6-progression free survival (PFS) ranging from the 20% reported by GICNO [5] and the best result of 48 and 52% reported, respectively by Scoccianti [6] and Fabrini [7]. In these papers, the disease control rate [stable disease (SD) + partial response (PR)] was similar ranging from 42.5 to 62. As concern the Scoccianti and Fabrini results, it could be questioned if the very high rate of 6-PFS observed could be due to the inclusion in the study of some patients experiencing a pseudoprogression rather than a disease recurrence. With the standard schedule (I + M) myelosuppression was the most common adverse event that occurred, mainly during the induction phase of treatment. It is observed in more than 30% of patients, and thrombocytopenia and leukopenia are more frequent and significant in Temozolomide pretreated patients.

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On the bases of the difficulties to manage the hematological toxicities several authors performed clinical trials enrolling recurrent glioblastoma multiforme (GBM) (after Stupp schedule), in order to assess both efficacy and the safety profile of new schedules of FTMS administrated at low doses. In 2009 Fabi et al. [8] treated 40 patients with recurrent pretreated malignant gliomas with FTMS at doses ranging from 65 to 100 mg/sqm. The 20% of patients responded to treatment, for a disease control rate (responses plus stabilizations) of 47.5%. The authors concluded that the low-dose fotemustine at 65–75 mg/sqm (I) followed by 75–85 mg/sqm (M) has an activity comparable to that of the conventional schedule. Grade three and four thrombocytopenia and neutropenia occurred in 20 and 15% patients, respectively. But they were only observed in group of patients treated at 100 mg/sqm.

A very interesting experience was reported by Addeo et al. [9]. In these series FTMS was administered at dose of 80 mg/sqm every 2 weeks for five consecutive administrations (I), and then every 3 weeks at 100 mg/sqm as maintenance. All 40 patients completed the induction phase, the main toxicities were hematologic but grade three thrombocytopenia was observed in only two cases. In these series 1 CR, 9 PR, and 16 SD were reported. PFS-6 was 61%. However, also in this case the favorable data could be, at least in part, interpreted on the basis of "pseudoprogression" occurrence that could overestimate the results.

The importance of MGMT in clinical resistance to alkylating agents has been shown in human studies that exhibited inverse correlations between MGMT activity and survival rates for patients treated with nitrosourea or TMZ. Several authors looking for the modulation of MGMT activity by dacarbazine, procarbazine or temozolomide pre-treatment before the administration of FTMS. Fazeny-Doerner et al. [10] reported the results of fotemustine (100 mg/sqm)–dacarbazine (200 mg/sqm) combination in recurrent glioblastoma. One PR (3%) lasting for 11 weeks was observed. A total of 16 (52%) patients reached SD lasting between 7 and 94 weeks. Median time to progression was 17 (3–101) weeks for all patients. Also, in this study the major toxicity was myelosuppression resulting in exclusion from the study for 23% of the patients.

In 2008, Silvani et al. [11] evaluated safety and efficacy of Procarbazine (PCB) and FTM combination. In these series PCB was administered as an oral dosage of 450 mg on days 1 and 2 and a total dose of 300 mg on day 3. FTM was administered on day 3, 3 h after the last PCB intake at a dose of 110 mg/sqm. The treatment was repeated every 5 weeks. The 11.2% of patients responded to treatment. The median PFS was 19.3 weeks and PFS-6 was 26.7%. Hematologic toxicity grade one was observed in 42 cycles (26.5%), grade two in 11 cycles (6.85%), grade three and four only in 4 cycles (2.5%).

In Fazeny-Doerner and Silvani series the lower observed efficacy, considered in terms of response rate, could be probably due to the different design of schedules that avoided the induction phase of standard treatment. However, in Silvani series the toxicities were limited and the results in term of 6 PFS are not dissimilar to the results reported by GINCO group with standard schedule.

Recently Gaviani et al. [12] reported the result of a study combining Temozolomide and FTM. In this study Temozolomide was administered as oral dosage of 90- 110 mg/sqm for 7 consecutive days every 15 days. At the end of the second week of Temozolomide treatment the FTMS was administered at a dose of 110 mg/sqm. Unfortunately, the study was prematurely stopped for the relevant hematological toxicities.

At the ASCO meeting of 2011, Soffietti et al. [13] reported the results of a multicenter, phase II study on 54 GBM recurrent patients combining FTMS with new anti-angiogentic agent bevacizumab (BVZ). The treatment consisted of an induction phase with BVZ at 10 mg/kg on day 1 and 15 and FTM at 75 mg/sqm on day 1 and 8, followed after 3 week interval by a maintenance phase with BVZ at 10 mg/kg i.v. and FTMS 75 mg/sqm every 3 weeks. The 6-PFS, 12-PFS and mPFS were 44%, 21% and 5.29 months, respectively. mOS was 9.13 months with 77.4% and 31% of patients surviving at 6 and 12 months, respectively. Response rates were: 2 CR (4%), 24 PR (44%), 22 SD (41%) and 6 PD (11%). The authors reported a significant neurological improvement in 57% of patients, with a reduced or interrupted steroids in 64%. The toxicities were mild the 22% of the patients with grade 3/4 piastrinopenia/leukopenia discontinued FTMS, whereas the 7.4% discontinued BVZ.

Conflict of interest The authors declare that there is no conflict of interest related to the publication of this article.

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