**RESEARCH TOPIC MEM12**

# Investigating blood pharmacokinetics proprieties, cerebrospinal fluid penetration and brain tissue distribution of Niraparib combined to temozolomide in patients with recurrent malignant gliomas

**Curriculum MEM Clinical**


**Clinical Unit name and address**
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**Abstract**
Malignant gliomas are the most common central nervous system tumors in adults, with poor prognosis and few treatment options. PARP inhibitors showed synergy with temozolomide (TMZ), amplifying DNA damages and antitumor effects. Among them, Niraparib has peculiar pharmacokinetics proprieties (higher volume of distribution and blood-brain barrier penetration), representing an ideal candidate to combine with TMZ for treating gliomas. However, first studies on this combination reported impressive hematological toxicities. For the high volume of distribution of Niraparib and the recovery in MGMT activity described for TMZ given on alternate weeks, different schedules and doses of both may improve tolerability without compromising anticancer activity. This phase I/II study explores safety, pharmacokinetics proprieties (blood, liquor, tumour tissue) and preliminary activity of Niraparib e TMZ "one week ON, one week OFF" in patients with recurrent glioblastoma or IDH mutant lower-grade (WHO GII-III) astrocytomas. For both drugs, measures in plasma and liquor will be performed by liquid-chromatography coupled with electro-spray ionization tandem mass spectrometry or UV detection, meanwhile mass spectrometry imaging will be used to evaluate concentration and distribution in tumor tissue.


**Main technical approaches**
The PhD candidate will be a postgraduate medical doctor specialized in medical oncology. His/her task will be focused on: evaluation and inclusion of patients in the clinical study;

drug administration in the clinical study; monitoring and managing adverse events related to experimental drugs; handling, using and storage of blood, cerebrospinal fluid and tissue samples; use of liquid-chromatography coupled with electro-spray ionization tandem mass spectrometry (HPLC-MS/MS) or UV detection for blood and cerebrospinal fluid samples; use of mass spectrometry imaging for tumor samples.

**Scientific references**

1. Tolcher AW, Gerson SL, Denis L, et al. Marked inactivation of O6-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules. Br J Cancer. 2003;88(7):1004-1011.
2. Sun K, Mikule K, Wang Z, et al. A comparative pharmacokinetic study of PARP inhibitors demonstrates favorable properties for niraparib efficacy in preclinical tumor models. Oncotarget. 2018;9(98):37080-37096.
3. Persico P, Lorenzi E, Losurdo A, et al. Precision Oncology in Lower-Grade Gliomas: Promises and Pitfalls of Therapeutic Strategies Targeting IDH-Mutations. Cancers (Basel). 2022;14(5):1125. Published 2022 Feb 22.
4. van Andel L, Zhang Z, Lu S, et al. Liquid chromatography-tandem mass spectrometry assay for the quantification of niraparib and its metabolite M1 in human plasma and urine. J Chromatogr B Analyt Technol Biomed Life Sci. 2017;1040:14-21.
5. Morosi L, Matteo C, Ceruti T, et al. Quantitative determination of niraparib and olaparib tumor distribution by mass spectrometry imaging. Int J Biol Sci. 2020;16(8):1363-1375. Published 2020 Feb 21.

**Type of contract**

Contract for continuative and coordinated service of at least € 26.000 activated Istituto Clinico Humanitas. This sum is subject to IRPEF income tax.

Contratto collaborazione coordinata e continuativa (cococo) pari ad almeno € 26.000 annui lordi attivato da Istituto Clinico Humanitas. Importo soggetto a tassazione IRPEF.



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