A real-world study on the use of machine learning to identify a germline signature of the best responders for CW treatment in GG4 gliomas

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Introduction

Glioma grade 4 (GG4) are the most common and aggressive primary tumours of the central nervous system[1–3]. Maximal safe resection followed by combination temozolomide (TMZ) chemotherapy and radiotherapy (RT) (TMZ/RT) is the most effective adjuvant treatment to increase survival[4,5] . Most GBMs recur close to the primary surgical site. Therefore, chemotherapy applied directly to the surgical site is a salvageable treatment option for recurrent and primary malignant gliomas.

Carmustine wafers (CWS) are biodegradable copolymers disc impregnated with the alkylating agent used as local chemotherapy[6–8]. The local application of this drug aims to provide a therapeutic bridge between the surgery and the start of the adjuvant oncological treatment, while minimising the risk of systemic complications[8,9].

After an initial promising success, CW implantation in HGG has been gradually abandoned in daily clinical practise for several reasons althought studies and meta-analyses have shown a positive effect of CW implantation on OS [8]

CW implantation likely increases the risk of postoperative adverse events, including surgical-site infections, with nonetheless variable reported rates in the literature [10,11].

The discovery of molecular biomarkers for predicting patient's survival is an essential step toward improving prognosis and therapeutic decision-making such as the CW implantation in the treatment of GG4.

AIMS

To better evaluate the possibility to reconsider the use CW wafer we need to improve our knowledge on the genomic mechanism of resistance and efficacy. In this context we evaluated the possibility to create a germline mutation signature to identify patient benefit of CW treatment.

Methods

The study included 108 patients who underwent a surgical resection of a newly diagnosed GG4 at the Neurosurgery Department of Udine Hospital between 2014 and 2019. Median age of diagnosis was 60 years. After surgery, all patients were treated with combinations of concomitant adjuvant radiotherapy and chemotherapy, followed by adjuvant chemotherapy, as recommended by Stupp. Treatment with CW was applied in 39 out of 108 GG4 cases.

By next-generation sequencing using a panel of 523 genes, we performed analysis selecting only SNV variants with high genomic quality.

By using RAINFOREST [12] to stratify the patients according to their overall survival and genomic information, we developed a pharmacogenomics model to detect patients having best benefits from the CW application.

Results

The median age of the 108 patients included in the study was 60 years (52-69) where 36 % (N=39) were treated by CW. The mean extend of resection (EOR) was 98 % (95-100%). 9.3% of patients had an IDH1 mutation and 62 % have a mgmt promoter methylated status. The patients who underwent to CW treatment were characterized by a precentral localization in 16 cases (41%) , postcentral localization in 10 cases (26 %) and temporoinsular localization in 13 cases (33%).
By Cox univariate analysis CW treatment resulted as a protective variable (HR=0.62 (0.41-0.93) pvalue=0.022).
Patients were sequenced by a panel-based approach in 523 genes. After primary analysis we selected only the germline SNV variant sequenced in all the cohort with high quality of genomic and coverage above 50 X. Then, we created a genotype matrix and we applyied the RAINFOREST(RFF) algorithm by using overall survival. From 844 SNV obtained by sequencing after hard-filtering we obtain only 65 snps to use for RFF : For each case, RFF requires treatment information, survival data and SNPS data to report foreach decision tree the class “benefit” and “non benefit”.
By applying the rainforest method in our 108 case we trained and validated its performance in a 3-fold cross validation. In this context we found 4 type of group of patients: 1) patients with improved survival treated by CW, 2) patients treated with CW but without benefit,3) patients not treated by CW and with benefit and 4) patients not treated with but showing benefit. To better define the germline features that help to stratify the cases we chose to concentrate on the patients treated by CW with a benefit by applying the RFF model. In this context 54 % of cases treated with CW were selected (HR 0.52 (0.31-0.85) p=0.010).
The significant SNV variant associated at this category of patients treated with CW and showing benefitwere associated with the pathway of negative regulation of intrinsic apoptotic signaling pathway correspond to genes like MDM2, ETV1, ROS, BCOR, KDM5A.

Conclusion

By applying a sequence panel and focusing on germline profile we developed a genomic signature that allow to identify patients showing benefit by treatment with CW wafer.

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