Real world experience of next generation sequencing-based, genomics-guided therapy for neuro-oncology patients in Hong Kong

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Objective:
For patients with advanced neuro-oncological conditions, conventional therapeutic options are limited. The development of next generation sequencing (NGS)-based genomic analysis has enabled identification of druggable targets of somatic mutations for these rare diseases. This case series reviewed the efficacy of NGS-based, genomics-guided therapy in a local neuro-oncology centre.

Method:
From May 2017 to Aug 2019, NGS panels were arranged for 33 neuro-oncology patients. All patients had exhausted conventional oncological treatments or received NGS panels for clinical trial screening. Targeted deep NGS was used to assess the mutational status, single nucleotide variants, small insertions and deletions and copy number variants of 440 cancer-related genes.

Patient Characteristics by Disease:

Table 1. Clinical data summary for patients (N = 33)

Characteristic	Number of patients (N)
Gender	
Male	15 (45.5%)
Female	18 (54.5%)
Type of tumour by histological diagnosis	
Glioma	24 (72.7%)
Glioblastoma multiforme	21 (63.6%)
Anaplastic oligodendroglioma	3 (9.1%)
Non-glioma	5 (15.15%)
Chordoma	3 (9.1%)
Metastatic atypical choroid plexus papilloma	1 (3%)
Atypical meningioma	1 (3%)
Brain metastasis	4 (12.1%)
Prostate cancer	1 (3%)
Breast cancer	1 (3%)
Dermatofibrosarcoma protuberans	1 (3%)
Cholangiocarcinoma	1 (3%)
Age (years)	
Median (range)	53 (28-83)
Median age by tumour type (range)	
Glioma	53 (23-67)
Non-glioma	58 (27-80)
Brain metastasis	50 (30-84)
Setting for NGS panel request	
1st line	10 (30.3%)
2nd line	23 (69.7%)

The diagnoses of the 33 patients were GBM (n=21), high grade glioma (n=3), brain metastases (n=4), chordoma (n=3), atypical choroid plexus papilloma (n=1) and meningioma (n=1). 10 received NGS for 1st line systemic treatment and 23 for 2nd line or beyond. In most of the patients (32/33.97%), NGS panel identified at least one druggable target, ranging from 0-6 with a median of 3.

Treatment Given:

Based on the NGS reports, 21 patients were given genomics-guided therapy (65.6%), with their respective treatments shown as follows.

Table 2. Treatment summary

Patient Number	Disease	Mutation	Treatment received
1	Glioblastoma multiforme	PTEN, BRCA2 deletion*	Olaparib
2	Glioblastoma multiforme	ATM mutation, BRCA2 deletion, IDH1 mutation*	Olaparib, bevacizumab, carboplatin
3	Glioblastoma multiforme	FGFR mutation	Dabrafenib, trametinib
4	Glioblastoma multiforme	PTEN deletion*	Olaparib, bevacizumab, carboplatin
5	Glioblastoma multiforme	FGFR mutation	Dabrafenib, trametinib
6	Glioblastoma multiforme	FGFR mutation	Dabrafenib, trametinib
7	Glioblastoma multiforme	CDKN2A deletion/CD4 amplification	Palbociclib, bevacizumab
8	Glioblastoma multiforme	FGFR mutation	Vemurafenib, cabozantinib
9	Glioblastoma multiforme	FGFR mutation	Dabrafenib
10	Glioblastoma multiforme	High tumour mutation burden (~108)	Nivolumab
11	Glioblastoma multiforme	PTEN, BRCA2 deletion*	Olaparib, temozolomide
12	Glioblastoma multiforme	CDKN2A deletion/CD4 amplification	Ribociclib
13	Anaplastic Oligodendroglioma	IDH1, M1H1 mutation*	Olaparib, temozolomide
14	Anaplastic Oligodendroglioma	IDH1 mutation*	Olaparib, bevacizumab, carboplatin
15	Anaplastic Oligodendroglioma	IDH1 mutation*	Olaparib, bevacizumab, carboplatin
16	Atypical choroid plexus papilloma	TP53 mutation*	Bevacizumab, carboplatin
17	Metastatic prostatic cancer	ATM mutation, PTEN deletion*	Olaparib
18	Chordoma	CDKN2A deletion/CD4 amplification	Palbociclib
19	Metastatic cholangiocarcinoma	PTEN, BRCA2 deletion	Olaparib, temozolomide
20	Metastatic breast cancer	FGFR mutation*	Everolimus, pazopanib
21	Atypical meningioma	PTEN deletion*	Rucaparib

*DNA damage repair deficiency

For the 12 patients who did not receive genomics-guided treatment, one had no druggable target identified, eight were still stable on standard therapies, one left Hong Kong and the last one was too weak when NGS report was available.

Results:

For best response achieved, the number of patients with complete response (n=1), partial response (n=7) or stable disease (n=6) was 14 out of 21 (67%). The genomics-guided treatments were relatively well-tolerated with two grade 3 (skin rash, pancytopenia requiring transfusion) and one grade 5 complication (fatal neutropenic fever).

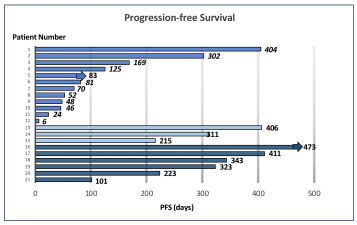

Figure 1.
PFS data for patients who received NGS-guided treatment in this study.
Patients with PFS in *italics* have passed away.
Arrows indicate patients who are still currently undergoing treatment.

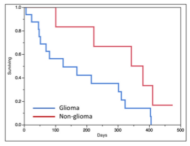

Figure 2.
Survival curve for patients who received NGS-guided treatment.
The median progression-free survival (PFS) was 215 days [95% confident interval (CI): 70-323 days]. For GBM/high grade glioma patients, median PFS was 125 days [95% CI: 48-311] and six-month PFS was 42%. For non-glioma patients, median PFS was 362 days [95% CI: 101-not reached].

Conclusion:
Early application of NGS-based genomics guided therapy for selected, advanced neuro-oncological patients yielded promising clinical efficacy and satisfactory safety profile. It holds potential to meet unmet clinical needs and should be further examined in clinical trial settings.

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