Systematic analysis of overall survival and interactions between tumor mutations and drug treatment

Francesco Gatto and Jens Nielsen*

Abstract

Background: Few exceptional responses in cancer treatment were attributed to a genetic predisposition of the tumor.

Methods: We analyzed a cohort of 3105 patients from 12 different cancer types and systematically sought the existence of a correlation between overall survival and the interaction of 21 antineoplastic treatments with 6 tumor mutations.

Results: We identified a single significant correlation resulting in increased overall survival from temozolomide in lower-grade glioma with IDH1 R132H mutations. The trend could not be attributed to either the treatment or the mutation alone. Univariate and multivariate Cox regression demonstrated that this interaction stood as an independent prognostic predictor of survival.

Conclusion: Our results suggest infrequent instances of exceptional responses ascribable to tumor genomics yet corroborate the existence of an interaction of temozolomide with IDH1 mutations in lower-grade glioma.

Keywords: Cancer genomics, Exceptional response, Large-scale data analysis, Systems biology, Lower-grade glioma

Findings

The cancer genome can elicit sensitivity to certain drugs not specifically designed to target the underlying genetic aberrations. To this end, genomic markers of drug sensitivity have been systematically assessed in cancer cell lines [1, 2]. Ideally, these markers can identify patients who may better benefit from a certain antineoplastic drug [3, 4]. In contrast to the increasing availability of data about genomics of drug sensitivity in vitro [5], the association with improved patient survival is so far limited to few clinical cases, e.g., exceptional responses to everolimus in bladder cancers with TSC1 mutations [6].

Here, we sought to systematically assess if the chances of overall survival in patients with a certain cancer type and treated with a given antineoplastic drug correlate with the presence of a certain genetic mutation in the tumor. The examined cohort comprised 3105 patients, spanning 12 cancer types (with 81–731 samples for each cancer type). Collectively, 21 antineoplastic drugs were administered each in at least 20 patients (median 82; IQR 29–150). Six cancer-associated mutations were detected in at least 20 patients in this cohort: V600E in BRAF (n = 29), R132H in IDH1 (n = 108), G12V in KRAS (n = 49), H1047R in PIK3CA (n = 89), R175H in TP53 (n = 45), and V777 deletion in ZFHX3 (n = 22). After binning samples by cancer type, out of 1512 potential associations, 9 associations between overall survival, drug treatment, and tumor mutation had sufficient sample size for each covariate and were hereby tested. The hazard ratio (HR) for each interaction between drug treatment and tumor mutation in a cancer type was estimated in a multivariate analysis using a nested Cox proportional hazard regression model.
adopted a likelihood ratio test to test whether there is a significant effect of the interaction on overall survival on top of the tumor mutation and administered drug alone (Additional file 1: Table S1).

We observed a significant effect only in one scenario, the interaction between temozolomide (TMZ) and R132H mutations in \textit{IDH1} on the overall survival of lower-grade glioma (LGG) (likelihood ratio test \( p = 0.026 \)). This test suggests that the correlation with survival is specific to the interaction between TMZ and R132H mutations in \textit{IDH1} and not associated with the drug treatment or the mutation per se, as demonstrated by the Kaplan-Meier curves generated for patients stratified upon these features (log-rank test \( p = 0.047 \), Fig. 1). The median overall survival for patients with the interaction was 95 months (95 \% CI, 63—N.E.) and for patients without the interaction was 62 months (95 \% CI, 49—87).

We detected a significant prognostic value for the interaction using a univariate Cox proportional hazard regression model \( (p = 0.016, \text{Table 1}) \). However, the interaction violated the proportional hazard assumption and showed a time-dependent effect. The univariate analysis was also run on validated prognostic factors in LGG [7] and additional clinical features (Table 1). A multivariate analysis based on significant factors from the univariate analysis and including a time-dependent effect for the interaction revealed an independent positive correlation between the interaction and overall survival (HR \( 0.09, 95 \% \text{CI} 0.01–0.58, p = 0.012 \)), which tends to diminish over time (Additional file 1: Figure S1).

In conclusion, we identified one genomic marker of drug sensitivity that was associated with better survival in patients, in contrast to patients treated with the same drug but with no detected mutation or vice versa. Indeed, mutations in \textit{IDH1} were previously implicated with good prognosis in brain tumors treated with TMZ [8, 9]. Our results independently validate these findings and further extend the reach of this correlation beyond some previous limitations [10]. First and foremost, the cohort size allowed discerning that an increase in patient survival was exquisitely associated with the interaction between \textit{IDH1} mutations and TMZ, suggestive of a synergy between

![Fig. 1 Kaplan-Meier survival plots for patients with or without an interaction between temozolomide and R132H mutations in \textit{IDH1} in lower-grade glioma](image-url)
treatment and tumor genomics. Second, it specifically correlated with R132H mutations. Finally, we recovered a negative time-dependent effect of the interaction, which is reminiscent of emergence of drug resistance and in line with the genetic evolution of lower-grade glioma attributed to TMZ treatment [11].

Table 1: Hazard ratio (HR) for clinical factors in the overall survival of lower-grade glioma

| Factors                        | N [n death] | HR Univariate |      | p       |         | HR Multivariate |         |
|-------------------------------|-------------|---------------|------|---------|----------|-----------------|---------|
|                              |             | 95 % CI       |      |         |          | 95 % CI        |         |
| Age                           | 261         | 1.07          | 1.05–1.09 | 5e−10  | 1.07     | 1.05–1.09      | 6e−9   |
| Gender                        |             |               |     |         |          | 95 % CI        |         |
| Female                        | 117 [30]    | 1             |     |         |          | 0.88           | 0.54–1.45 | 0.620 |
| Male                          | 144 [33]    | 0.88          | 0.54–1.45 | 0.620  |          |                 |         |
| Temozolomide                  |             |               |     |         |          | 95 % CI        |         |
| No                            | 41 [24]     | 1             |     |         |          | 0.80           | 0.47–1.35 | 0.398 |
| Yes                           | 220 [39]    | 0.80          | 0.47–1.35 | 0.398  |          |                 |         |
| R132H in IDH1                 |             |               |     |         |          | 95 % CI        |         |
| Undetected                    | 166 [45]    | 1             |     |         |          | 0.74           | 0.43–1.29 | 0.292 |
| Detected                      | 95 [18]     | 0.74          | 0.43–1.29 | 0.292  |          |                 |         |
| Interaction drug-mutation     |             |               |     |         |          | 95 % CI        |         |
| Absent                        | 181 [57]    | 1             |     |         |          | 0.35           | 0.15–0.83 | 0.016 |
| Present                       | 80 [6]      | 0.35          | 0.15–0.83 | 0.016  |          | 0.09           | 0.01–0.58 | 0.012 |
| Histology                     |             |               |     |         |          | 95 % CI        |         |
| Astrocytoma                   | 107 [27]    | 1             |     |         |          | 0.67           | 0.40–1.10 | 0.112 |
| Oligoastrocytoma/oligodendroglioma | 154 [36]  | 0.67          | 0.40–1.10 | 0.112  |          |                 |         |
| Tumor grade                   |             |               |     |         |          | 95 % CI        |         |
| Grade II                      | 77 [18]     | 1             |     |         |          | 2.06           | 1.18–3.61 | 0.011 |
| Grade III                     | 184 [45]    | 2.06          | 1.18–3.61 | 0.011  |          | 1.52           | 0.85–2.71 | 0.159 |
| Laterality                    |             |               |     |         |          | 95 % CI        |         |
| N.A.                          | 1           |               |     |         |          |                 |         |
| Left                          | 131 [28]    | 1             |     |         |          | 0.34           | 0.04–2.64 | 0.304 |
| Midline                       | 5 [1]       | 0.34          | 0.04–2.64 | 0.304  |          |                 |         |
| Right                         | 123 [33]    | 0.82          | 0.49–1.37 | 0.443  |          |                 |         |
| Tumor site                    |             |               |     |         |          | 95 % CI        |         |
| N.A./other                    | 3           |               |     |         |          | 1             |         |
| Supratentorial, frontal lobe  | 160 [36]    | 1             |     |         |          |                 |         |
| Supratentorial, occipital lobe| 5 [1]       | 0.71          | 0.10–5.20 | 0.736  |          |                 |         |
| Supratentorial, parietal lobe | 23 [4]      | 0.84          | 0.30–2.38 | 0.748  |          |                 |         |
| Supratentorial, temporal lobe | 70 [21]     | 1.86          | 1.08–3.22 | 0.026  |          | 1.22           | 0.70–2.11 | 0.481 |
| Symptoms at diagnosis         |             |               |     |         |          | 95 % CI        |         |
| N.A./other                    | 19          |               |     |         |          |                 |         |
| Headaches                     | 62 [18]     | 1             |     |         |          |                 |         |
| Mental status changes         | 22 [8]      | 1.84          | 0.80–4.27 | 0.153  |          |                 |         |
| Motor/movement changes        | 22 [6]      | 1.20          | 0.47–3.06 | 0.698  |          |                 |         |
| Seizures                      | 119 [23]    | 0.58          | 0.31–1.08 | 0.087  |          |                 |         |
| Sensory changes               | 11 [2]      | 1.07          | 0.24–4.66 | 0.929  |          |                 |         |
| Visual changes                | 6 [2]       | 0.69          | 0.16–2.98 | 0.617  |          |                 |         |
Additional file

Additional file 1: Supplemental methods, figures, and tables. (PDF 138 kb)

Competing interests
The authors declare no conflict of interest in relation to the submitted work.

Authors’ contributions
FG conceived and designed the study and performed the analyses; JN supervised the study. All authors approved the manuscript in its final form.

Acknowledgements
The authors acknowledge Knut and Alice Wallenberg Foundation for financing this work.

Received: 28 January 2016 Accepted: 24 February 2016
Published online: 02 March 2016

References

1. Barretina J, Caponigro G, Stransky N, Venkatesan K, Margolin AA, Kim S, et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity (vol 483, pg 603, 2012). Nature. 2012;492:290.
2. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, et al. (2012). Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature 483, S70-U587.X
3. Garraway LA, Lander ES. Lessons from the cancer genome. Cell. 2013;153:17–37.
4. Stratton M, Garnett M, Edelman EJ, Heidorn S, Futreal PA, Haber D, et al. The genomics of drug sensitivity in cancer. European Journal of Cancer. 2012;48:58.
5. Yang WJ, Soares J, Greninger P, Edelman EJ, Lightfoot H, Forbes S, et al. Genomics of drug sensitivity in cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells. Nucleic acids research. 2013;41:D955–61.
6. Iyer G, Hanrahan AJ, Milowsky MI, Al-Ahmadie H, Scott SN, Janakiraman M, et al. Genome sequencing identifies a basis for everolimus sensitivity. Science. 2012;338:221.
7. Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20:2076–84.
8. Houillier C, Wang X, Kaloshi G, Mokhtari K, Guillemin R, Laffaire J, et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology. 2010;75:1560–6.
9. Kong DS, Kim HR, Choi YR, Seol HJ, Lee JL, Nam DH. Prognostic impact of molecular phenotype in patients with recurrent anaplastic glioma treated with prolonged administration of temozolomide. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2015;22:1425–9.
10. Dubbink HJ, Taal W, van Marion R, Kros JMA, van Heuvel I, Bronberg JE, et al. IDH1 mutations in low-grade astrocytomas predict survival but not response to temozolomide. Neurology. 2009;73:1792–5.
11. Johnson BE, Mazor T, Hong C, Barnes M, Alhara K, McLean CY, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science. 2014;343:189–93.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at www.biomedcentral.com/submit