News Release

Title

Mathematical modeling and mutational analysis reveal optimal therapy to prevent malignant transformation in grade II IDH-mutant gliomas

Key Points

・Aoki et al. developed a mathematical model of tumor progression based on serial tumor volume data and treatment history of 276 IDH-mutant WHO grade II diffuse gliomas (IDHmut-LGGs), which enabled us to identify the quantitative effects of chemotherapy and radiotherapy on tumor cell growth and malignant transformation.

・This mathematical model revealed that prompt adjuvant chemoradiotherapy prolonged malignant transformation-free survival in small IDHmut-LGGs (≤ 50 cm^3). By contrast, optimal treatment differed according to extent of resection and genetic alterations for large IDHmut-LGGs (> 50 cm^3)

・This study also revealed that early diagnosis and treatment was extraordinary important in preventing malignant transformation of these tumors.

Summary

WHO grade II isocitrate dehydrogenase mutant gliomas (IDHmut-LGGs) grow slowly but frequently undergo malignant transformation, which eventually leads to premature death. Chemotherapy and radiotherapy treatments prolong survival, but can also induce genetic (or epigenetic) alterations involved in the transformation. Here, Aoki et al. developed a mathematical model of tumor progression based on serial tumor volume data and treatment history of 276 IDHmut-LGGs classified by chromosome 1p/19q codeletion ($IDH^{mut}/1p19q^{codel}$ and $IDH^{mut}/1p19q^{noncodel}$) and performed genome-wide mutational analyses, including targeted sequencing and longitudinal whole exome sequencing data. These analyses showed that tumor mutational burden was positively correlated with malignant transformation rate, and chemotherapy and radiotherapy significantly suppressed tumor growth but increased malignant transformation rate per cell by 1.8-2.8 times compared to that before treatment. This model revealed that prompt adjuvant chemoradiotherapy prolonged malignant transformation-free survival in small IDHmut-LGGs (≤ 50 cm^3). Furthermore, optimal treatment differed

according to genetic alterations for large IDHmut-LGGs (> 50 cm^3); adjuvant therapies delayed malignant transformation in $IDH^{mut}/1p19q^{noncodel}$ but often accelerated it in $IDH^{mut}/1p19q^{codel}$. Notably, phosphoinositide 3-kinase mutation was not associated with malignant transformation but increased net postoperative proliferation rate and decreased malignant transformation-free survival, prompting the need for adjuvant therapy in $IDH^{mut}/1p19q^{codel}$. Overall, the mathematical and bioinformatic analysis of multi-institutional clinical data uncovered therapeutic strategies that could prevent malignant transformation and, consequently, improve overall survival in patients with IDHmut-LGGs.

Research Background

Diffuse glioma accounts for about 80% of central nervous system malignancies and is classified by the World Health Organization (WHO) as grade II-IV according to its histopathological and clinical behavior. About 80% of WHO grade II diffuse gliomas have IDH (IDH1 or IDH2) mutations and are usually referred to as low-grade IDH mutant gliomas (IDHmut-LGGs). These tumors are generally slow-growing, but often become malignant and recur as high-grade, life-threatening tumors. Historically, so-called "wait-and-see" treatment was often preferred for low-grade IDH mutant gliomas, in which no treatment was given until symptoms appeared. However, since surgery has been shown to be effective in the early stages of the disease, and since surgery alone cannot be expected to cure the disease due to its diffuse invasion, chemotherapy and radiation therapy are now widely used along with surgery. While chemotherapy and radiotherapy inhibit tumor growth, they induce genomic or epigenomic abnormalities that can promote malignant transformation. For each patient, it is not known which treatment and at what timing is the best treatment to prevent malignant transformation. Mathematical and computational approaches (mathematical models) have been applied to interpret experimental and clinical data in various cancers. In this study, Aoki et al, designed a mathematical model based on time-series data, including tumor volume and matched clinical information of 276 IDHmut-LGGs to investigate tumor progression dynamics, calculate the risk of malignant transformation, and suggest optimal therapeutic strategies. Aoki et al. also performed genome-wide mutational analysis, including targeted deep sequencing (n=111) and whole exome sequencing with serial multisampling (n=100 [45 patients]) to elucidate the relationship between genetic alterations and the risk of malignant transformation.

Research Results

IDHmut-LGGs are classified into two subtypes: those with deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) (1p/19q) ($IDH^{mut}/1p19^{codel}$) and

those without ($IDH^{mut}/1p19^{noncodel}$) according to the 2016 revision of the WHO Classification of Tumors of the Central Nervous System. Aoki et al. estimated the net proliferation rate in each treatment based on time-series data of tumor volume, and found that a significant decrease in the net proliferation rate of post-radiotherapy, during-chemotherapy, during-chemoradiotherapy, and post-chemoradiotherapy, compared with that of surgery alone in both subtypes. Aoki et al. then used a mathematical approach to estimate the malignant transformation risk per cell. Specifically, Aoki et al. hypothesized that 1) tumor cells rarely acquire "malignant transformation events" such as genetic or epigenetic alterations, and when a certain number of these events accumulate, the cells undergo malignant transformation, and 2) chemotherapy and radiotherapy change the "malignant transformation events" rate additionally. Aoki et al. estimated the cumulative malignant transformation risk (cMTrisk) during the course of each case (Fig. 1). Aoki et al. compared cMTrisk of patients who actually underwent malignant transformation with that of patients who did not, and adopted the value that was most applicable. The results showed that chemotherapy and radiotherapy increased malignant transformation rate per cell by 1.8-2.8 times compared to before treatment. Using the estimated values, Aoki et al. simulated the scenario with IDHmut-LGGs classified by tumor volume at surgery and the extent of resection and investigated the optimal therapeutic strategy for each case. This analysis revealed that prompt adjuvant chemoradiotherapy prolonged malignant transformation-free survival in small IDHmut-LGGs ($\leq$ 50 cm^3). Furthermore, optimal treatment differed according to genetic alterations for large IDHmut-LGGs (> 50 cm^3); adjuvant therapies delayed malignant transformation in $IDH^{mut}/1p19q^{noncodel}$ but often accelerated it in $IDH^{mut}/1p19q^{codel}$. Notably, phosphoinositide 3-kinase mutation was not associated with malignant transformation but increased net postoperative proliferation rate and decreased malignant transformation-free survival, prompting the need for adjuvant therapy in $IDH^{mut}/1p19q^{codel}$ (Fig. 2). Aoki et al. also examined malignant transformation-free survival with an assumption of earlier diagnosis of the same tumors. Comparing the case where the IDHmut-LGG with a tumor volume of 50 cm^3, the maximal tumor volume for which prompt initiation of

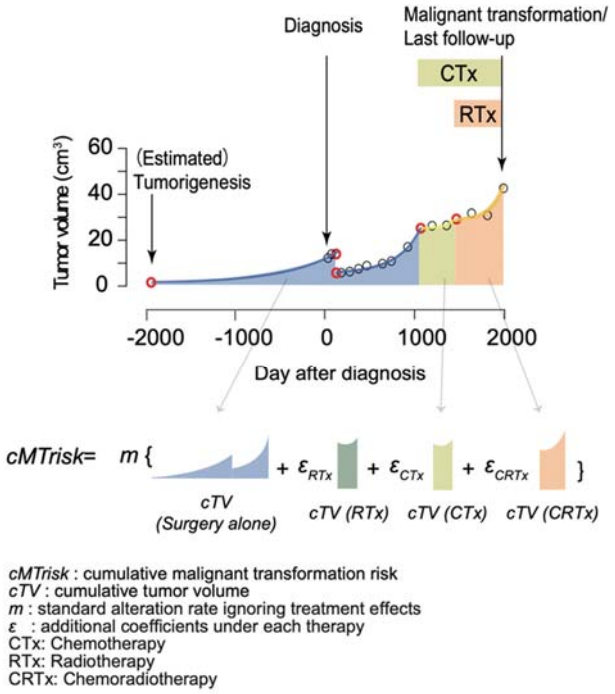

Fig.1 The method for estimation of cumulative malignant transformation risk.

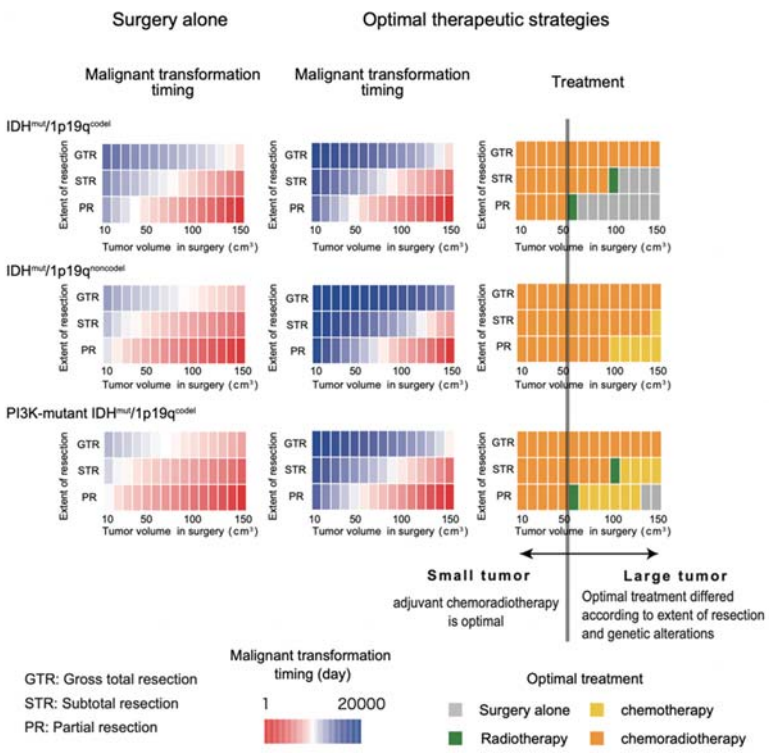

Fig 2. The malignant transformation timing and optimal treatment estimated by mathematical model.

chemoradiotherapy was optimal treatment, was surgically removed and immediately treated by chemoradiotherapy to the case where the same tumor had been diagnosed when the tumor volume was 10 cm^3, surgically removed and followed by prompt initiation of chemoradiotherapy, the latter scenario had substantially delayed malignant transformation. These results suggest the importance of early diagnosis and intensive treatment, if possible, before the onset of neurological symptoms.

Research Summary and Future Perspective

Overall, Aoki et al. have developed a model that can accurately estimate the malignant transformation-free survival and predict the optimal treatment strategy to minimize the risk for IDHmut-LGGs. These analyses also successfully revealed a link between genetic alterations and the increased risk of malignant transformation or rapid tumor expansion, and emphasized the importance of early diagnosis and treatment for IDHmut-LGGs. The methodology of this study can be applied to different types of cancer, which benefits to find an optimal treatment strategy to improve quality of life and survival.

Publication

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Authors: Kosuke Aoki, Hiromichi Suzuki, Takashi Yamamoto, Kimiyo N Yamamoto, Sachi Maeda, Yusuke Okuno, Melissa Ranjit, Kazuya Motomura, Fumiharu Ohka, Kuniaki Tanahashi, Masaki Hirano, Tomohide Nishikawa, Hiroyuki Shimizu, Yotaro Kitano, Junya Yamaguchi, Shintaro Yamazaki, Hideo Nakamura, Masamichi Takahashi, Yoshitaka Narita, Mitsutoshi Nakada, Shoichi Deguchi, Masahiro Mizoguchi, Yasutomo Momii, Yoshihiro Muragaki, Tatsuya

Abe, Jiro Akimoto, Toshihiko Wakabayashi, Ryuta Saito, Seishi Ogawa, Hiroshi Haeno, and Atsushi Natsume

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