KAMPO MEDICINE

An Attempt to Maintain Stable Disease and QOL Using Juzentaihoto during Remission in a Patient with Recurrent Residual Low-Grade Glioma

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ABSTRACT

Background: **About 10 years ago, a patient (Pa.) began taking Juzentaihoto, a traditional Japanese herbal medicine, aiming to prevent recurrence of low-grade glioma, declines in antitumor immunity and in quality of life (QOL). To date, the tumor has remained stable. This single case study reports the record of observations in the first year of taking Juzentaihoto.**

Case Presentation: **Pa. was diagnosed at the age of 4 with a cerebellar tumor, subtotal resection was performed. The recurrent tumor was removed subtotally 4 years later. The tumor temporarily shrank after gamma knife radiosurgery at the age of 20. Due to recurrence, the gamma knife was reperformed when Pa. was 24. At the age of 32, the tumor recurred. Chemotherapy was administered until remission was achieved at the age of 36.**

Methods: **Changes in tumor size, QOL, cognitive functions, and peripheral blood testing were analyzed during the first year of remission.**

Results: **Juzentaihoto significantly improved the indicator of attention, processing speed, and mental fatigue, and might have contributed to the maintenance of stable disease and QOL, as well as enhancement of antitumor immunity.**

Conclusion: **Juzentaihoto could be used to prevent tumor recurrence and maintain QOL during remission in patients with residual low-grade glioma.**

KEY WORDS

brain tumor, Juzentaihoto, Kampo medicine, low-grade glioma, natural killer cell activity, quality of life

BACKGROUND

A decade and a half ago, one of the authors (Pa.) started taking Juzentaihoto (JTT), a Kampo medicine, in expectation of antitumor effects[1,2)]. Pa. aimed to prevent recurrence of residual brain tumor (pilocytic astrocytoma) in the cerebellum (partly medulla oblongata), and to maintain quality of life (QOL) by using relatively inexpensive JTT with minimal adverse effects[3)]. To date, there have been no recurrences or adverse effects. In this single case study, data taken for observation in the first year of treatment are presented in order to help devise a treatment regimen using complementary and integrative medicine for patients with recurrent residual low-grade glioma at fatal sites.

CASE PRESENTATION

Pa. was diagnosed at the age of 4 with a cerebellar tumor, subtotal resection was performed. The recurrent tumor was removed subtotally 4 years later. The tumor temporarily shrank after gamma knife radiosurgery at the age of 20. At 24, the gamma knife was reperformed due to recurrence. At 32, the tumor recurred (Figure 1a). Two cycles of combination therapy with carboplatin and vinblastine and 12 cycles of carboplatin and vincristine were administered. MRI performed at the end of cycle 8 revealed shrinkage of the tumor, which was roughly equivalent to the size of the tumor before recurrence. Subsequently, monotherapy with vinblastine biweekly for 9 months was performed, and the treatment was completed because of stable disease at the age of 36 (Figure 1b).

METHODS

The administration of daily JTT extract (7.5 g, Tsumura Co., Tokyo, Japan) began 1.5 months after completion of chemotherapy. Treatment outcomes were monitored by MRI every 3 months, and peripheral blood testing and psychological examinations were performed every month.

The maximum sagittal diameter of the spherical portion in the lower part of the tumor was examined because the growth of this segment was particularly notable at recurrence (Figure 1).

Peripheral blood testing measured the number of red blood cells, white blood cells, platelets. Natural killer (NK) cell activity was also measured before, and at 3 months and 1 year after starting JTT using the 51 Cr release assay at two different effectors: target ratios (20: 1, 10: 1), because a prospective cohort study showed that NK cells play an important role in antitumor immune responses[4)], and a potential relationship between the antitumor effects of JTT and NK cells was shown in a study using mice with glioma[1)]. Additionally, a recent study demonstrated that oral administration of JTT may improve immune function by activating NK cells[2)].

For psychological examinations, the WHO Quality of Life 26 and the General Health Questionnaire 28 were performed. Next, the fixed task (task F) of the Advanced Trail Making Test (ATMT), which is a

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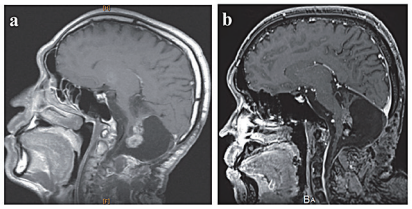

Figure 1: Contrast-enhanced sagittal T1-weighted MRI of the patient.
(a) MRI of the tumor recurrence taken before chemotherapy.
(b) MRI taken after completion of chemotherapy and before treatment with Juzentaihoto.
The size of the tumor did not change during the 1-year study period.

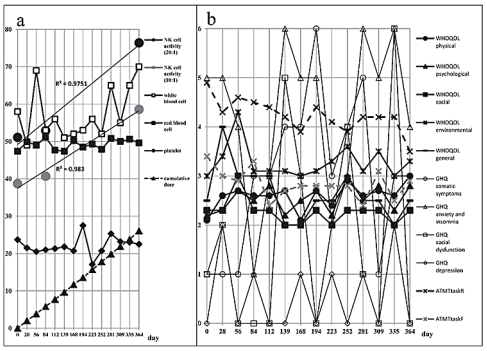

Figure 2: Changes in clinical parameters during the administration of Juzentaihoto.
The x-axis represents days after the start of Juzentaihoto intake, and the y-axis represents arbitrary units.
(a) Changes in hematological results and the cumulative dose of Juzentaihoto.
Instead of broken lines, linear regression lines with the determination coefficient (R2) are shown only for natural killer cell activity.
(b) Changes in QOL questionnaire items and mean response time of 99 touches in the ATMT.
High QOL was indicated by high scores in WHOQOL and low scores in GHQ.

ATMT, Advanced Trail Making Test; GHQ, General Health Questionnaire 28; NK, natural killer; QOL, quality of life; task F, fixed task; task R, random task; WHOQOL, World Health Organization Quality of Life 26.

trail making test with a touch panel capability, was performed to assess attention, processing speed, working memory[5], and mental fatigue[6], which are easily affected by brain injury[7]. The ATMT random task (task R), in which the numbers displayed on the touch panel relocated after each touch, was also performed to assess attention, processing speed, and mental fatigue.

Pearson's correlation coefficient was used to examine the relationship between these data and the cumulative JTT dose. For multiple comparisons, the level of significance was corrected using the Bonferroni method.

RESULTS

The tumor was 9 mm in all three measurements (Figure 1b). NK cell activity before administration (38.7% and 51.1% at 10:1 and 20:1) continued to increase linearly through the 3-month (40.7% and 52.9%) and 1-year time points (58.6% and 76.4%, respectively) (Figure 2a). The mean response time in the ATMT task R was the only item showing a significant correlation with the cumulative dose of JTT (r = -0.751, p = 0.002) (Figure 2b).

DISCUSSION

Recurrence was not observed during the 1-year study period. NK cell activity, as a robust biomarker of antitumor immunity, increased linearly. A significant decline in QOL was not observed, which is considered essential for the maintenance of NK cell activity[8]. Distress over recurrence compromises antitumor immunity and creates environment prone to recurrence.

Attention, processing speed, and mental fatigue significantly improved depending on the cumulative JTT dose. Since mental fatigue may cause a decrease in processing speed and attention[9], this result seems consistent with the utility of JTT as a revitalizer[2,3]. JTT would help maintain QOL of pediatric brain tumor survivors because 70% of them suffer from mental fatigue[10].

CONCLUSION

Relatively inexpensive JTT, with minimal adverse effects, could be used as complementary and integrative medicine long term to prevent tumor recurrence and maintain QOL during remission in patients with residual low-grade glioma.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL STATEMENT

The patient and the relevant authority gave their consents to be published in this paper for the images, all the experimental data, and case details.

REFERENCES

1. Kamiyama H, Takano S, Ishikawa E, Tsuboi K, Matsumura A. Anti-angiogenic and immunomodulatory effect of the herbal medicine "Juzen-taiho-to" on malignant glioma. Biol Pharm Bull. 2005; 28: 2111-6. doi: 10.1248/bpb.28.2111.
2. Ogawa-Ochiai K, Katagiri T, Sato Y, *et al*. Natural killer cell function changes by the Japanese Kampo Medicine Juzentaihoto in General fatigue patients Adv Integr Med. 2021; 8: 33-43. doi: 10.1016/j.aimed.2019.12.003.
3. Shin IS, Yu YB, Seo CS, *et al*. Subchronic toxicity of Sipjeondaebo-tang (SDT) in Sprague-Dawley rats. Regul Toxicol Pharmacol. 2011; 59: 375-84. doi: 10.1016/j.yrtph.2010.09.018.
4. Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. Lancet. 2000; 356: 1795-9. doi: 10.1016/S0140-6736(00)03231-1.
5. Nakahachi T, Ishii R, Iwase M, *et al*. Frontal cortex activation associated with speeded processing of visuospatial working memory revealed by multichannel near-infrared spectroscopy during Advanced Trail Making Test performance. Behav Brain Res. 2010; 215: 21-7. doi: 10.1016/j.bbr.2010.06.016.
6. Horikoshi T, Matsue K, Takahashi T, *et al*. Objective determination of fatigue development following sun exposure using Advanced Trail Making Test. Int J Cosmet Sci. 2004; 26: 9-17. doi: 10.1111/j.0142-5463.2004.00200.x.
7. Calvillo M, Irimia A. Neuroimaging and psychometric assessment of mild cognitive impairment after traumatic brain injury. Front Psychol. 2020; 11: 1423. doi: 10.3389/fpsyg.2020.01423.
8. Nakata A, Irie M, Takahashi M. Psychological distress, depressive symptoms, and cellular immunity among healthy individuals: A 1-year prospective study. Int J Psychophysiol. 2011; 81: 191-7. doi: 10.1016/j.ijpsycho.2011.06.009.
9. Irestorm E, Ora I, Linge H, Tonning Olsson I. Cognitive fatigue and processing speed in children treated for brain tumours. J Int Neuropsychol Soc. 2021; 27: 865-74. doi: 10.1017/S1355617720001332.
10. Irestorm E, Tonning Olsson I, Johansson B, Øra I. Cognitive fatigue in relation to depressive symptoms after treatment for childhood cancer. BMC Psychol. 2020; 8: 31. doi: 10.1186/s40359-020-00398-1.