IMSUT Hospital

Department of Surgical Neuro-Oncology
脳腫瘍外科

Professor	Tomoki Todo, M.D., Ph.D.	教　授	博士(医学)	藤　堂　具　紀
Project Professor	Minoru Tanaka, M.D., Ph.D.	特任教授	博士(医学)	田　中　　実
Assistant Professor	Hirotaka Ito, M.D., Ph.D.	助　教	博士(医学)	伊　藤　博　崇
Assistant Professor	Seisaku Kanayama, M.D.	助　教		金　山　政　作
Assistant Professor(Thoracic surgeon)	Yoshinori Sakata, M.D., Ph.D.	助　教	博士(医学)(呼吸器外科医)	坂　田　義　詞

All kinds of brain tumors, especially malignant glioma, are treated at our department. Malignant glioma is incurable by standard therapy alone, therefore refined, personalized treatment regimens utilizing non-standard radiation therapy and chemotherapy are considered. In addition, G47Δ, the first oncolytic virus therapy drug for malignant glioma in the world, developed by this department, is commercially available and used for treatment since November 2021. Based on scientific evidence and findings from basic research, we conduct advanced medical practices in addition to standard therapy.

Introduction

Department of Surgical Neuro-Oncology was established in 2011. Our department started treating out-patients in October 2011 and in-patients in April 2012. Our department focuses on malignant tumors of the brain, such as gliomas or metastatic brain tumors. Glioblastoma is one of the most aggressive and malignant cancers of the central nervous system. The standard upfront treatment includes resection to remove as much of the tumor as possible while preserving function, followed by radiation of 60Gy and temozolomide. Established good prognostic factors are limited but include young age, high Karnofsky Performance Status (KPS), high mini-mental status examination score, O^6-methylguanine methyltransferase promoter methylation, and resection of > 98% of the tumor. Nevertheless, glioblastoma is refractory to conventional therapies and has a poor prognosis with a 5-year survival rate of less than 5%. Therefore, we should consider refined and personalized treatment approaches for selected patients: high dose radiation therapy of 80Gy for newly diagnosed glioblastoma or extended field stereotactic radiosurgery for recurrent gliomas. We also conduct translational research based on scientific evidence. We are developing recombinant herpes simplex virus type I (HSV-1), which has genetic modifications in the viral genome so that the viruses replicate selectively in cancer cells while eliciting an immune response against tumor-associated proteins. Clinical trials using a third-generation, triple-mutated oncolytic herpes simplex virus type 1 (HSV-1), G47Δ, were performed in patients with glioblastoma from 2015 to 2020 and malignant pleural mesothelioma from 2018 to 2021. A clinical trial targeting patients with olfactory neuroblastoma has been ongoing since 2013. Additionally, an investigator-initiated trial utilizing T-hIL12 for malignant melanoma, conducted in collaboration with Shinshu University, has been underway since January 2020.

Drug approval of a replication-competent, HSV-1, G47Δ for malignant glioma

Genetically engineered, conditionally replicating HSV-1is promising therapeutic agents for solid carcinomas. We developed G47Δ by introducing an additional genetic mutation to a second generation, dou-

ble-mutated oncolytic HSV-1, G207, used in the phase I clinical trial for glioblastoma in the United States in 1998. We conducted a phase II clinical trial of G47Δ in patients with recurrent or residual glioblastoma since December 2014 to June 2020. The patients received repeated stereotactic injections with G47Δ every 4 weeks, 6 injections being the maximum total. In the final analysis, the 1-year survival rate after initiation of G47Δ treatment (the primary endpoint) was 84%. The most common side effect of G47Δ was fever followed by vomiting, nausea, lymphopenia, and leukopenia. A new drug application (NDA) for G47Δ for malignant glioma has been submitted to the Ministry of Health, Labour and Welfare in December 2020. In June 2021, G47Δ was approved as the world's first oncolytic virus drug for malignant glioma. Since its commercial release as Delytact in November 2021, the Department has begun treating patients with malignant gliomas and evaluating its safety and efficacy in real-world clinical practice.

A clinical study of G47Δ in patients with progressive olfactory neuroblastoma

Olfactory neuroblastoma is an uncommon malignant neuroectodermal tumor, which is thought to originate from the olfactory membrane of the sinonasal tract. Patients should receive aggressive treatment with combined treatment such as surgery, radiation therapy, and chemotherapy because there is no effective treatment once it recurs: An aggressive en bloc resection, with combined radiation therapy was recommended. We have been conducting a phase I clinical trial of G47Δ in patients with progressive olfactory neuroblastoma since August 2013. G47Δ was repeatedly inoculated to the residual tumor in nasal cavity every 4 weeks until tumor progression or excessive toxicity occurred. The primary endpoint was safety, and the secondary endpoints included efficacy analysis. Participant recruitment has been completed, and data analysis is currently underway.

A clinical study of G47Δ in patients with progressive malignant pleural mesothelioma

Malignant pleural mesothelioma is a rare asbestos-induced malignancy with an estimated incidence of approximately 2,000 new cases diagnosed in Japan. Worldwide, nearly 80% of mesothelioma deaths occur in ten countries, with Japan, the United Kingdom, and the United States being in the top three. It is expected to continue to increase over the next several decades. Median survival ranges from 9 to 18 months and correlates with stages. Radiotherapy can be used for different indications in mesothelioma: palliation, as a preventive treatment, and as part of multimodality treatment. Combination doublet chemotherapy of cisplatin, with either pemetrexed or raltitrexed, has shown a more prolonged survival compared with cisplatin alone in randomized phase III trials. Carboplatin is an acceptable alternative to cisplatin and may be better tolerated in the elderly population. We conducted a phase I clinical trial of G47Δ for inoperable, recurrent or progressive malignant pleural mesothelioma from 2018 to 2021. A fixed dose of G47Δ was administered into the pleural cavity every 4 weeks, maximum 6 times. The primary endpoint was safety, and the secondary endpoints included efficacy analysis. We completed the enrollment and confirmed the safety of repeated intrapleural administration with G47Δ.

A phase 1/2 clinical trial of a recombinant herpes simplex type 1 with human IL-12 expression, T-hIL12, in patients with malignant melanoma

Malignant melanoma is a tumor produced by the malignant transformation of melanocytes. Melanocytes are derived from the neural crest; consequently, melanomas, although they usually occur on the skin, can arise in other locations where neural crest cells migrate, such as the gastrointestinal tract and brain. The 5-year relative survival rate for patients with stage 0 melanoma is 97%, compared with about 10% for those with stage IV disease. We started a phase 1/2 clinical trial of T-hIL12 in patients with malignant melanoma since January 2020 jointly with Shinshu University. T-hIL12 is a G47Δ-based recombinant herpes simplex type I with human IL-12 expression. This IL-12-mediated antitumor immunity could be T-cell-mediated. The main inclusion criteria in phase 1 are 1) histologically confirmed malignant melanoma with stage 3 or 4, 2) patients who have at least one metastatic skin lesion with 10 mm or larger (the longest diameter), or at least one metastatic lymph node with 15 mm or larger (the shortest axis), 3) patients who were administered with anti-PD-1 antibody, or targeted molecular drugs, 4) the size and distribution of all the metastatic lesions are recognized with clinical findings including imaging studies (CT, MRI), 5) age >= 20 years, 6) more than 30 days have passed from the previous treatment, 7) Eastern Cooperative Oncology Group (ECOG) performance Status (PS) of 0-2, 8) patients without severe disorders (severe myelosuppression, liver dysfunction, chronic renal dysfunction), whereas in phase 2 they are eight items, which are defined in the same way as in the phase 1 except for 3) of phase1. The 3rd inclusion criterion of phase2 is 3) patients who have not been administered with anti-PD-1 antibody or targeted molecular drugs. T-hIL12 will be administered into the tumor of skin or lymph node metastases in patients with advanced stage of malignant melanoma. The assigned dose will be repeatedly inoculated into the metastases 2 or 4 times, with an interval of 14 (14 -28) days. The primary endpoint in phase 1 is safety, and in phase 2 a response rate (RECIST 1.1). The Phase 1 part of our phase 1/2 clinical trial of T-hIL12 in patients with malignant melanoma has concluded, and the Phase II

part is progressing as planned.

Routine activities

Patients with brain tumors are treated by four faculty neurosurgeons and one resident. A total of 119 operations were carried out in 2024 including 118 gliomas and one meningioma. More than 100 cases of oncolytic virus therapy were performed. Standard craniotomies and image guided stereotactic biopsies of deep seated lesions, as well as high-tech brain tumor resections are performed. The high-tech equipment regularly used in brain tumor resection surgeries includes an operative microscope, a 3-D neuro-navigation system, intraoperative motor evoked potential (MEP and SEP) recording, intraoperative ultrasonography and an ultrasonic surgical aspirator.

Patients with newly diagnosed malignant glioma have been treated with high dose or standard dose radiation therapy and concomitant chemotherapy. Temozolomide was administered to glioma patients during radiation therapy followed by a maintenance therapy every 28 days for as long as possible. The overall survival of patients with glioblastoma was 30.3 months (95% confidence interval, 24.5-36.1 months. The five-year overall survival rate was 26.5%.

Recurrent malignant glioma patients are treated with innovative non-standard therapies whenever possible. Recurrent glioma patients who have small lesions, receive extended field stereotactic radiosurgery. To enhance the efficacy of stereotactic radiosurgery (SRS), the irradiation field is enlarged to include as many tumor cells invasive to the surrounding tissue as possible. We demonstrated 93% local control in patients who received 20 Gy to a 0.5-1.0 cm extended field SRS compared to 47% of patients who were treated with 20 Gy to the gadolinium-enhancing margin only.

Treatment of primary central nervous system lymphoma

Primary central nervous system lymphoma patients will first undergo biopsy for pathological diagnosis. Standard treatment includes high-dose methotrexate-based chemotherapy, often combined with agents such as rituximab, procarbazine, and vincristine (R-MPV regimen), followed by consolidation therapy with high-dose cytarabine (Ara-C). whole-brain radiation therapy may still be considered in certain cases, depending on individual patient factors and disease characteristics.

Development of next-generation oncolytic HSV-1 for malignant glioma

As a next-generation oncolytic HSV-1 that follows G47Δ, we are currently developing G47Δ-based oncolytic HSV-1 that expresses bevacizumab (anti-VEGF monoclonal antibody), T-BV. The protocol for the phase I clinical trial of T-BV for grade 4 malignant glioma has been drafted. We expect to start the clinical trial in the near future.

Publications

1. Khasraw M, Hotchkiss KM, Karschnia P, Schreck KC, Geurts M, Cloughesy TF, Huse J, Duke ES, Lathia J, Ashley DM, Nduom EK, Long G, Singh K, Chalmers A, Ahluwalia MS, Heimberger A, Bagley S, Todo T, Verhaak R, Kelly PD, Hervey-Jumper S, de Groot J, Patel A, Fecci P, Parney I, Wykes V, Watts C, Burns T, Sanai N, Preusser M, Tonn JC, Drummond KJ, Platten M, Das S, Tanner K, Vogelbaum MA, Weller M, Whittle JR, Berger M. A brave new framework for glioma drug development. Lancet Oncol 25(10):e512-e519, 2024 [doi: 10.1016/S1470-2045(24)00190-6].