Neuro-Oncology: An Emerging Neurologic Subspecialty in Thailand

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INTRODUCTION

During the past decades, there has been a tremendous progress in the field of neuroscience and clinical neurology. Increased understanding of pathogenesis at the genetic and molecular levels has translated into development of precise diagnostic techniques and new therapies for various neurological diseases that traditionally lack of treatment options. At present, the number of neurologists in Thailand is limited with less than 500 board-certified neurologists. However, the number of neurology applicants for residency programs in Thailand has been steadily increasing during the past 5 years reflecting the growing interest in this field among senior medical students and medical school graduates. Most neurology graduates continue their practice in general neurology, while some opt to have additional subspecialty training. Two accredited neurology subspecialty programs in Thailand are epilepsy and stroke fellowships. Several emerging subspecialties with potential accreditation in the future may include but are not limited to clinical neurophysiology and Parkinsons disease and movement disorders.

Neuro-oncology is a developing subspecialty worldwide even in the United Stated (US) and in Europe. Most neuro-oncologists in the US are neurologists, who undergo fellowship training in neuro-oncology.[1] This subspecialty represents a borderland between oncology and neurology. Neuro-oncologists have expertise to provide diagnosis and treatment including administration of chemotherapy for patients with a wide variety of brain tumors. In addition, neuro-oncologists are familiar with the management of patients, who suffer from a myriad of challenging neurological disorders derived from cancers and their treatments.

Neuro-oncology in Thailand

At present, there are only few medical neuro-oncologists in Thailand. Our role as a neuro-oncologist is to coordinate with other specialties to provide optimal management of patients with brain tumors. The inter-disciplinary brain tumor group at Siriraj Hospital includes neurosurgeons, neuroradiologists, radiation oncologists, neuropathologists, medical oncologists and a neuro-oncologist. Our group has monthly academic case conferences organized by the Siriraj Cancer Center with the goals to: cross-educate ourselves and our trainees from different specialties; enhance collaboration between multiple specialties; and obtain the best treatment plan for difficult cases. In the future, this conference may evolve into more frequent and regular *brain tumor boards* to serve as a core teaching and a venue to provide optimal treatment for individual patients at Siriraj Hospital.

The neuro-oncology service in the Division of Neurology, Department of Medicine at Siriraj Hospital offers consultation in both outpatient and inpatient settings. Neurology and rotating internal medicine residents have opportunities to gain exposure to neuro-oncology. Trainees can exercise their skills in clinical neuroanatomy as most patients with brain tumors exhibit focal neurological deficits that correspond to their abnormal neuroimaging findings. Patients with CNS metastases including leptomeningeal disease can present an additional diagnostic challenge, as their neurologic deficits may be multifocal or diffuse. Trainees learn to be assertive in formulating treatment plans for brain tumor patients with the goal of not only to increase survival, but also to improve or at least preserve the patients quality of life. In addition, they have hands-on experience about dealing with difficult issues in both neurology and oncology such as breaking bad news and providing end-of-life care for patients and their families. Apart from clinical works, trainees also have exposure to research advances in neuro-oncology. The recent explosion of research in genomics and molecular studies, some of which have already translated into clinical practice, makes neuro-oncology one of the most exciting subspecialties for neurologists. Research opportunities range from basic and translational to clinical studies.

At the national level, the Thai Brain Tumor Society (TBTS) was established by several initiatives from various subspecialties in early 2011. The missions of TBTS are to: 1) Disseminate knowledge in neuro-oncology to physicians and allied health personnel in Thailand; 2) Facilitate

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collaboration in all aspects among physicians involved in the management of patients with brain tumors within institutions and nationwide; 3) Provide education concerning brain tumors to patients and the general public. In addition, we hope to establish the National Brain Tumor Registry and to design multi-center, investigator-initiated, clinical trials of novel therapeutics for brain tumors in Thailand. This approach may serve as a strong foundation for development of a national collaborative brain tumor research network, which may also help to increase access of new drugs to brain tumor patients in Thailand.

On the international level, the Asian Society for Neuro-Oncology (ASNO) represents an organization which fosters collaboration between neuro-oncologists in Asia with annual scientific meetings of the society every year. The Society for Neuro-Oncology (of North America), the worlds largest neuro-oncology society, also has an international outreach committee to support neuro-oncology education and training in developing countries. One-year International fellowship positions with funding support have been offered since 2009 to allow fellow applicants from developing countries to gain research experiences in neuro-oncology at participating academic institutions in the North America.

Recent advances in neuro-oncology

Primary brain tumors

Although primary brain tumors are relatively uncommon cancers, they are often associated with disability and high mortality. Gliomas are the most common primary brain tumors in adults with the incidence of 3-5 cases per 100,000 populations.[2] Malignant gliomas are defined by the 2007 World Health Organization (WHO) classification as anaplastic gliomas (WHO grade 3) and glioblastoma (GBM; WHO grade 4). The median survival despite maximal therapy for patients with anaplastic gliomas and GBM are only 2-5 years and 10-20 months, respectively.[2] GBM is the most common and the most malignant type of gliomas in adults. In the past, the treatment for GBM involved only surgical resection and radiation therapy. However, since 2005, the standard-of-care treatment has incorporated temozolomide (TMZ), an oral DNA-methylating agent, given concurrently with radiation followed by six monthly adjuvant courses.[3] TMZ is the first chemotherapy drug which has demonstrated significant and durable survival benefit in a large randomized phase III trial for patients with newly diagnosed GBM. The 2-year survival rate was 27% for patients who received TMZ with radiation, whereas that for patients who had radiotherapy alone was only 11%.[3] TMZ is generally well tolerated with less than 10% risk of severe hematologic toxicities and it is not associated with worsened quality of life during the treatment. Subsequent post-hoc analysis demonstrated that patients aged less than 50 and good performance status seemed to derive the most benefit from TMZ with the 5-year survival rates of up to 28%.[4] One of the critical areas in neuro-oncology research is to identify biomarkers of response or resistance to therapeutics. Epigenetic silencing by promoter methylation of a DNA-repair enzyme gene, O6-methylguanine-DNA-methyltransferase (*MGMT*) in tumor samples may predict the benefit of TMZ in GBM.[4] Methylation-specific polymerase chain reaction (PCR) to detect this tumor epigenetic abnormality may reasonably offer a rational approach to select patients for TMZ administration, particularly in countries with inadequate resources including Thailand.

Despite its rarity, GBM was selected among various cancers for comprehensive genome characterization by The Cancer Genome Atlas (TCGA) project sponsored by the US National Institute of Health. In fact, GBM is the first cancer upon which the TCGA preliminarily reported the complete genomic landscape.[5] Despite the genetic heterogeneity of GBM, common aberrations in molecular pathways can be found. For instances, eighty-eight percent of primary GBM have deregulation of protein kinase signaling involving receptor tyrosine kinases, RAS or phosphatidylinositide-3-OH kinase (PI3K) pathways. These findings may lead to a rational development of molecularly targeted therapy for GBM. As the genome sequencing technology becomes cheaper and less laborious, identification of genetic signatures that predict the response to specific therapeutics may be more available to guide optimal treatment for individual patients. This personalized medicine approach is now undergoing clinical trial evaluation in other cancers.

One of the pathologic hallmarks of GBM is angiogenesis, the new blood vessel formation from existing vasculature.[6] Angiogenesis is tightly regulated between proangiogenic and antiangiogenic factors in the tumor microenvironment. Vascular endothelial growth factor (VEGF) is a key proangiogenic factor and its expression correlates with the WHO grading and prognosis of gliomas. Therefore, targeting VEGF may represent an attractive approach for GBM. Bevacizumab is a VEGF-neutralizing monoclonal antibody with established anti-tumor activity in colorectal cancer, non-small cell lung cancer and renal cell carcinoma. Bevacizumab administered alone or in combination with irinotecan was associated with radiographic response rates of 26-57%, 6-month progression-free survival rates (PFS-6) of 29-50% and overall survival of 8-9 months in recurrent GBM.7-9 Of note, historical salvage therapies for recurrent GBM rendered PFS-6 of only less than 20% and radiographic response rates of less than 10%. In addition, bevacizumab displays an anti-edema effect resulting in symptomatic benefit, reduction of use of corticosteroid and stabilized or improved neurocognitive function during the time of response. Owing to remarkable radiographic response rates and promising progression-free survival benefits, bevacizumab was granted accelerated approval for progressive GBM by the US Food and Drug Administration (FDA) in 2009. The Thai FDA has also approved bevacizumab for this indication since March 2010. Two large randomized phase III trials of bevacizumab plus radiotherapy and TMZ versus radiotherapy and TMZ in newly diagnosed GBM are in progress. As only subsets of patients enjoy benefit from bevacizumab, the identification of predictive biomarkers of response is important. Several studies have demonstrated candidate biomarkers derived from tissue gene/protein expression, circulating cells or proteins and neuro-imaging parameters.[10] These candidate biomarkers require prospective validation in larger patient cohorts to confirm their predictive value before routine clinical use. In addition to gliomas, neuro-oncologists work closely with medical oncologists, hematologists and radiation oncologists in taking care of patients with less common brain tumors such as intracranial germ cell tumors and primary CNS lymphoma.

Neurologic complications of cancer

Apart from the management of patients with primary brain tumors, neuro-oncologists also provide diagnosis and treatment for neurological disorders in cancer patients. The

most common neurologic complication of cancer is brain metastases. In fact, brain metastases are the most common brain tumors in adults.[11] Furthermore, the incidence of brain metastases may increase as the survival of patients with systemic cancers becomes longer due to more effective systemic treatment which may not necessarily cross the blood-brain barrier. Neuro-oncologists work closely with medical oncologists, neurosurgeons and radiation oncologists to deliver the appropriate treatment for patients with brain metastases.

Some patients presented with neurologic abnormalities preceding the diagnosis of cancer. These patients along with cancer patients, who developed neurologic symptoms or signs not attributed to direct effects of tumors or their treatments, may suffer from a unique disorder called paraneoplastic neurologic syndrome. This rare syndrome has several suggestive clinical characteristics which are as follows: 1) Subacute, rapidly progressive, focal or multifocal, neurologic symptoms which usually plateau in 2-4 weeks; 2) Neurologic symptoms which often precede cancer diagnosis; 3) Neuroimaging can be normal or abnormal and cerebrospinal fluid (CSF) for CNS disorders may suggest an inflammatory process during the first two weeks; 4) Onconeural (paraneoplastic) antibody is present in blood and/or CSF.12 In addition, some neurologic disorders are highly associated with paraneoplastic etiology such as Lambert-Eaton myasthenic syndrome, subacute cerebellar degeneration, subacute sensory neuronopathy, opsoclonus-myoclonus ataxia syndrome, dermatomyositis, limbic encephalitis, encephalomyelitis and chronic gastrointestinal pseudo-obstruction. Small-cell lung cancer represents the most common cancer associated with paraneoplastic neurologic syndromes. The diagnosis of paraneoplastic neurologic syndrome is usually based on a clinical suspicion which leads to testing for paraneoplastic antibodies. If a paraneoplastic antibody is present, a search for systemic cancer is indicated. A thorough physical examination including breast and testicular palpation should be performed. It should be noted that a chest radiograph is not sensitive for detecting small-cell lung cancer in patients with paraneoplastic syndromes as the tumor is usually small and is often limited to a small mass in the mediastinum. Computed tomography is therefore recommended for an initial evaluation. A positron-emission tomography (PET)-CT scan is the most sensitive, but is an expensive test for tumor detection.[13] Treatments for paraneoplastic syndromes consist of tumor-directed treatment such as surgery, radiation or chemotherapy and immunomodulatory therapy. Recently, new antibodies associated with encephalitis have been identified. This discovery has expanded the concept of autoimmune encephalopathy, some of which are paraneoplastic in origin.[14] Most of these autoantibodies bind to cell surface receptors or synaptic proteins such as N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leucine-rich glioma-inactivated 1 (LGI-1; formerly known as voltage-gated potassium channel) receptors, contactin-associated protein-like 2 (caspr2) receptors and γ-aminobutyric acid-B ($GABA_B$) receptors. Patients usually present with neuropsychiatric disturbance or seizures followed by other variable neurologic manifestations. Despite the severe and protracted clinical course of encephalitis, treatment with intravenous immunoglobulin or plasma exchange with an attempt to remove pathogenic antibodies and complements often leads to partial or complete recovery.[14] Neuro-oncologists play an important role in the diagnosis and treatment for patients with these unique disorders.

CONCLUSION

Neuro-oncology is an emerging neurologic subspecialty with exciting advances. Neuro-oncologists provide diagnosis and treatment for patients with brain tumors and neurologic complications of systemic cancers. Neuro-oncologists are actively involved in multi-disciplinary care for patients with brain tumors in order to provide optimal treatment for individual patients. GBM, the most common primary brain tumor in adults, has remained the focus of research in neuro-oncology. Medical therapies were not effective until the past 7 years, when two new drugs i.e. temozolomide and bevacizumab demonstrated significant survival benefit that led to regulatory approval. Cutting-edge technology in biomedical and bioinformatics research will continue to uncover the pathogenesis of brain tumors and neurologic disorders afflicting cancer patients, while new therapies will be simultaneously developed. Tremendous opportunities for career development in both academic and private medical sectors are available for aspiring neuro-oncologists. Taken together, there has never been a more exciting time to study and invest in neuro-oncology.

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