oncogene) in multiple pediatric brain tumors, and is even pointing towards a critical role in the activation of HMGB1-mediated toll-like receptor 2 (TLR2) immune signaling. The presence of those signals may facilitate immune activation, and immunogenic induced cell death, and eventually result in tumor destruction.

In this presentation, Daniela Bota, MD, PhD, will review the clinical results of Optune in the treatment of GBM, and will discuss the novel biologic mechanisms underlying the effects of Optune in controlling tumor growth and promoting the immune responses in GBM.

Key words: glioblastoma, tumor treating fields, novel mechanisms

SL1
GENETICS OF PEDIATRIC BRAIN TUMORS: RECENT ADVANCES AND FUTURE PERSPECTIVES
David T. W. Jones; German Cancer Research Center (DKFZ), Heidelberg, Germany

The last decade has seen a true revolution in our understanding of the oncogenic mechanisms underlying human tumors, brought about by transformative advances in the technologies available to interrogate the (epi)genetic composition of cancer cells. The dynamic pediatric neuro-oncology community has proven to be very agile in adapting to these changes, and has arguably been at the forefront of some of the most exciting new discoveries in tumor biology in recent years. For example, high-throughput genomic sequencing has revealed highly frequent mutations in histone genes in pediatric glioblastoma; highlighted an ever-expanding role for oncogenic gene fusions in multiple pediatric brain tumor types, and also shed light on novel phenotypic patterns such as chromothripsis (dramatic chromosomal shattering) and somatic hypermutation - the latter being a possible marker for response to novel immunotherapeutic approaches. Epigenetic profiling has also identified a role for ‘enhancer hijacking’ (whereby genomic rearrangement brings an active enhancer element in close proximity to a proto-oncogene) in multiple pediatric brain tumors, and is even pointing towards a fundamentally new way in which tumors may be molecularly classified.

In coming years, the major challenge will be to harness the power of these discoveries to more accurately diagnose patients and to identify potential therapeutic targets in a more personalized way, so that these major biological advances can also be translated into substantial clinical benefit. Examples such as the dramatic responses observed in childhood brain tumor sufferers to BRAF V600E and NTRK inhibitors demonstrate the promise that such an approach can hold, but it will require a fundamental shift in the way that clinical trials are planned and conducted in order to optimize patient care.

This talk will highlight some of the most striking developments in the field, and look at the challenges that remain before these can lead to improved patient outcomes.

Key words: Genomics, Pediatric, Epigenetics

AS1-KL1
DEVELOPMENT OF HIGH-DOSE CHEMOTHERAPY INCLUDING THIOTEPA COMBINED WITH AUTOLOGOUS PERIPHERAL BLOOD STEM CELL RESCUE
Junichi Hara; Children’s Medical Center, Osaka City General Hospital

Thiotepa is a classic alkylating agent that was launched in 1958 in Japan. We have consistently developed thiotepa-containing HDC since 1992, inspired by the fact that thiotepa was used as an alternative to melphalan as a high-dose chemotherapy (HDC) drug for neuroblastoma in the United States. Thiotepa is considered to be a drug suitable for brain tumor treatment because of its good BBB permeability, equal concentration in cerebrospinal fluid and blood, and the characteristics of alkylating agents that enhance the effect by high-ratio of dose. Melphalan, which is also an alkylating agent as a central agent of HDC, has a strong antitumor effect, so we planned to use both at the maximum tolerated dose for each. Therefore, in order to reduce toxicity, it was decided to divide it into two doses at weekly intervals and to administer thiotepa for 24 hours in order to prevent hepatic sinus obstruction syndrome (SOS). Since 1993, a dose determination study was conducted, and the doses of thiotepa and melphalan were determined to be 800 mg/m2 and 280 mg/m2, respectively. Autologous peripheral blood stem cell transplantation using this regimen was performed as a consolidation therapy for metastatic pediatric medulloblastoma in 28 and 15 patients, respectively, in 2 series. Five-year progression-free survival rates of 82.1 ± 7.2% and 92.9 ± 6.9% were obtained. After that, the supply was stopped in 2009. This time, a domestic study was conducted with the dose of melphalan reduced to 210 mg/m2, and this year, a new indication (pretreatment for autologous hematopoietic stem cell transplantation in childhood malignant solid tumors) was acquired and launched. By this dose reduction, reduced gastro-intestinal toxicity such as mucosal damage is expected. The JCCG clinical trials incorporating HDC will be conducted in medulloblastoma, ATRT, and refractory germ cell tumors.

Key words: thiotepa, melphalan, high-dose chemotherapy