Topotecan

see Convection-enhanced delivery of Topotecan.

Topotecan (trade name Hycamtin) is a chemotherapeutic agent that is a topoisomerase inhibitor. It is a synthetic, water-soluble analog of the natural chemical compound camptothecin. It is used in the form of its hydrochloride salt to treat ovarian cancer, lung cancer and other cancer types.

After GlaxoSmithKline received final FDA approval for Hycamtin Capsules on October 15, 2007, topotecan became the first topoisomerase I inhibitor for oral use.

High-dose chemotherapy (HDC) and autologous stem cell transplantation (auto-SCT) are used to improve the survival of children with high-risk brain tumors who have a poor outcome with the standard treatment.

A study of Choi et al. from Seoul aimed to evaluate the outcome of HDC/auto-SCT with topotecan-thiotepa-carboplatin and melphalan-etoposide-carboplatin (TTC/MEC) regimens in pediatric brain tumors.

They retrospectively analyzed the data of 33 children (median age 6 years) who underwent HDC/auto-SCT (18 tandem and 15 single) with uniform conditioning regimens.

Eleven patients aged < 3 years at diagnosis were eligible for HDC/auto-SCT to avoid or defer radiotherapy. In addition, nine patients with high-risk medulloblastoma (presence of metastasis and/or postoperative residual tumor ≥ 1.5 cm2), eight with other high-risk brain tumor (six CNS primitive neuroectodermal tumor, one CNS atypical teratoid rhabdoid tumor, and one pineoblastoma), and five with relapsed brain tumors were enrolled. There were three toxic deaths, and two of which were due to pulmonary complications. The main reason for not performing tandem auto-SCT was due to toxicities and patient refusal. The event-free survival (EFS) and overall survival (OS) rates of all patients were 59.4% and 80.0% at a median follow-up with 49.1 months from the first HDC/auto-SCT, respectively. The EFS/OS rates of patients aged < 3 years at diagnosis, high-risk medulloblastoma, other high-risk brain tumors, and relapsed tumors were 50.0/81.8%, 87.5/85.7%, 66.7/88.9%, and 20.0/60.0%, respectively.

Although tandem HDC/auto-SCT with TTC/MEC regimens showed promising survival rates, treatment modifications are warranted to reduce toxicities. The survival rates with relapsed brain tumors were unsatisfactory despite HDC/auto-SCT, and further study is needed [1)].

BT183 cells are very sensitive to the topoisomerase inhibitors topotecan and doxorubicin, to the epigenetic agents decitabine and panobinostat, to actinomycin D, and to targeted drugs such as the polo-like kinase 1 (PLK1) inhibitor volasertib, the aurora kinase A inhibitor alisertib, and the mammalian target of rapamycin (mTOR) inhibitor MLN0128. In xenograft mice, monotherapy with topotecan, volasertib, and actinomycin D led to a temporary response in tumor growth and a significant increase in survival. Finally, using multi-agent treatment regimens of topotecan or doxorubicin combined with methotrexate and vincristine, the response in tumor growth and survival was further increased compared with mice receiving single treatments [2)].

Protein SUMOylation is a dynamic post-translational modification shown to be involved in a diverse set of physiologic processes throughout the cell. SUMOylation has also been shown to play a role in the pathobiology of myriad cancers, one of which is glioblastoma multiforme (GBM). As such, the clinical significance and therapeutic utility offered via the selective control of global SUMOylation is readily apparent. There are, however, relatively few known/effective inhibitors of global SUMO-conjugation. Herein we describe the identification of topotecan as a novel inhibitor of global SUMOylation. We also provide evidence that inhibition of SUMOylation by topotecan is associated with reduced levels of CDK6 and HIF-1α, as well as pronounced changes in cell cycle progression and cellular metabolism, thereby highlighting its putative role as an adjuvant therapy in defined GBM patient populations [3].

Mella et al. report two rare cases of encephaloclastic cyst with intraventricular topotecan use. The patients were diagnosed and treated at The University of Texas MD Anderson Cancer Center. They consented to the publication of their laboratory results and imaging studies for educational purposes.

The patients presented with metastatic cancers (breast/lung) complicated by leptomeningeal disease. Ommaya reservoirs were placed in both cases and patients were initiated on intraventricular topotecan at 0.4 mg twice weekly. After approximately 12 intraventricular treatments, both patients developed confusion, seizures and headaches. MRI of the brain demonstrated cystic dilatation of the brain parenchyma around the catheter that connects to the reservoir dome and delivers the drug to the intraventricular space. The catheter was surrounded by vasogenic edema. Catheters were removed and analyzed and were found to be intact. CSF analyses showed no evidence of infection or malignancy. Intraventricular topotecan was discontinued and both patients demonstrated sustained clinical and radiological responses.

These cases highlight an atypical complication of intraventricular use of topotecan with successful management [4].

1)
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