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A Multi-Institutional Phase II Clinical Trial of a Novel Salvage Induction Chemotherapy Regimen-Gemcitabine Paclitaxel and Oxaliplatin (GemPOx) Followed by a Single High dose Chemotherapy (HDC) and Autologous Hematopoietic Progenitor Cell Rescue (AuHPCR) for Patients with Recurrent or Progressive Intracranial Germ Cell Tumors

New Developments in 2008 in the Management of Childhood and Adolescent Germ Cell Tumors of the Brain:



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1. Recurrent Germ Cell Tumors of the Brain:

Fortunately, over 90% of patients with primary germinoma of the brain, and around 65-75% of patient with the less common non-germinomatous (or mixed malignant) germ cell tumors of the brain, are now cured with initial therapy including both irradiation and chemotherapy.

Unfortunately, that still leaves a significant albeit minority of patients whose tumor does recur, and who need further treatment to afford long term tumor-free survival, hopefully cure.

Thanks to a grant from the Childhood Brain Tumor Foundation, a Consortium of North American pediatric brain cancer centers has now embarked upon the first of a series of treatment protocols to determine which are the most effective at (a) achieving a second remission (ie. disappearance of the recurrent tumor) and (b) resulting, after further therapy, in cure. The first combination being tested, based upon evidence from adults with the more common situation of recurrent germ cell tumors arising outside the brain, is oxaliplatin, gemcitabine and paclitaxel – administered in the out-patient setting every 2 weeks. This clinical trial should be completed in about 18 months, with results available shortly thereafter. The design of these studies will permit rapid replacement of this combination of drugs by another single or combination of drugs, so we can rapidly evaluate a series of treatment regimens in this otherwise rare group of brain tumors.

2. Primary Germinoma of the Brain:

It is very encouraging to know that over 90% of children with primary pure germinoma of the brain-which represents almost three-quarters of all germ cell tumors of the brain –can now be cured with fairly straightforward chemotherapy (carboplatin and etoposide, based on early work by Dr. Jeffrey Allen from New York University) followed by reduced dose ventricular field irradiation.

Unfortunately, even the reduced doses and fields of irradiation now used are damaging to the normal brain of the younger, pre-pubertal children. Furthermore, tragically, some children are already cognitively damaged by the time of presentation due to damaging effects of their tumor; addition of irradiation to the brain only handicaps them further. Finally, germ cell tumors of the brain are 15 times more common in large areas of South East Asia –areas where modern

radiation therapy techniques are simply not available. For these reasons, this author has for many years conducted series of international clinical trials (under the aegis of the International CNS Germ Cell Tumor Study Group) attempting to avoid the use of radiotherapy to the brain *completely*. To date, these studies have been successful in only about one-third of germinoma patients who can be cured with chemotherapy only.

However, hope for realizing the goal of irradiation-free therapy for pure germinomas may be at hand. A drug called Dasatinib is now available, similar to its “parent” drug Imatinib (Gleevec). These drugs are designed to kill cancer cells that either overexpress or have mutations of a cell surface receptor called *ckit*. Thus, the rare GIST tumor (gastro-intestinal stromal tumor) is cured by Imatinib alone. Germinoma tumors have been found uniformly to overexpress *ckit*, and a proportion have been shown to have mutations of *ckit*. There are indeed individual case reports of patients with germ cell tumors arising outside the brain, having failed all conventional chemotherapies, who then achieved complete and lasting responses to Imatinib.

However, Imatinib only poorly penetrates into the brain. Dasatinib, on the other hand, has been shown to penetrate the brain very well, and has been shown to cure patients with brain involvement of GIST tumors as well as certain leukemias in the brain which are treatable by this family of drugs.

Accordingly, this author hopes to launch in 2009 a new international germinoma study in which, following four courses of the conventional chemotherapy (carboplatin and etoposide), instead of administering irradiation, patients will receive Dasatinib by mouth daily for up to 2.5 years. The drug is tolerated very well by children and young adults at the proposed doses, based upon clinical trials already conducted in North America.

3. Primary Non-germinomatous (Mixed Malignant) Germ Cell Tumors of the Brain:

The largest multi-center trial ever conducted in North America in patients with these complex tumors was completed in 2008, under the auspices of the Childrens Oncology Group (COG), specifically under the direction of Dr. Stewart Goldman of Childrens Memorial Hospital, Chicago. This study used 6 cycles of more intensive chemotherapy than that used for children with germinoma, carboplatin and etoposide alternating with ifosfamide and etoposide. Following the six cycles, patients then underwent full dose (3600cGy) whole brain and spinal cord irradiation with ‘boosts’ to sites of the primary tumor.

No data are yet available from this important clinical trial, but when results do become available in 2009, they will no doubt guide important changes in the future management of such patients. At the moment, based upon European and Japanese studies, the next study –currently in the development phase – will likely reduce the doses and fields of irradiation for a proportion of these patients, at least those achieving complete responses to the chemotherapy and with initially localized tumor.

4. Biological Basis for Advancements in Management of Patients with Germ Cell Tumors of the Brain:

Significant improvements in the management of patients with germ cell tumors of the brain will require a greater understanding of the biology of these complex tumors. For example, the use of Dasatinib in germinoma patients may best be rationalized by demonstrating, at initial diagnosis,

which patients' tumors have mutations in the *ckit* receptors or other targets for which this family of drugs is known to be directed. We are planning such a molecular biologic study on tumor tissues of patients with germinomas at Childrens Hospital Los Angeles within the next few months, provided sufficient funds can be secured to perform these complex studies.

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