Oligodendrogliomas: The Achilles' Heel of Malignant Gliomas

Can. J. Neurol. Sci. 2001; 28: 187-188

Achilles was the greatest warrior in Agamemnon's army during the Trojan War. As a child his mother Thetis dipped him into the river Styx and he became invulnerable except, of course, for the part of his heel by which he was held. Handsome, brave and apparently indestructible, he was an awesome warrior. The war was almost over when he was killed by Paris'arrow, guided to his vulnerable heel by Apollo.

The War against Malignant Gliomas has been more Homeric than Homer's Greek Mythology. There has been little progress in the Glioma War and many disappointing battles. The median survival of patients with glioblastoma multiforme (GBM) is still only about a year and only 2% of patients survive more than three years.[1] "Cure", if it occurs, is very rare. Like Achilles, who ravaged the country around Troy with impunity for years and was "indestructible", malignant gliomas still kill at least 1600 Canadians per year.[2] They too, seem indestructible. The paper by Fortin and colleagues[3] is another contribution by Dr. Cairncross and colleagues that targets a weakness of this terrible foe – oligodendrogliomas are the Achilles'heel of malignant gliomas.

How did they find this important "hole" in the armor of malignant glioma?

Let me tell you the story so far … In 1985, David MacDonald returned to London, Ontario after completing his fellowship with Victor Levin at the University of California, San Francisco. Dr. Levin had begun using a combination chemotherapy called PCV-procarbazine, CCNU and vincristine[4] in patients with gliomas. Dr. Gregory Cairncross used PCV to treat a patient with a recurrent anaplastic oligodendroglioma and found the patient responded. David MacDonald treated a second patient and found she too responded. Remarkably the next eight patients with anaplastic oligodendrogliomas treated with PCV responded.[5] In a typical Canadian fashion, they conservatively concluded that PCV was "probably" useful since 100% of patients responded. They then used PCV on newly diagnosed "aggressive" oligodendrogliomas and found three of three (100%) patients responded![6] This represented a departure in the treatment paradigm and they coined the term "aggressive oligodendroglioma". This term is meant to include both histologically anaplastic tumors as well as those that behave malignantly in terms of their radiographic appearance (i.e. plentiful enhancement) or clinical behaviour (i.e. clinically aggressive or rapidly growing). Dr. Cairncross and colleagues then performed a phase II study of PCV with Elizabeth Eisenhauer at the National Cancer Institute of Canada, published in 1994.[7] In newly developed or recurrent anaplastic oligodendrogliomas, 75% of patients responded and rendered this among the most chemosensitive tumors in oncology.[8] A trial by the Radiation Therapy Oncology Group is nearing completion and compares the use of radiotherapy (RT) alone versus RT and PCV "upfront" for newly diagnosed patients with aggressive oligodendrogliomas. This phase III randomized study will determine if the addition of adjuvant chemotherapy prolongs disease-free or overall survival in patients with aggressive oligodendrogliomas and should be regarded as "standard" treatment.

Because these tumors are so sensitive to alkylator chemotherapy, it was postulated that patients with recurrent aggressive oligodendrogliomas might benefit from post-PCV consolidation with high-dose (myeloablative) chemotherapy (Thiotepa 900mg/m^2 over three days) and then by stem-cell rescue. Unfortunately the delayed toxicities related to high-dose Thiotepa in patients treated with prior brain radiation were more common than expected; there was a 20% mortality rate.[9] A trial in newly diagnosed, previously nonirradiated patients with aggressive oligodendrogliomas is currently underway.

In January 1995, Drs. Gregory Cairncross and David Louis spoke at our Brain Tumor meeting in Banff and began a collaboration to identify markers of resistance to chemotherapy in oligodendrogliomas. They speculated that tumors with mutant p53 would be more resistant to chemotherapy. Instead, they found that deletion of the short arm of chromosome 1, or concurrent losses of chromosomal arms 1p and 19q were markers of chemotherapy sensitivity and long survival following our current therapies.[10,11] It remains to be seen if 1p and 19q deletions are true markers of sensitivity or identify the only "true" oligodendrogliomas. But, for the first time in brain tumors, Cairncross and colleagues have raised the possibility that genetic information might influence the management of patients with anaplastic oligodendrogliomas. For example, patients with deletions of 1p and 19q seem to have durable responses to chemotherapy alone (lasting >7.4 years) and provides a rationale for a trial evaluating whether RT should be delayed, or indeed used at all, in these patients.[11] They have also identified molecular predictors of extraordinarily poor outcome which will likely affect clinical decision making. Perhaps novel therapies in aggressive oligodendrogliomas should be evaluated in this subgroup of poor prognosis patients who do so poorly with our current treatments.

In this issue, Fortin and colleagues[3] report their experience in attempting to identify clinical factors that predict survival and chemosensitivity in 53 oligodendrogliomas treated with PCV. These patients were all treated at the London Regional Cancer Centre over nineteen years. They were largely treated in a consistent manner with surgery and PCV chemotherapy before or after RT and in a Centre that has conservative and consistent diagnostic criteria for oligodendroglioma. Four factors that predicted long survival were found: 1) symptoms present for ≥ two months before diagnosis, 2) low grade oligo/oligo-astrocytoma, 3) low cellularity of specimen, and 4) the presence

of calcification histologically. They found no clinical predictors of chemosensitivity. Finally, and surprisingly, they discovered that a two tier grading system (i.e. low grade versus anaplastic) was sufficient to predict outcome in these patients and the presence of astocytic components did not adversely predict outcome in these patients.

"So what?" you ask. This approach is just the first step, technologically it is a simple one, and only applies to less than 4% of brain tumor patients. However, genomic and proteomic data are now being collected at an astonishing rate and these data will lead to an explosive growth in our ability to molecularly classify all brain tumors in clinically meaningful ways. For example, we will be able to identify patients with a better prognosis, select a particular treatment on the basis of the molecular profile of a patient's GBM, or decide when a particular treatment is no longer effective and should be stopped. The future is not only bright for brain tumor patients but closer than we think.

Cairncross, Louis, MacDonald and colleagues have made the most significant contribution to neuro-oncology in the last 20 years. They have done this by making careful observations, conservative conclusions and conducting well-designed studies. Their important observations have given patients and cancer researchers real hope that this disease can be cured one day.

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https://doi.org/10.1017/S0317167100001311 Published online by Cambridge University Press