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BREAKTHROUGHS IN CANCER THERAPY:

NEW AND IMPROVED CTO SHOWS PROMISE

One thing is certain about cancer treatment: The active ingredient must achieve high concentrations in the brain – without causing unacceptable toxicity in the patient. That's an especially tricky balance to achieve in treating gliomas and glioblastomas; that's because the treatment compound must cross the blood brain barrier to reach the tumor target; otherwise patient survival rates won't rise. But when that happens, neurotoxicity may follow.

That's why any advance in brain-penetrating drugs with reduced toxicity is welcome news in the cancer research community, and that's why so many key opinion leaders find themselves increasingly excited about carboxyamidotriazole orotate (CTO), the second-generation, "new and improved" version of 5-amino-1-(4-(4-chlorobenzoyl)-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, known from more than a dozen clinical trials in the 1990s as CAI.

Technically, CTO is the orotic salt version of CAI, explains Rashida A. Karmali, PhD, CEO at Tactical Therapeutics Inc. While CAI demonstrated promising efficacy in preclinical and clinical studies, she says, observed toxicities, neurotoxicity in particular, limited the use of higher doses. CTO boasts better tumor-fighting properties with a neurotoxicity profile that promises wide tolerance in refractory brain cancer patients.

The problem was the hydrophobic properties of CAI caused binding to plasma proteins and poor absorption, according to Dr. Karmali, resulting in poor bioavailability and efficacy. But CTO has increased bioavailability and reduced toxicity. Also, the CAI that forms a stable complex with orotic acid is manufactured by a new process using different ingredients. In other words, it appears that some of CAI's toxicities could have been caused by ingredients that are not present in the "new and improved" CTO.

In addition, in new preclinical studies, CTO has demonstrated a reduction in exosome-stimulated angiogenesis and in vascular endothelial growth factor expression and secretion; as well, Dr. Karmali points out, researchers have seen a reduction in proliferation, adhesion, motility and vascular tube formation. Inflammation inhibition has been demonstrated, accompanied by a reduction in TNF-α and IL-1β levels. And through non-voltage-dependent calcium signaling, several transduction pathways are impacted in parallel, including multiple tyrosine kinase signaling pathways.

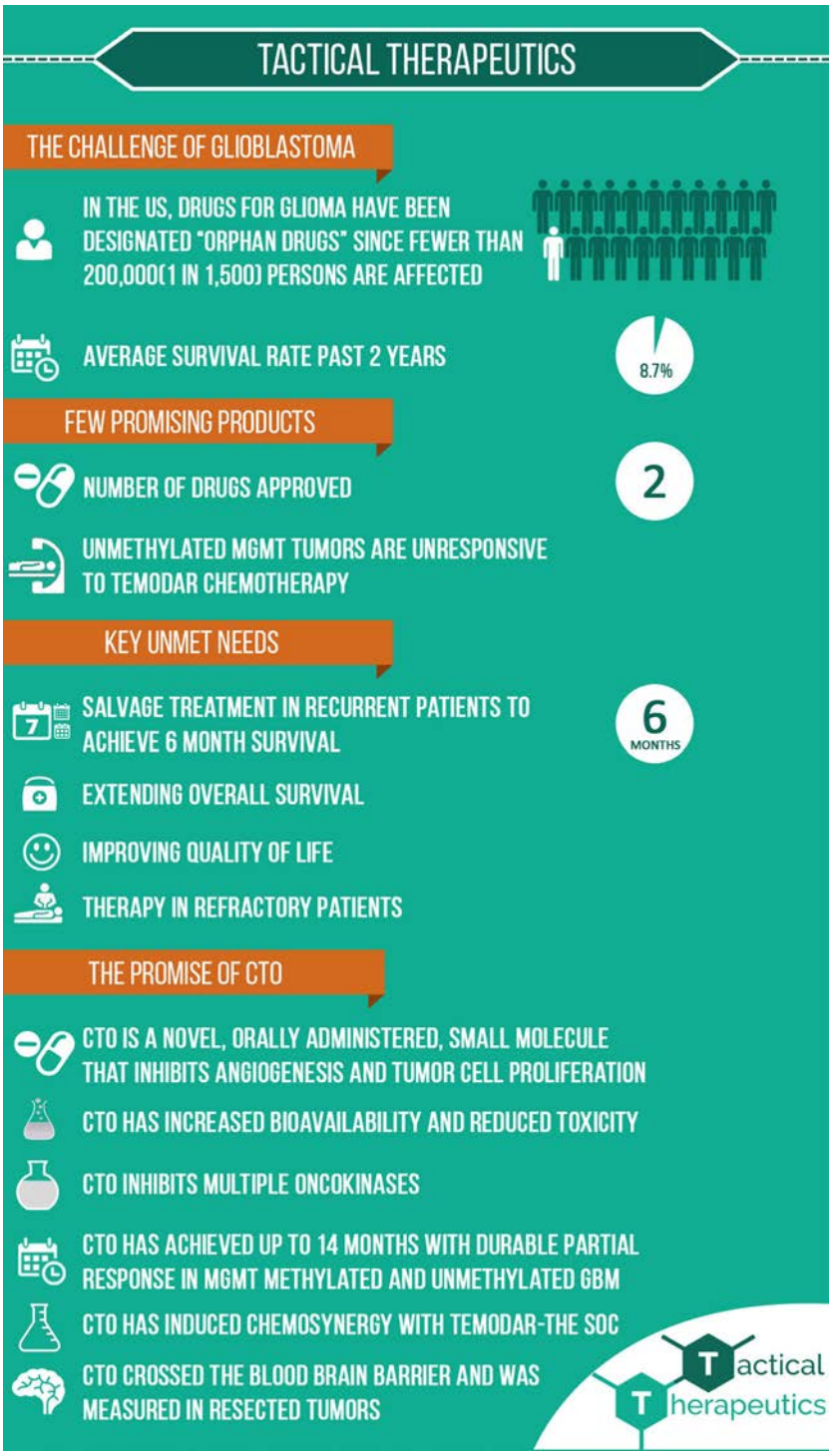
CTO, in short, may work just the way oncologists hoped.

CTO Clinical Program: Success in Multiple Studies

"We're seeing responses that we rarely see in Phase 1 in brain tumors. We are detecting therapeutic levels of the drug in the tissue itself. That is very important – and really encouraging."

That's how Antonio M. Omuro, MD, a neuro-oncologist at Memorial Sloan Kettering Cancer Center and the Principal Investigator in the development of carboxyamidotriazole orotate, describes the current state of research. The CTO clinical program includes multiple studies; here are details:

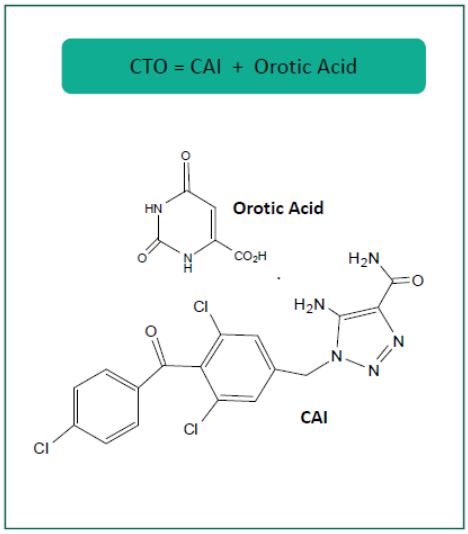
- A study on refractory solid tumors has shown safety and tolerability with no dose-limiting toxicities; a subset of nine of the 42 patients responded to CTO despite having multiple resistance mutations.
- In a study on refractory gliomas and GBMs, CTO in combination with Temodar showed no Grade 4 or 5 adverse events and, importantly, no dose-limiting toxicities – just fatigue, nausea, vomiting and dizziness. Four patients continue treatment with stable disease, a partial durable response has been demonstrated in two and a complete response has been demonstrated in an MGMT-negative patient. Responses were seen in patients failing bevacizumab, a group of patients that is very hard to treat.
- And in a new study on newly diagnosed GBMs, CTO will be studied in combination with Temodar and radiation therapy.



CTO: PART OF THE POTENTIAL $1.4B GLIOBLASTOMA MARKET

The big news about carboxyamidotriazole orotate is, of course, that it might work. And the number of patients who could benefit from it – especially if it's successfully used to treat solid tumors besides gliomas and glioblastomas – combined with the lack of effective alternatives mean CTO is a potentially blockbuster opportunity. Tactical Therapeutics, which owns a patent for the compound that's good through 2030, is seeking a strategic development and commercialization partner; indeed, the company is eager to negotiate a licensing deal with a suitable pharma company.

CTO is currently in multiple trials for malignant gliomas and glioblastomas at Duke University and Memorial Sloan Kettering Cancer Center, among other leading research institutes. The average incidence of glioblastoma in Europe and the U.S. stands at about 3.5 cases per 100,000 individuals; in 2011, some 22,000 U.S. adults were diagnosed with primary malignant tumors of the brain and spinal cord. Overall, the market potential for glioblastoma alone will increase to $1.4B by 2022 – from less than $800 million in 2012.



"The pharma industry is paying much more attention to brain tumors than ever before, which is exciting" notes Antonio M. Omuro, MD, a neuro-oncologist who coordinates a multidisciplinary team of neurosurgeons and radiation oncologists at Memorial Sloan Kettering Cancer Center. "There's a big need there that everybody is aware of." But despite the substantial market opportunity, existing therapies won't capture a significant share because of their efficacy or tolerability failures. That means that not only does CTO seem to work well in gliomas and GBMs without crippling neurotoxicity, Dr. Omuro explains, it may also have a wide forward-looking application in other solid tumors and brain metastasis.

Some Relevant CTO Key Patents

Patent #	Filed	Expiry Date	Geographies	Description
8,377,973	3-Sep-2010	3-Sep-2030	ARIPO, Australia, Brazil, Canada, Chile, China, EP, Hong Kong, India, Indonesia, Israel, Japan, Korea, Malaysia, Mexico, New Zealand, Philippines, Russia Fed, Singapore, South Africa, Thailand, Ukraine, Vietnam, WO (24)	Compositions and processes for preparing 5-amino or substituted amino 1,2,3-triazoles and triazole orotate formulations *Divisional application in the US: 13/694,895 (US 16-Jan-2013)*
13/986,103	1-Apr-2013	1-Apr-2033	US	Methods and composition for treating cancers having acquired resistance to prior chemotherapeutic and targeted drugs with Carboxyamidotriazole (CAI) orotate
13/957,720	2-Aug-2013	2-Aug-2033	US	Methods and molecular pharmacodynamic biomarkers for multiple signaling pathways in response to Carboxyamidotriazole (CAI) orotate
7,750,018	6-Dec-2006	6-Dec-2026	US	Use of carboxiamidotriazole (CAI) orotate in macular degeneration
8,420,658	24-May-2010	24-May-2030	Australia, Canada, China, China(2), EP, India, Israel, Japan, Korea, WO (10)	

CTO Clinical Trial Estate: Clinical Development in Oncology

Indication	Treatment	Phase of Development					
		Pre-clinical	Phase I	Phase II	Phase III	NDA	Launched
Malignant Gliomas and Glioblastoma	*CTO +/- Temodar, Avastin, CCNU*						
Ovarian Cancer	*CTO + Paclitaxel*						
Non-small Cell Lung Cancer (NSCLC)	*CTO + Carboplatin*						
Small Cell Lung Cancer (SCLC)	*CTO + SOC*						
Metastatic Colorectal Cancer	*CTO + Xeloda*						
Renal Cell Carcinoma	*CTO + SOC*						
Head and Neck Cancer	*CTO + SOC*						
Metastatic Melanoma	*CTO + Temodar*						
Prostate Cancer	*CTO + SOC*						

SOC = Standard of Care

Tactical Therapeutics

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