Dr. Kübler GmbH

"CANCER IS A MOLECULAR ACCIDENT
THAT OUGHT TO BE AVOIDED"

Stem Cells for Diagnostics and Therapy of Glioblastoma

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Glioblastoma is the most common and lethal brain tumor in adults. 80% of all surgical cases return within 18 months. Metastasis is not detected in time. Metastasis prevention by radiotherapy or chemotherapy disappoints. Previous vaccination strategies, for example against EGFR, extended the average survival from 6.3 months to 14.2 months. But these monovalent vaccines generated resistances of surviving cells by selection pressure of the immune response.[1]

Causes

Until now, vaccination takes place against tumor cells only, not against tumor stem cells. The underlying cause of glioblastoma is the loss of controllability of normal glial cells and the formation of tumor stem cells in a stem cell niche. Dr. Kübler GmbH succeded first in biopsy-free characterization of these cells by a patented apheresis method.[2]

Proceedings

This method allows:

1. detection of circulating tumor stem cells without biopsy
2. quantification of these cells
3. their complete molecular characterization: c-Met, Oct-3/4, GFAP, EGFR, erb/B2, erb/B3, c-myc, Urokinase

These tumor stem cells are angiogenic, they recruit their own blood vessels, they remain and proliferate in so-called stem cell niches, where they are beyond the reach of scalpel. They are resistant against chemo and radiation treatment. [3-5]

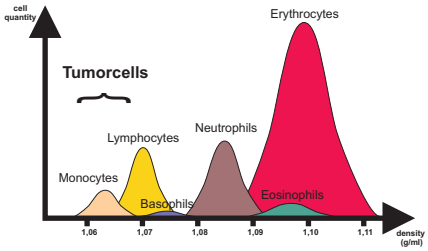
After isolation and culturing of the tumor stem cells, we use their complete antigenic material for immunization of the patient and to initiate a NK cell response.

In addition, we use biological deacetylation inhibitors and protease inhibitors, which prevent further degeneration of the tumor stem cells and protect from their invasive potential. This gives the patients survival time that is in most cases longer than those of standard therapy.

In particular, we avoid evolutionary pressure by toxic chemotherapy and radiation therapy on the tumor stem cells. By this way, we extend the survival of patients by means of non-toxic treatment.

Diagnostic Apheresis

The Diagnostic Apheresis enables a quantitative extraction of circulating Cancer Stem Cells from the bloodstream and their complete molecular-pathological characterization without any biopsy.[2],[6]



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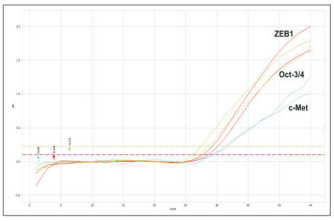
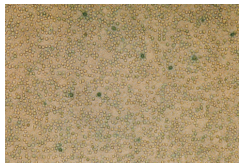
Real-Time RT-PCR

The Real-Time RT-PCR (reverse transcriptase-polymerase chain reaction) allows the detection of circulating cells with deranged epithelio-mesenchymal transition in the bloodstream.

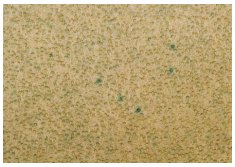


Detection

A specifically developed ELISA test (enzyme linked immuno-sorbent assay) as well as FISH techniques (fluorescence in situ hybridisation) provide a single cell detection and consequently a quantification. Furthermore an expression profile of circulating tumor cells is created by determination of different biomarkers.[6]



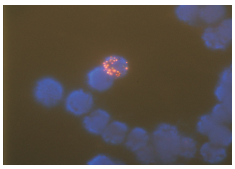
c-Met positive cells



Oct-3/4 positive cells

Prognostic und predictive BIOMARKERs:

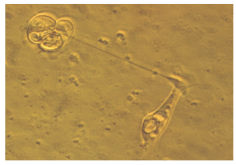
myc	CD44v5/v6
ras	VEGF
p53m	Akt/mTOR
EGFR	GFAP
erb/B2	Indolamindeoxygenase
erb/B3	Survivin
MDR	Oct-3/4
c-Met	

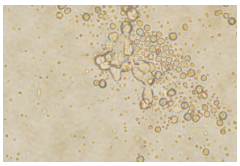


c-erb/B2 gene amplification

Therapeutic consequences

A combined immunotherapy consisting of Natural Killercells (NK cells) and heat-shock proteines can specifically attack and destroy Cancer Stem Cells.[6]





NK cells

Literature

[1] Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor vIII peptide vaccination in patients with newly diagnosed glioblastoma, Sampson, J.H. *et al*, JCO 2010, 28:4722-4729.
[2] Process for the *in vitro* diagnosis of a glioma or an astrocytoma, 26.01.2011, No. of document 1486787B1
[3] Cancer Stem Cells, Jordan, CT., Guzman, ML., Noble, M., N. Engl. J. Med. 2006 355;12, 1253-61
[4] Tumor Cells circulate in the peripheral blood of all major carcinomas, but not in healthy subjects or patients with non-malignant diseases, Allard, J. *et al*, Clin Cancer Research 6897, 2004
[5] The evidence for Cancer Stem Cells, Niederhuber, J., (NCI, Bethesda) 5th Int. H.F.C. Behr-Symposium 2008, DKFZ Heidelberg
[6] Dr. Kübler GmbH Deutsches Bundespatent 4228389; Europ. Patent 0.584.715; US-Patent 5,529,903; Japan. Patent JP 211352
Further Literature: www.kueblergmbh.com