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Trial shows which brain cancer patients benefit from temozolomide

Genetic predictive test clears way for targeted drug treatment

Geneva, Switzerland: An international team of scientists and cancer specialists has identified which patients with the deadly form of brain tumours called glioblastomas are likely to live longer if they are treated with temozolomide, and which patients are likely to get only marginal, if any, benefit.

The genetic predictive test on tumour biopsies to identify who will benefit from the drug could be carried out fairly easily in any genetics laboratory and takes only two to three days, although the availability and quality of the tissue is an important issue. If implemented widely it would mean that temozolomide would become a targeted treatment.

Dr. Monika Hegi told the EORTC-NCI-AACR[1] Symposium on Molecular Targets and Cancer Therapeutics in Geneva today (Wednesday 29 September) that the key to predicting which patients will gain from temozolomide was a gene called O-6-methylguanine-DNA methyltransferase (MGMT) – which is involved in DNA repair – and its respective methylation status in the patient's tumour.

Methylation is one of the ways that cells control which genetic information they will use. If the MGMT promoter is methylated, the MGMT gene is silenced and this means that no MGMT repair enzyme will be produced, thus preventing correction of faults in the DNA.

Dr. Hegi, head of the laboratory of tumour biology and genetics at the Department of Neurosurgery, University Hospital of Lausanne, Switzerland, said that of a total of 573 patients, biopsies from 206 glioblastoma patients had been tested successfully so far in a seven-country trial organised by the EORTC and National Cancer Institute of Canada Clinical Trials Group (NCIC). 45% had a methylated MGMT promoter, meaning that the MGMT gene was silent and their DNA repair system was impaired.

In this tested group 106 of the patients have been treated with radiotherapy and temozolomide. There was a 46% survival rate at two years for the 46 patients in the group who had a methylated MGMT promoter (silent MGMT gene) but for the 60 patients with non-methylated promoter (active MGMT gene) status the two-year survival rate was only 13.8%, a statistically highly significant difference.

"These results are important because temozolomide is a drug that acts directly against DNA to slow down the replication of cancer cells. So, it is bad news if the patient has non-methylated status because the DNA in these rogue cancer cells is being repaired as fast as the drug causes damage. This means the cancer cells are able to survive the drug's onslaught," said Dr. Hegi, who is also project leader at the national Centre of Competence in Research Molecular Oncology at ISREC in Epalinges, Switzerland.

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She said that the study was the first randomised trial to test MGMT methylation status in a large patient population. "The test will provide the opportunity to select patients that might profit from temozolomide. In other words, temozolomide can become a targeted treatment. It is a first step towards molecular diagnostics. In the future, biopsy material optimally conserved for molecular testing should be collected for all patients as a routine diagnostic procedure."

It also meant, she added, that for patients without methylation, future clinical trials could be designed evaluating new treatments rather than treatments with temozolomide. Temozolomide would now certainly become the standard treatment for those patients whose tests predict that they would benefit from the drug.

Dr. Hegi said these results were important not only for patients who were likely to benefit, but also for those that were not. Even though the drug was well tolerated it still had inherent toxicity. Patients who were unlikely to respond could be spared side effects and possibly benefit from other treatments that would be more effective for them. Another drug called 06-Benzyl-guanine – a substrate for the MGMT enzyme – was currently being tested to see if it would deplete the activity of MGMT. Combined with this drug it was possible that temozolomide might also then become effective in patients with an unmethylated MGMT promoter, although it would be likely to increase toxicity to other organs as MGMT protected against DNA mutations. The research team is also analysing the trial biopsies for molecular patterns that might indicate possible new drug targets.

Temozolomide is the first chemotherapy for 30 years to have been proven effective for glioblastomas, which make up around 12 to 15% of all brain cancers with 2-3 new cases diagnosed per 100,000 population annually in Europe and North America. The drug was approved in 1999 for use in patients who have relapsed after initial treatment.

"Our results should encourage and fuel further multidisciplinary research, bridging the gap between basic research and clinical practice," said Dr. Hegi. "Whether temozolomide will cure some patients remains to be demonstrated. Glioblastoma remains a dreadful disease without a cure, and there is still a long way to go."
(ends)

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[1] EORTC [European Organisation for Research and Treatment of Cancer
NCI [National Cancer Institute]
AACR [American Association for Cancer Research]

[2] Source: World Health Classification o f Tumours, Pathology & Genetics. Tumours of the nervous system. Kleihues, P. and Cavenee, W.K. (Eds) pp 29-39. IARC*Press*. Lyon. France, 2000.

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