Improving outcome for brain tumor patients

Martin J van den Bent*: Martin J van den Bent is trained as a neurologist. Since 1992, he has worked at the Neuro-Oncology Unit of Erasmus MC – Daniel den Hoed Cancer Center in Rotterdam, The Netherlands. In 2002 he became the head of the Neuro-Oncology Unit, which is focused on the treatment of primary brain tumors and on neurological complications of cancer and its treatment. He is currently Professor of Neuro-Oncology at Erasmus University, Rotterdam. He has been the principle investigator of a large number of international multicenter trials on both high- and low-grade glial tumors, most of which were conducted

through the European Organisation for Research and Treatment of Cancer Brain Tumor Group. Many of these trials included translational research projects, focusing on the identification of prognostic and predictive molecular parameters of outcomes of treatment. He was Secretary of the European Organisation for Research and Treatment of Cancer Brain Tumor Group from 1996 to 2002 and from 2002 to 2009 he was Chair of this internationally recognized group. He has served as Chairman of the CNS section of the 14th European Cancer Conference and of the Dutch Neuro-Oncology Working Group. He has published widely, not only on the treatment of primary brain tumors, but also on neurological complications of systemic cancers. He has chaired and lectured at numerous national and international educational symposia and scientific meetings on neuro-oncology and serves on the editorial board of several oncology journals, including *CNS Oncology*. He has written chapters in many textbooks on neuro-oncology and is active in the Response Assessment in Neuro-Oncology Group revising the end points and response criteria of trials in neuro-oncology.

Q What originally led to your interest in glioma?

I decided that working in a cancer hospital was more of a challenge than working in a general hospital. I was previously a resident in neurology, and had developed my own clinical study in herniated cervical disk, which is still one of the very few randomized studies on that topic. I found the clinical study part interesting, but most of the daily patient work was on lower back pain, headache and other unclear complaints. I became interested in brain tumors because of my experience with a strange primary

CNS lymphoma case with a prolonged response on steroids and felt that 2 years in a cancer hospital could be interesting. Shortly after my arrival in the cancer hospital, interesting results were reported on oligodendroglial tumors and we set up several studies to further investigate this.

Q What was particularly interesting about these studies & how did this influence your work?

At that time (1992) chemotherapy was not given to brain tumor patients, and the medical oncologists were doing trials with

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a combination of ifosfamide and cisplatin, and we decided to try the same approach in recurrent high-grade glioma. Reports then appeared on procarbazine, lomustine and vincristine (PCV) chemotherapy in anaplastic oligodendroglioma and we developed a similar approach as well, although it took some discussions with our partners, the medical oncologists, to convince them that these brain tumors should be treated differently. I then started to collect cases from elsewhere, and things started to build up. We saw a good percentage of responding patients and were considering a prospective trial. By the time I had been at the cancer hospital for 2 years, I had too many interesting things on my plate to leave.

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Q Which researchers have influenced or inspired your research?

Professor Greg Cairncross (University of Calgary, Canada) has inspired me, and not only with his reports on oligodendroglioma tumors. It is the combination of good clinical work and asking good clinical questions as well as molecular side studies that particularly inspired me. With Dr David MacDonald (London Regional Cancer Program, Ontario, Canada), Professor Cairncross developed the first response criteria, he identified oligodendroglioma tumors as a chemotherapy-sensitive disease, had a good eye for the impact of steroids and analyzed bias in trials; all very relevant basic research.

Q What has been your biggest achievement in the field?

The European Organisation for Research and Treatment of Cancer study 26951, which investigated adjuvant PCV in anaplastic oligodendroglioma tumors has been my biggest achievement [1]. In particular, the long-term follow-up and the correlation of outcome with molecular features.

With this trial, we showed that the addition of PCV chemotherapy significantly improves survival in anaplastic oligodendroglioma patients with combined 1p/19q codeletion. In this group, after a median follow-up of almost 12 years, median survival had still not been reached in radiation therapy (RT)/PCV-treated

patients, but was only 9 years in patients randomized to RT. What is equally relevant is that 75% of progressing patients in the RT arm received chemotherapy at the time of progression. Thus, this really was a trial convincingly showing the benefit of early chemotherapy versus delayed chemotherapy. The benefit was much less in the patients without the 1p/19q codeletion, and did not reach significance here.

Q You are a member of the Response Assessment in Neuro-Oncology Working Group; what are the aims of this group?

The basic aim of this group is to improve the quality of neuro-oncological research, in part by a better definition of outcome, but also by improving trial design. The Response Assessment in Neuro-Oncology Group has been successful in bringing people together to discuss the way we are conducting trials. We are also seeing the first critical evaluation of our papers, which is good. There is also much more emphasis on the choice of end points, and they are discussed more fundamentally before trials start. But, it should be well understood that the Response Assessment in Neuro-Oncology is no dramatic change, but more an evolutionary process.

Q You have worked extensively on clinical trials in neuro-oncology, what are the biggest challenges when conducting trials in this field?

The biggest challenge is the funding of trials. There are many interesting research questions, but they cannot be pursued because of the budgets required. Furthermore, sites participating in studies need to be rewarded and recognized for that, as they contribute to the improvement of care for cancer patients. We also need to be aware of the increasing bureaucratic demands of trials; conducting trials is much more complicated than a decade ago.

Q What changes in clinical trials do you think are required in order to advance neuro-oncology drug development?

One of the major changes we need is to see more frequent controlled designs, to allow a better interpretation of results. We are still facing too many uncontrolled and

small Phase II studies that do not really contribute to advances in patient care. Controlled trials must be used early on in studies on glioma. They allow a better understanding of the random bias in trials (and these are much more frequent than we think – they explain some of the recent disappointments, e.g., with enzastaurin) and they allow better translational research studies, which may identify predictive factors for outcome. If uncontrolled trials show something that looks like a good outcome, that may be simply the effect of patient selection or center effects. Any marker picked up in an uncontrolled study may merely be a prognostic marker, not reflecting outcome modification because of the study treatment. The drawback is that more patients are needed, but the results are more reliable. To make trials more acceptable for patients, we may need more placebo-controlled trials.

Q You recently presented an abstract at the American Society of Clinical Oncology on the benefit of radiotherapy plus chemotherapy for the treatment of anaplastic oligodendroglioma. Could you briefly describe the results & their clinical implications?

We have shown that the addition of PCV to RT greatly increases survival in 1p/19q codeleted anaplastic oligodendroglial tumors [1]. Despite the fact that 75% of patients randomized to RT received chemotherapy at progression, median survival was 9 years in the radiotherapy group and was still not reached after almost 12 years in the group randomized to radiotherapy and PCV. This trial will now be practice changing, in that patients with 1p/19q codeletions will be treated with a combination of RT and chemotherapy.

Which chemotherapy is unclear; we investigated PCV and that is now considered standard because of these trials. However, without any formal trial PCV has been replaced by temozolomide because of its better tolerability. The ongoing CODEL trial (a trial on 1p/19q codeleted patients with a RT control arm) has been halted because of these trials. Most likely, that arm will be modified into RT/PCV, with the

other arms being RT/temozolomide and temozolomide alone.

Q You also have an interest in molecular markers of disease, how successfully do you think the use of clinical markers has been incorporated into clinical practice? How do you envisage this changing over the next 5–10 years?

With the current trials, testing for 1p/19q will become part of standard diagnostics. Moreover, the role for MGMT testing is increasing, although the assay for this remains cumbersome. I also expect testing for IDH will gain clinical significance in the next 1–2 years.

Q What do you see as the hot topics for neuro-oncology research over the coming years?

We are expecting the results of the big trials on bevacizumab and cilengitide. I hope they will show some improvement of patient outcome and that they will lead to new questions. Furthermore, the basic assumptions of personalized medicine in glioblastoma will become a topic of investigation in several projects. The most important challenge remains, however, to identify active drugs in neuro-oncology.

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Reference

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