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Interview with Dr Martin van den Bent (Rotterdam) about the EORTC CATNON Trial on Grade-3 Gliomas

Ufuk Abacioglu

From the Department of Radiation Oncology, Marmara University Medical School Hospital, Istanbul, Turkey

Q: Dr van den Bent, what can you tell us about the ongoing CATNON trial on grade-3 gliomas? What is its background?

A: The background of this trial is the fact that both the North American and the European trials on adjuvant PCV chemotherapy failed to improve outcome in anaplastic oligodendroglial tumors, whereas the EORTC trial on chemo-irradiation with temozolomide improved survival in glioblastoma - a much less chemotherapy-sensitive disease compared to anaplastic oligodendroglial tumours. And although many people have intuitively felt that grade-2 and grade-3 tumours were simply less aggressive compared to glioblastoma, the current developments in the IDH1 arena clearly show that these are different diseases. Thus, the question is on the table whether combined chemo-irradiation improves outcome in anaplastic glioma. Just the fact that it occurs in the same organ does not justify a similar treatment - the best treatment needs to be investigated. After all, we are not treating ovarian cancer in the same way as breast cancer, simply because they occur both in females.

Q: How is the trial designed?

A: It is a randomized phase-III study requiring 740 patients, using a 2×2 design. Patients are randomized to radiotherapy alone, radiotherapy followed by adjuvant temozolomide, radiotherapy with concomitant temozolomide, and radiotherapy with both concomitant and adjuvant temozolomide. That design will also allow us to investigate whether the outcome is improved with early temozolomide treatment, and whether both adjuvant and concomitant temozolomide are contributing to the improved outcome.

Q: Which groups, countries, and how many centers participate in the trial?

A: This is truly an intergroup effort with contributions from 3 continents. In Europe, EORTC, MRC, and NOA are contributing, in the United States the effort is led by the RTOG with active participation of NCIC and NCCTG. On top, our colleagues in Australia and New Zealand are very active and have entered more than 20 patients.

Q: Why did you choose to do a 4-arm trial?

A: It is not really a 4-arm trial, but the 2×2 design allows us to make a more meaningful analysis than a 2-arm study. A true 4-arm study would lead to a huge study, which would not be feasible in this disease.

Q: What are the stratification factors?

A: In this trial, the stratification factors are institution, performance status, age, loss of 1p, the presence of oligodendroglial elements, and the MGMT promoter methylation status. This implies that, prior to randomization, patients are both tested for 1p/19q status and MGMT promoter methylation. This trial really marks the transition from inclusion based on histology to inclusion based on molecular features.

Q: There is a central pathology review. How do you do that and what kind of difficulties do you have about it? Do you have any preliminary MGMT data for anaplastic tumours? Do you plan to implement IDH-1 mutation analysis in the trial?

A: It is at present well understood that the diagnosis of grade-2 and grade-3 gliomas is subject to a considerable interobserver variation. To be eligible a confirmation of the grade-3 diagnosis and absence of a combined 1p/19q co-deletion is required. Patients can be entered for central review once a local diagnosis of a grade-3 tumour has been made. It was expected that we would experience a high interobserver variation, and to make the central reviewer process less subjective we included 2 central reviewers. The rule for this trial is that a patient becomes eligible if both central reviewers make the diagnosis of a grade-3 tumour. Indeed, so far, our experience in this trial confirms the experience of other projects, with a high interobserver variation. However, I would like to stress the importance of submitting sufficient and representative material. As an example, from a recent patient, we only received a fragment of tissue with some dural membrane in it. Another important element is to submit tissue blocks. This is of particular relevance for future research. This type of research has been pivotal for many of the important discoveries that were made in the recent EORTC trials.

Currently, a trial amendment is in preparation that will include testing for IDH mutations as part of the obligatory testing within the study. A pre-specified study analysis based on the IDH1 mutational status will also be part of this amendment.

Q: In recent clinical trials, we observe more quality assurance issues. How is that issue taken care of in CATNON?

A: Apart from more regular monitoring of sites, there is quality control of radiotherapy. This means that the site is asked to fill in a questionnaire and an RT dosimetry study prior to local trial activation. After study activation and patient entry, the radiotherapy planning of a certain number of patients will be reviewed. For this, the actual radiotherapy plan has to be submitted.

Q: How is the accrual and when do you expect to reach the accrual goal? When can we get the first results?

A: Currently, all groups have activated the study and this is truly a multi-continental study with participation of European groups (EORTC, MRC, NOA), North-American groups (RTOG, NCCTG, NCIC) and Australian/New Zealand sites (through the TROG). With all these groups being activated, accrual has gone up steeply, in the last month [ie, April 2011] 15 patients were entered. A total of more than 200 patients have now been entered into this study that requires 740 patients. The accrual will take another 3–4 years, and it is expected that after completion of the accrual another 3–4 years are needed to get the first results.

Thank you very much!

Correspondence to:

Ufuk Abacioglu, MD Department of Radiation Oncology Neolife Medical Center Yucel Sok # 6 1. Levent, Besiktas 34340 Istanbul Turkey e-mail: ufuk@abacioglu.com