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Abacioglu U

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Interview with Dr James Perry about the NCIC-CTG Elderly Glioblastoma Trial

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Can you tell us about the ongoing “Elderly Glioblastoma” trial? What is the rationale and background for this trial?

A: Thank you for giving us the forum to discuss this international cooperative group study that addresses an important unmet need in the management of older patients with glioblastoma. We know from the EORTC/NCIC-CTG study that the addition of concurrent and adjuvant temozolomide (TMZ) to standard radiotherapy (60 Gy/30 fx) clearly improves survival [1]. However, a trend-benefit analysis by the EORTC found decreasing benefit with increasing age. We do not know if this was due to the size of the subgroup of elderly patients in the trial (and therefore a problem with statistical power) or if there is truly less benefit seen with increasing age. Therefore, a randomized trial testing the same clinical question (RT ± concurrent and adjuvant TMZ) was proposed for newly diagnosed elderly patients. We learned from the Roa et al trial that 40 Gy/15 fractions (ie, 3 weeks) of radiotherapy appears to give similar survival results to 60 Gy/30 fractions in the elderly [2]. We also learned from the ANOCEF trial that so-called “short-course” radiotherapy plus supportive care is superior to supportive care alone [3]. Therefore, this trial was built around the central premise that many older patients are given short-course radiotherapy in brain tumour centres across the world; yet we do not know if the addition of concurrent and adjuvant TMZ is of benefit.

Q: What are the design and inclusion criteria?

A: This is a randomized phase-III trial for patients over the age of 65 with newly diagnosed glioblastoma. Local pathological diagnosis is sufficient for study randomization but tissue is being collected for molecular companion analyses, especially determination of MGMT promoter methylation status. Patients are stratified within predefined age groups, by PS, and by centre. There was one planned interim futility analysis and the independent DSMB has recommended proceeding with the trial.

Q: What is your definition of the elderly? Why did you choose 65 as cut-off?

A: Initially we designed this study with age restricted to 70 and above. This “pure” approach would therefore not overlap with patients who were in the previous EORTC/NCIC-CTG study and for whom level-1 evidence suggests treatment with “full-course” radiation plus chemotherapy. However, we felt that the statistical power of the results over the age of 65 left the 65–70-year-old age group in an uncertain category and, after discussions with colleagues at the EORTC Brain committee, we came to realize that many centres use shorter-course radiotherapy routinely over the age of 65. So this be-

came a pragmatic point in terms of maximizing accrual opportunity. To date, the median age of patients in the study is 73 years; so we believe that we are collecting an older cohort of patients ($\frac{1}{3}$ is 65–70, $\frac{1}{3}$ is 71–75, and $\frac{1}{3}$ is > 75). It is important to remember that the central question of this study is to test whether or not the addition of chemotherapy is important for patients who are recommended short-course radiation therapy. We expect that some centres will continue to offer 60 Gy/30 fractions to suitably fit patients between 65 and 70; so this study requires and allows for clinical judgement of the best radiotherapy prescription on a case-by-case basis.

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

A: The study is led by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) with major participation from the EORTC, the Trans-Tasman Radiation Oncology Group (TROG), Japan, and most recently by the new American cooperative group (ACTION). Accrual to date is NCIC-CTG 17 sites, n = 135; EORTC 27 sites, n = 122; TROG 14 sites, n = 53, and Japan 2 sites, n = 6.

Q: Recent results from the German NOA-8 and Nordic trials showed somehow contradictory results on first-line treatment with radiotherapy or temozolomide [4, 5]. Taking into account those 2 other trials, how will your trial answer the question of treatment for this population? Would you prefer to have a third arm with temozolomide alone within the trial?

A: These 2 important clinical trials did not show superiority of radical radiotherapy in newly diagnosed elderly patients with glioblastoma. Taken together with prior radiotherapy studies in the elderly we feel it is now reasonable to consider shorter-course radiotherapy (such as 40 Gy/15 fx) as standard of care. These results fortuitously make the study question in our trial an important one. Our ongoing study will be the first to test the efficacy and toxicity of concurrent and adjuvant TMZ added to this radiation scheme. We initially included a chemotherapy-alone arm; however, this resulted in a very large sample size and, at that time, would have conflicted with the ongoing European trials.

Q: Do you have any translational or biological investigation in this trial?

A: Tissue is being collected and a full translational analysis will be coordinated and conducted through the NCIC-CTG headquarters in Kingston, Ontario, Canada.

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

A: The addition of the EORTC provided a meaningful increase in accrual and we anticipate the participation of US centres in early 2012. In order to have 90-% power to detect a 25-% increase in the primary outcome of overall survival (increased MST from 6 to 8 months) between arms, using a 2-sided 5-% alpha, a minimum of 520 deaths must be observed prior to analysis. Total sample size is 560. As of September 30, 2011, there were 316 patients randomized. The accrual rate is approximately 10–12 per month at present, so we estimate the trial will complete accrual by the end of 2013.

Thank you very much!

James Perry is NCIC-CTG study co-chair (along with Dr Normand Laperriere) for the trial entitled “A randomized phase III study of temozolomide and short-course radiation versus short-course radiation alone in the treatment of newly diagnosed glioblastoma multiforme in elderly patients”.

Contact details:

James R Perry, MD, FRCPC
Division of Neurology
Sunnybrook Health Sciences Centre
University of Toronto
A402, 2075 Bayview Avenue
Toronto, Ontario, Canada M4N 3M5
Phone: (001) 416-480-4766
Fax: (001) 416-480-5054
e-mail: james.perry@sunnybrook.ca

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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