The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Intrinsic molecular subtypes of glioma are prognostic and predict benefit from adjuvant PCV chemotherapy in combination with other prognostic factors in anaplastic oligodendroglial brain tumors. A report from EORTC study 26951

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Eligibility criteria

Patients were eligible for this study if they a) had been diagnosed by the local pathologist with an AOD or with a mixed AOA with at least 25% oligodendroglial elements according to the WHO 1993 classification for brain tumors(1), b) with at least 3 out of 5 anaplastic characteristics (high cellularity, mitosis, nuclear abnormalities, endothelial proliferation or necrosis), c) were between 16 and 70 years of age, d) had an ECOG Performance status 0 - 2, e) had not received prior chemotherapy or radiotherapy to the skull, g) with adequate bone marrow, renal and hepatic function and h) with written informed consent according to local and national guidelines. All centers had to obtain approval of the study design from their local ethical board prior to study activation. All tumor specimen were centrally reviewed (by J.M.K.) who scored the histology subtype and the presence or absence of the above mentioned pathological features according to the WHO 1993.(1)

Treatment

RT was to begin within 6 weeks from surgery and consisted of a dose of 45 Gy to be delivered to the planning target volume (PTV-1) in 25 daily fractions of 1.8 Gy, 5 fractions a week. Thereafter, a boost of 14.4 Gy (up to a cumulative dose of 59.4 Gy) was delivered to the PTV-2 in eight fractions of 1.8 Gy, 1 fraction a day, 5 fractions a week. PTV-1 was defined as the low-density area on preoperative computed tomography (CT) scanning and/or the high-density area on preoperative T2-weighted magnetic resonance imaging (MRI) scan with a margin of 2.5 cm. The PTV-2 was to include the nonenhancing tumor area and/or the enhancing area as visible on the postoperative CT scan with contrast with a 1.5-cm margin; in case of an unenhancing tumor on CT scan, a postoperative MRI scan with and without gadolinium was recommended to further define the tumor volume.

PCV chemotherapy consisted of six cycles of standard PCV chemotherapy and had to start within 4 weeks after the end of RT. Each cycle consisted of lomustine 110 mg/m^2 orally on day 1 with antiemetics (domperidone or metoclopramide, and if necessary, ondansetron or a similar agent), procarbazine 60 mg/m^2 orally on days 8 to 21, and vincristine 1.4 mg/m^2 intravenous on days 8 and 29 (with a maximum dose of 2 mg). Cycles were to be repeated every 6 weeks, with dose reductions as previously described.(2)

During the entire treatment period, corticosteroids were to be kept at the lowest possible dose. Treatment at the time of progression was left to the discretion of the local investigators, but the protocol advised the treating physicians to consider PCV chemotherapy.

Statistical design

With a sample size of 292 patients and expecting a median survival in the control group of about 2 years, after 4 years of accrual and 2 years of follow-up, with 192 deaths observed the study would have an 80% power at a significance level of 0.05 to detect an increase a 1 year in median overall survival. Because of the observed disconcordant pathology review the sample was increased by 20% (58 patients) in amendment 2, requiring 350 patients to be included in order to assure that a least 292 patients were randomized with an anaplastic oligodendroglial tumor at central pathology review. In amendment 3 (May 2001) 1p/19q

testing and a pre-planned exploratory correlative analysis of 1p/19q status with OS and PFS were incorporated in the study design. Patients were stratified by age (≤ 40 years. vs. > 40 years), extent of resection (biopsy vs. resection) , WHO-ECOG Performance Status (0 or 1 vs. 2), possible prior surgery for a low-grade oligodendroglioma (yes or no), using the minimization technique of Simon and Pocock.(3)

Primary endpoints of the study were OS and PFS in the intent to treat population. Of note, in amendment 3 (May 2001) 1p/19q testing and a pre-planned exploratory correlative analysis of 1p/19q status with OS and PFS were incorporated in the study design. All survival analyses were done according to the Kaplan Meier method with 2-sided log-rank statistics with 0.05 level of significance, and were performed using SAS v9.2. Log rank test for interaction was used to compare treatment effect in different molecular subset. Multivariate analyses with Cox regression were performed in the whole dataset and in molecular subgroups to correct treatment effect measured by hazard ratio (HR) for possible imbalance in important prognostic factors (age (<=40,>40), extent of surgery (biopsy/surgery), WHO PS (0,1,2), previous resection for low grade (Y/N)).

References

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