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EORTC Clinical Trial in Perspective

Farewell to monomodality treatment in patients with WHO lower grade glioma?

The recent publication of interim results of European Organisation for Research and Treatment of Cancer (EORTC) 26053, better known as the 'CATNON' trial (NCT00626990), has established radiotherapy (RT) followed by up to 12 cycles of temozolomide (TMZ) as the new standard of care for patients with newly diagnosed anaplastic glioma without 1p/19q codeletion [1]. The trial had been initiated more than 10 years ago in a scenario in which (i) the survival benefit of treating glioblastoma patients with TMZ during and after RT and (ii) the strong prognostic role of the 1p/19q codeletion in patients with anaplastic oligodendroglial tumours had just been established. Conversely, the standards of care for the prognostically intermediate group of 'malignant gliomas' that did not qualify morphologically for glioblastoma, but also exhibited no 1p/19q codeletion, were poorly defined then. Of note, the opening of the CATNON trial preceded the detection of isocitrate dehydrogenase (IDH) mutations in a majority of WHO grade II/III gliomas, which subsequently triggered the major changes in understanding and classifying diffuse gliomas of adulthood and culminated in the revision of the WHO classification in 2016 [2].

Over the last two decades, several large clinical trials have been conducted, largely by academic consortia such as EORTC, to confirm traditional or to establish new standards of care for the management of patients with WHO (World Health Organization) grade II or III gliomas (Table 1). The prognostic role of 1p/19q codeletion as a marker of benefit from chemotherapy was initially reported in a cohort of 39 patients with newly diagnosed or recurrent anaplastic oligodendroglioma [3]. Interim analyses of two large randomized trials, EORTC 26951 and RTOG 9402, demonstrated prolonged survival of patients with anaplastic oligodendroglial tumours with, as opposed to without, 1p/19q codeletion irrespective of whether the patients had been treated with RT alone or RT followed (EORTC 26951 trial) or preceded (RTOG 9402 trial) by procarbazine, lomustine (CCNU) and vincristine polychemotherapy (PCV) [4,5]. Longer follow-up was required to establish the 1p/19q codeletion as a predictive biomarker for the benefit from alkylating agent chemotherapy added to RT. In the EORTC 26951 trial, patients with newly diagnosed anaplastic oligodendroglial tumours were randomized between RT (59.4 Gy) followed by 6 cycles of PCV chemotherapy (n = 183) or RT alone (59.4 Gy) (n = 185). The co-primary end-points were progression-free survival (PFS) and overall survival (OS). After a median follow-up of 140 months, both PFS and OS were significantly longer in the RT → PCV arm: 24.3 versus 13.2 months and 42.3 versus 30.6 months. When analysing the data according to the 1p/19q codeletion status as planned in an amendment instituted during the accrual phase of the study, the benefit was more prominent in patients with 1p/19q-codeleted tumours. In this group, OS was not reached in the RT → PCV arm versus 112 months in the RT arm, whereas in the patients with 1p/19q non-codeleted tumours, OS only tended to be better in combined modality treatment arm: 25 months with RT → PCV versus 21 months with RT alone [6]. In RT0G 9402, patients with anaplastic oligodendroglial tumours were randomized between up to 4 cycles of PCV prior to RT (59.4 Gy) (n = 148) or RT alone (59.4 Gy) (n = 143). The primary end-point of OS was similar between both the arms; however, in patients with 1p/19q-codeleted tumours, the survival was significantly longer with combined modality treatment, 14.7 versus 7.3 years. No difference in OS was observed for the patients with 1p/19q non-codeleted tumours: 2.6 versus 2.7 years [7].

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Table 1: PFS and OS outcomes in randomized trials

		Progression-free survival		Overall survival		
		Median (95% CI)	At 5 years (95% CI)	Median (95% CI)	At 5 years (95% CI)	
RTOG 9802 'high risk' grade II gliomas	RT followed by PCV (n = 125; 54 patients dead)	10.4 years (6.1-NR)	61% (53–70)	13.3 years (10.6-NR)	72% (64–80)	Buckner *et al.*, 2016 [8]
	RT alone (n = 126; 84 patients dead)	4.0 years (3.1–5.5)	44% (35–53)	7.8 years (6.1–9.8)	63% (55–72)	
RTOG 9802 'low risk' grade II gliomas	No further treatment after surgery (n = 111)	9 years	48%	Not reached	93%	Shaw *et al.*, 1998 [20]
EORTC 22033-26033 trials WHO grade II gliomas requiring intervention	RT (50.4 Gy) (n = 240)	50.99 months (39.79–61.63)	40.18% (29.94–50.19)	Not reached	Not reported	Baumert *et al.*, 2016 [12]
	Temozolomide (75 mg/m^2 once daily for 21 days, 28-day cycles) (n = 237)	40.48 months (35.25–46.05)	28.92% (19.78–38.69)	Not reached	Not reported	
NOA-04 WHO grade III gliomas	RT (n = 139)	30.6 months (16.3–42.8)	Not reported	72 months (not reported)	Not reported	Wick *et al.*, 2009 [10,11]
	PCV or temozolomide (n = 135)	31.9 months (21.1–37.3)	Not reported	82.6 months (not reported)	Not reported	
EORTC 26951 trial WHO grade III oligodendroglial gliomas	All patients	13.2 months (9.2–17.9)	22% (9.2–17.9)	30.6 months (21.5–44.5)	37.0% (30.0–44.0)	van den Bent *et al.*, 2013 [6]
	RT alone (n = 183)	24.3 months (17.4–40.7)	37.5% (30.5–44.4)	42.3 months (28.7–62.0)	43.3% (36.2–50.5)	
	RT plus PCV (n = 185)					
	1p19q codel	49.9 months (27.8–101.8)	46.0% (29.6–60.9)	NR	73.0% (55.6–84.4)	
	RT alone (n = 37)	156.8 months (68.1-NR)	71.4% (55.2–82.7)	11.8 months (75.7–134.3)	76.2% (60.3–86.4)	
	RT plus PCV (n = 43)					
	Non-codeleted tumours	8.7 months (7.1–11.7)	13.5% (8.1–20.2)	21.1 months (17.6–28.7)	25.1% (17.7–33.0)	
	RT alone (n = 122)	14.8 months (9.9–21.1)	25.4 (17.8–33.7)	25 months (18.0–36.8)	31.6% (23.3–40.2)	
	RT plus PCV (n = 144)					
	IDH mutant	36.0 months (17.2–58.6)	33.3% (18.8–48.6)	64.8 months (36.9–111.8)	52.8% (35.5–67.4)	
	RT alone (n = 36)	71.2 months (47.1-NR)	59.1% (43.2–71.9)	NR	68.2% (52.3–79.8)	
	RT plus PCV (n = 45)					
	IDH wildtype	6.8 months (5.4–8.6)	4.0% (11.9–31.8)	14.7 months (11.9–19.1)	16.0[§] (7.5–27.4)	
	RT alone (n = 50)	10.0 (7.8–18.2)	17.0% (8.0–29.0)	19.0 months (14.6–30.2)	21.3 (11.0–33.8)	
	RT plus PCV (n = 47)					
RTOG 9402 WHO grade III oligodendroglial gliomas	All patients	Not reported	Not reported	4.6 years	Not reported	Cairncross *et al.*, 2013 [7]
	RT alone (n = 143)			4.7 years		
	RT plus PCV (n = 148)					

	1p19q-codeleted tumours	2.9 years	Not reported	7.3 years	Unpublished	
	RT alone (n = 67)	8.4 years		14.7 years	data	
	RT plus PCV (n = 59)					
	Non-codeleted tumours	1.2 years	Not reported	2.6 years	Not reported	
	RT alone (n = 61)	1.0 year		2.7 years		
	RT plus PCV (n = 76)					
CATNON EORTC 26053-22054 trials (interim analysis)	RT and adjuvant temozolomide (373 patients; 92 patients dead)	42.8 (28.6–60.6)	43.1% (35.0–50.9)	Not reached	55.9% (47.2–63.8)	van den Bent *et al.*, 2017 [1]
WHO grade III, without 1p/19q codeletion	RT alone (372 patients; 129 patients dead)	19.0 months (14.4–24.6)	24.3% (17.7–31.6)	41.1 months (36.6–60.7)	44.1% (36.3–51.6)	

These two studies reconfirmed the worse outcome for patients with 1p/19q non-codeleted anaplastic gliomas than that for those with 1p/19q-codeleted tumours already observed at the first report [4,5] and illustrated the necessity to further study these tumours in separate trials, one being CATNON (see below). Accordingly, the CODEL trial (EORTC 26081) was designed to define the best therapeutic approach for patients with 1p/19q-codeleted anaplastic gliomas by comparing RT alone versus RT followed by PCV and included a TMZ alone arm, reminiscent of the NOA-04 trial (see below). The survival benefit with combined modality treatment in EORTC 26951 and RT0G 9402 trials published in 2013 required a change in the design of CODEL: RT followed by PCV shall now be compared with RT plus concomitant and maintenance TMZ (TMZ/RT → TMZ) (NCT00887146).

Independently, efforts to optimise the standards of care for patients with WHO grade II gliomas were taken both in the US and in Europe. RTOG 9802 trial was a randomized study comparing RT alone (54 Gy) versus RT (54 Gy) followed by 6 cycles of PCV in 'high-risk' WHO grade II glioma patients where high risk was defined by patients being aged either less than 40 years and having undergone biopsy or subtotal resection only or patients aged greater than or equal to 40 years. Patients treated with RT → PCV had a significantly longer survival than patients treated with RT alone: 11.3 versus 7.8 years. The superiority of RT → PCV over RT was seen in all histological subtypes: astrocytoma, oligoastrocytoma and oligodendroglioma. Patients with $IDH1^{R312H}$-mutant tumours had longer survival than patients with $IDH1^{R312H}$ non-mutant tumours, but only 45% of tumours could be assessed for $IDH1^{R132H}$ status by immunohistochemistry. The number of patients with $IDH1^{R132H}$ non-mutant tumours was too small to evaluate an association of treatment with outcome, and data on 1p/19q codeletion status were reported to be insufficient for interpretation [8]. The superiority of combined modality treatment had thus been confirmed for 1p/19q-codeleted anaplastic gliomas in two trials and in 'high risk' WHO grade II gliomas in one trial.

CATNON (EORTC 26053-22054 trials) (NCT00626990) was an intergroup randomised 2 × 2 factorial design, open-labelled, phase III trial in newly diagnosed 1p/19q non-codeleted adult anaplastic glioma patients on stable or decreasing steroids. It compared RT alone (59.4 Gy in 33 fractions), the same RT regimen followed by maintenance TMZ (12 cycles of 150−200 mg/m^2 given on days 1−5 of 4-week cycles), RT with concurrent TMZ (75 mg/m^2 per day) and RT with concurrent TMZ followed by maintenance TMZ. The primary end-point was OS adjusted for WHO performance status, age, loss of heterozygosity 1p, the presence of oligodendroglial elements, and O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status. The interim results from a pre-planned analysis when 41% of death had occurred and after a median follow-up of 27

months—and which took place shortly after the end of accrual—demonstrated a significant increase in the survival at a hazard ratio of 0.65 (95% confidence interval: 0.45−0.93, p = 0.0014) for patients treated with maintenance TMZ. Survival at 5 years was accordingly increased, too: 55.9% versus 44.1%, an intent-to-treat analysis. Progression of disease was noted in 54% of patients who did not receive maintenance TMZ, as opposed to 39% for patients treated with maintenance TMZ. The treatment was well tolerated up to the time of this interim analysis [1]. These data were practice-changing and supported the use of 12 months of maintenance TMZ after RT for the treatment of newly diagnosed 1p/19q non-codeleted anaplastic glioma [9]. Yet, there are inherent limitations of CATNON: data on IDH1/2 mutation status, MGMT status and on quality of life and cognition await analysis and publication, and the role of concurrent TMZ remains to be defined.

Is there still a role for non-combined modality treatment in diffuse adult glioma of WHO grades II and III after four randomized trials have demonstrated a survival advantage of combination therapy compared with RT alone? Two trials in similar patient populations have shown that RT alone and alkylating agent chemotherapy alone result in similar outcome. NOA-04 was a phase III trial that evaluated as the primary end-point the time to treatment failure defined as the second progression, after RT (60 Gy) and one line of alkylating chemotherapy (PCV or TMZ) in either sequence, in patients with newly diagnosed anaplastic glioma. After a median follow-up of 9.5 years, there was no difference for PFS or OS between arms, for all patients pooled or stratified for the three major molecular subgroups: IDH wild-type, IDH mutant, 1p/19q non-codeleted, and IDH mutant, 1p/19q-codeleted, although data for the latter group are immature [10,11]. The EORTC 22033-26033 phase III trial compared RT (50.4 Gy) alone and TMZ alone (12 cycles, 75 mg/m^2 at days 21−28 of 28-day cycles) in patients with WHO 2007 grade II glioma with 'high-risk' features, such as age greater than 40 years, progressive disease, tumour diameter above 5 cm, tumour crossing the midline, and neurological symptoms. PFS, the primary end-point, did not differ between arms (RT: 46 months, TMZ: 39 months). Median OS was not reached at the time of a pre-planned interim analysis performed after a median follow-up of 48 months [12]. The equivalence of RT with alkylating agent-based chemotherapy in NOA-04 and EORTC 22033-26033 trials together with the superiority of combined modality treatment over RT alone in four subsequent trials lends strong support to the assumption that chemotherapy alone would result in inferior survival compared with combined modality treatment, too, although this has not been formally demonstrated.

The main concern of using a combined modality approach in young patients with a relatively long life expectancy is the risk of late treatment-induced neurotoxicity notably in long-term surviving patients. Health-related quality of life and cognition were evaluated in a sub-analysis of EORTC 26951 trial including 37 surviving patients. At the time of assessment, the median OS was 147 months, and 27 patients were free of progression. Of these 27 patients, 8 (30%) showed a decline in four or more cognitive domains out of 6, 11 patients (41%) were employed, and 22 patients (81%) lived independently, relative to an initial assessment at 2.5 years after initial therapy. No detrimental effect of adding PCV to RT was noted on the EORTC QLQ C20 and BN20 scales in this small group of patients [13]. Only a single randomized trial has indicated potential efficacy of a cognitive rehabilitation program in glioma patients [14], and no randomized trial has shown an efficacy of any pharmaceutical intervention for the treatment of cognitive decline in glioma patients. Preservation of cognition while reducing potential treatment-related toxicity therefore remains to be of interest in long-term survivors with glioma.

Just like we still do not understand which molecular makeup of gliomas determines benefit from RT alone, we also remain with the question which molecular features allow to expect the largest benefit from the addition of chemotherapy to RT. IDH1/2 mutations, CpG island methylator phenotype or MGMT promoter methylation have been discussed [15−17], but all these are obviously interrelated [18]. More importantly, all six studies reviewed herein suffer from a lack of power to inform on relative treatment efficacy when trial results are stratified for molecular subgroups defined by IDH1/2 mutation and 1p/19q codeletion status. This is particularly true for IDH1/2 wild-type gliomas, which were a minority of tumours with poorer outcomes in all trials where molecular data are available. In fact, the median PFS in EORTC 22033-26033 trials for patients with IDH wild-type WHO grade II gliomas of below 24 months with either treatment modality is inferior to the PFS of IDH mutant gliomas of WHO grade III, e.g. in NOA-04, again irrespective of treatment [10−12]. Accordingly, future clinical trial initiatives need to separate the three major molecular categories of diffuse gliomas of WHO grades II and III, acknowledging that molecular status overrides WHO grade [18]. Furthermore, the WHO grade III versus II distinction may have only limited significance within molecular subgroups, as shown in a large series of IDH mutant, 1p/19q non-codeleted tumours [19]. Accordingly, the revised CODEL trial has also broadened its inclusion criteria to enrol both WHO grade II and III tumours with 1p/19q codeletion.

Where do we go from here in Europe? The EORTC Brain Tumor Group has committed to participate in the CODEL trial although there is concern that there are more important questions to address than the replacement of RT → PCV by TMZ/RT → TMZ. EORTC 1635, provisionally termed iWOT, is a new concept for the next randomized phase III trial in the spectrum of

IDH mutant, 1p/19q non-codeleted tumours that shall address what the Brain Tumour Group, after a dedicated brainstorming meeting in February 2016, felt to be most burning question in the current landscape where monomodality treatment seems to be no longer an option: is there a population of patients with IDH mutant, 1p/19q non-codeleted gliomas who can be safely managed by a watch-and-wait strategy, without compromising survival, but with the goal of potentially delaying the development of delayed treatment-related neurotoxicity? RTOG 9802 trial had included a third, non-randomized arm of 111 patients with favourable prognostic criteria defined as age <40 years and image-verified complete resection who were observed without further treatment. After a median follow-up of 4.4 years, PFS at 5 years was estimated at 48%, and OS at 5 years was 93%. PFS was longer for patients with pre-operative tumours with a diameter of less than 4 cm, residual postoperative tumour of less than 1 cm diameter on MRI, and oligodendroglioma histology [20]. This observational arm defines a framework for further exploring observation alone after surgery for lower grade gliomas.

Accordingly, EORTC 1635 is designed to compare a watch-and-wait strategy with RT (50.4 Gy) within 6 months of diagnostic surgery or first resection followed by up to 12 cycles of maintenance TMZ in patients with IDH mutant, 1p/19q non-codeleted WHO grade II or III tumours who at the time of randomisation have no enhancing tumour, no functional deficits due to tumour, with the exception of seizures only which can be controlled, no signs of increased intracranial pressure after surgery, a WHO performance status of 0–2 and for whom a wait and watch policy appears to be an option. Although this will be beyond doubt as a challenging trial in terms of investigator adherence to protocol and of convincing patients to participate, it nevertheless addresses an important question in daily clinical practice. Meanwhile, the CATNON trial provides an important step forward in establishing a new standard of care for a subgroup of adult patients with anaplastic glioma, and upcoming secondary analyses based on molecular subgroups will further refine treatment strategies for this group of patients.

Conflict of interest statement

None declared.

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