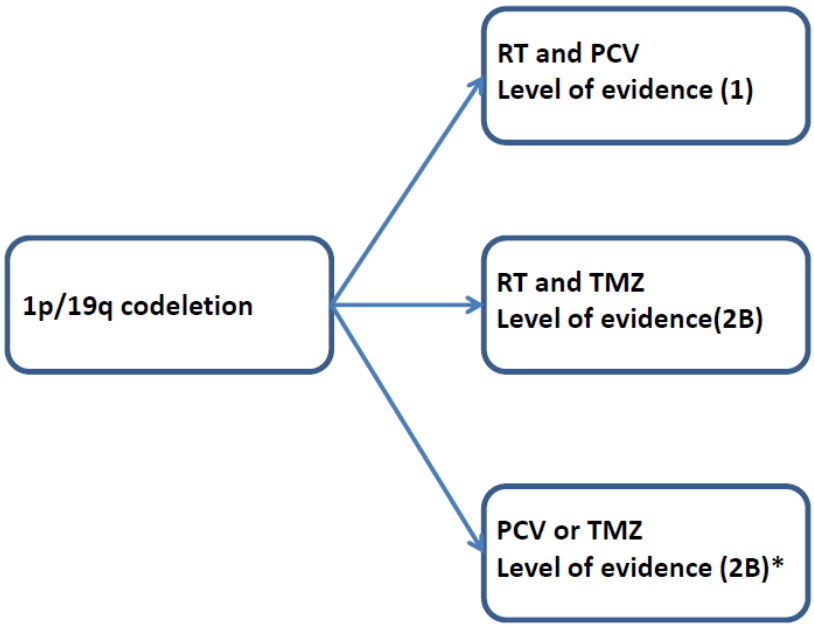
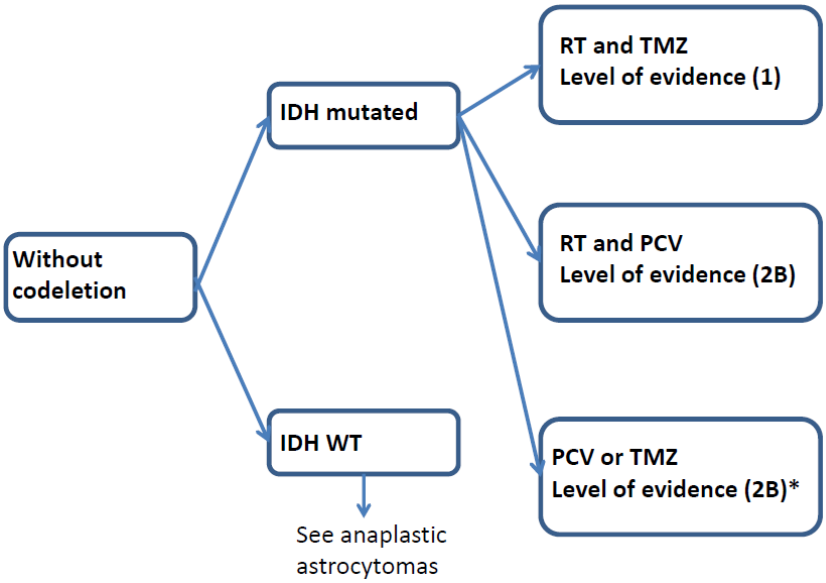
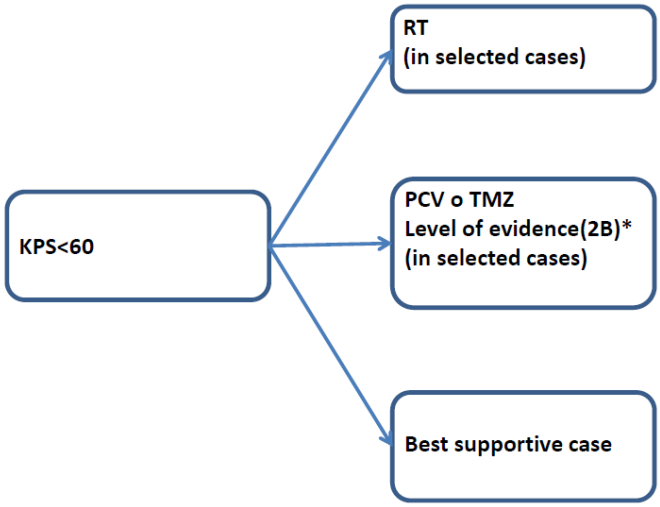
GEINO GRUPO ESPAÑOL DE INVESTIGACIÓN EN NEUROONCOLOGÍA

ANAPLASTIC OLIGODENDROGLIOMAS AND OLIGOASTROCYTOMAS



*Data from phase III trials comparing chemoradiotherapy to chemotherapy alone are lacking. In the case of diffuse involvement of more than 3 lobules, the irradiation volume should be considered and, occasionally, avoid RT and use chemotherapy alone (level of evidence: III).





Anaplastic oligodendrogliomas (AO) present low incidence (approximately 0.07-0.18 /100,000 inhabitants/year), and account for the 5-20% of the glioma population. Typically young adults are affected (45-50 years old), with a better outcome and response to the therapies than astrocytomas, and a median overall survival of 4.5 years and a 5-year survival of 40% (1).

Recently, the postsurgical therapeutic approach has experienced a relevant change due to the publication of the final results of two international phase III studies, the Radiation Therapy Oncology Group (RTOG) 9402 and the European Organization for Research and Treatment of Cancer (EORTC) 26951.

On the other hand the molecular profiling studies had allowed the identification of different genetic patterns, mainly characterized by combined deletion of 1p and 19q, methylation of the promoter of O(6)-methylguanine methyltransferase (MGMT), and isocitrate dehydrogenase (IDH) 1 and 2 mutations. These molecular alterations are known prognostic and predictive factors for anaplastic oligodendroglial tumours. Three phase III clinical trials had reported that the patients with combined 1p/19q codeletion have a better chance of survival when they receive radiation therapy and alkylating agents based chemotherapy or both.

The EORTC 26951 study was initially reported in 2006 and updated in 2012. In this study 368 patients with anaplastic oligodendroglioma or anaplastic oligoastrocytoma (locally diagnosed) were randomized to RT or RT followed by PCV (RT-PCV). 78 patients (21%) presented 1p/19q codeletions. Initially, this trial showed that the addition of PCV after RT increased progression-free survival (PFS) (23 vs 13.2 months, p=0.0018), but not the median overall survival (OS) (40.3 vs 30.6 months, p=0.23) with a median follow-up of 60 months (2).

In the recently published update there was a survival benefit favouring the early adjuvant PCV in patients with codeleted tumours. With long-term follow-up (more than 10 years), median survival has not been reached in the 42 patients with codeleted tumours and RT-PCV, compared with a median survival of 9.3 years for the 38 patients who received RT alone, (p=0.059). Most of them received chemotherapy at progression. Interestingly, median OS for patients with no codeletion was similar in both arms, 21 months for RT alone vs 25 months for RT-PCV (p=0.19) (3).

In the ROTG 9405 trial 289 patients with anaplastic oligodendroglioma or anaplastic oligoastrocytoma were randomized to neoadjuvant PCV chemotherapy followed by RT (PCV-RT) compared to RT alone, but 80% of the patients in this arm received chemotherapy at progression. There was a central pathology review and also 1p/19q codeletion was assessed centrally. In this study 93 patients presented combined loss (46%). In the first analysis with a minimum follow-up of 3 years, the median PFS was 2.6 years for PCV-RT versus 1.7 years for RT alone (p=0.004); but the median OS was similar (4.9 years with PCV-RT vs 4.7 years with RT alone (p=0.26)). OS was longer in 1p/19q codeleted tumours (0.7 years vs 2.8 years, p=0.001) but there was no effect of different treatment by 1p/19q status (4). However, in the recent update the median OS for 1p/19q codeleted tumours was 14.7 years with PCV-RT compared to 7.3 years with RT alone

(p=0.03) (5).

The third randomized study, the German NOA-04, enrolled 318 patients with anaplastic astrocytoma, anaplastic oligodendroglioma, and mixed anaplastic oligoastrocytoma to receive RT alone, or two different chemotherapy regimens: PCV or temozolomide (TMZ), and at progression patients assigned to RT were randomized to PCV or TMZ, while patients randomized to chemotherapy received RT. There was a central histology revision, and in this trial 74 patients (23%) had 1p/19q codeletion by FISH. The 1p/19q codeletion was a favourable prognostic factor, but the follow-up in this study is too short to evaluate at this point the predictive value of this alteration (6).

These results, especially those from the RTOG 9402 and EORTC 26951 studies, have relevant clinical implications for standard practice. (Algorithm 1)

In recent years new evidence has been reported regarding the initial therapeutic approach for non-codeleted anaplastic tumours. Secondary analyses from the RTOG 9402 and EORTC 26951 studies suggest that other molecular factors, like the IDH1 mutation, may affect the response to the therapy as well as the prognosis of these patients (7). Patients harbouring the IDH1 mutation, but without 1p/19q codeletion, may derive benefit from chemo and RT, although with less impact than codeleted tumours (8).

In June 2016 Dr Van den Bent presented at ASCO the preliminary results from the CATNON trial. More than 700 patients have been included in this phase III study, for anaplastic gliomas without 1p/19q codeletion. Patients that received temozolomide after RT, with or without concomitant chemotherapy, showed a better progression-free survival (PFS). The median PFS for the patients randomized to temozolomide was 42.8 months, compared to 19 months for the other group. (Algorithm 2)

UNRESOLVED QUESTIONS IN THE MANAGEMENT OF ANAPLASTIC GLIOMAS:

One of the open controversies in the field is which type of chemotherapy should be used. Adjuvant PCV or TMZ? Is there a role for concomitant TMZ? There is preliminary evidence that TMZ could be equivalent to PCV, however, there are no direct comparative results in this regard (9,10). There is no consensus in the Neuro Oncology community (given the better tolerance of TMZ) but, to date, the only available data from phase III trials involves PCV.

The other relevant question is whether or not to delay RT in this population (NOA-04). There is no data from phase III trials to support this approach.

On the other hand, is there an optimal molecular marker to identify patients that derived more benefit from chemotherapy besides 1p/19q? IDH-1? Methylation phenotype? 1p/19q codeletion is a known predictive factor, but there are evidences that other molecular subgroups can also benefit from chemotherapy (RNA expression profiles, IDH1, CIMP…).

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