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RESEARCH ARTICLE

SAFETY AND EFFECTIVENESS OF NIMOTUZUMAB IN HIGH GRADE GLIOMA PATIENTS. PHASE IV STUDY RESULTS

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ABSTRACT

Purpose: A multicentric, Phase IV clinical trial to evaluate safety and effectiveness of nimotuzumab, a monoclonal antibody against epidermal growth factor receptor added to standard therapy for newly diagnosed high grade glioma.
Methods: Patients were recluted after surgery to receive nimotuzumab 200 mg weekly in combination with radiotherapy (RT) or chemoradiation (CRT), followed by the same doses biweekly until clinical worsening or intolerance toxicity. Safety profile, Progression-free survival (PFS) and overall survival (OS) were main endpoints based in Common Toxicity Criteria, Macdonald criteria and time to death since inclusion date.
Results: 127 patients were treated, 93 glioblastoma, 25 anaplastic astrocytoma and 9 anaplastic oligoastrocytoma. Mostly patients received nimotuzumab in combination with radiation: concurrently 54.3 %, sequentially to RT 15.7 % and 6.3 % in combination to RT and Temozolomide; however 23.6 % received nimotuzumab as monotherapy. Completed induction phase 87.4% of patients and continued in maintenance beyond 2 years 11.1 %. Only 10.5 % of adverse events were related to nimotuzumab. Headache, transaminase increased, fever and skin rash, were the most frequents as mild intensity. Median PFS time was 8.97 and 21.77 months and OS was 10.57 and 28.27 months for glioblastoma and anaplastic astrocytoma patients respectively.
Conclusions: This study was consistent to safety and adherence as continues maintenance treatment, prior described in controlled trials. Nimotuzumab in combination with RT might improve survival over RT alone, but it was marginal with respect to chemoradiation. For enhance the clinical benefit patients would be select according predictor biomarkers unknown yet.

INTRODUCTION

Glioblastoma (GBM) and Anaplastic Astrocytoma (AA), commonly considered as High Grade Glioma (HGG), are the most frequent primary brain tumors in adults, and despite decades of research, continue to be aggressive diseases which invariable cause the patient´s death. Standard treatment

approaches for GBM and AA result in median survivals of 9-12 months and 2-5 years respectively(1).

Therefore this is unmet medical need and novel therapeutics is urgently required and could be targeted therapies change the natural course of this lethal disease.

Nowadays two monoclonal antibodies(MoAb) are already approved in different countries for recurrent GBM and newly diagnosed HGG patients: Bevacizumab, targeting Vascular Endothelial Growth Factor (VEGF) and nimotuzumab aiming Epidermal Growth Factor Receptor (EGFR)respectively(2, 3).Nimotuzumab is a MoAb binds EGFR, interferes the interaction of EGFR with its ligand (EGF), inhibits EGF/EGFR signaling cascade, and has anti-proliferative, anti-angiogenic and pro-apoptotic effects in malignant epithelial cells(4, 5). This MoAb passes the blood-brain barrier and sensitizes tumor cells to radiation (6-8).

Based on these previous finding, nimotuzumab has been evaluated in randomized clinical trials (RCT), in combination with radiotherapy (RT)(9)or chemoradiation (CRT) in HGG(10). Survival advantage was revealed in both combination modalities, however, reached statistically significance when nimotuzumab was added to RT, but did not in combination of CRT(9, 10).The results of RCT with nimotuzumab plus RT in newly diagnosed HGG patients granted the approval as a front-line therapy.

After launch, a post-marketing surveillance studies is relevant for the identification, assessment and management of risks when a new drug is approved. Therefore, a Phase-IV study was launched in agreement with the national regulatory authority for evaluate safety, effectiveness in terms of progression-free survival (PFS) and overall survival (OS) in an open population. Final data is reported.

MATERIAL AND METHODS

A multicentric, open label, Phase IV clinical trial was conducted in newly diagnosed HGG patients, who received nimotuzumab added to RT or CRT and were followed during 2 years.

Patients had a diagnosis of HGG according to a local pathologist´s report, which was confirmed by a centralized second pathologist, blinded to clinical data.

Other eligibility criteria were age older than 18 years, Karnofsky performance status (KPS) ≥ 50 %, adequate bone marrow, liver and renal function; a negative pregnancy test (effective contraceptive methods were used in those patients in fertile age).

Surgical resection was attempted in all patients and performed as total or partial resection or just biopsy. Tumor samples were available for EGFR expression assessment through immunohistochemistry performed in agreement with the indirect enzyme immunoassay, previously described(11).

Compliant with the statement on the package insert, nimotuzumab was administered by six weekly intravenous infusions at 200 mg, as induction phase, followed by every two weeks infusions as maintenance, until worsening performance status (KPS < 40 %) or unacceptable toxicity(12).

Nimotuzumab was combined with external beam radiotherapy. Fractionated, conformal RT or intensity-modulated radiotherapy (IMRT) was given within protocol-defined guidelines at institutions, at a daily dose of 2 Gy, delivered 5 days a week for 6 weeks, for a total dose of 60 Gy.

Addition of Temozolomide (TMZ) chemotherapy was allowed, as standard scheme (13).

Full patient evaluation included complete physical examination, laboratory tests (blood cell counts and blood chemistry), and CT-scan or Nuclear Magnetic Resonance images, at inclusion and every three months.

Adverse events (AEs) were classified according to the Common Terminology Criteria for Adverse Events version 3.0 (14). Serious adverse events as death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly, required intervention or any other important medical event to prevent permanent impairment or damage were also recorded and analyzed separately. Adverse events considered as related to nimotuzumab use were classified as adverse drug reaction (ADR).

For assessment clinical response, was used Macdonald criteria (15).

Statistical Analysis

The statistical significance of the possible association among ADR and dosage, exposure time and treatment schedule was assessed using the X^2test.

For patients who achieved objective response (either complete or partial) or stable disease, progression- free survival (PFS) was calculated as time from inclusion to progression or death. Overall survival (OS) was defined as time from inclusion until death or last news alive.

The relationship between either PFS or OS and treatment was assessed in all patients, by intent to treat, using the Kaplan-Meier test. Univariate and multivariate Cox proportional hazards models were also used. Data were processed using the software: SAS for Windows, release 9.3, x 64-7pro platform.

This trial was performed in compliance with the Helsinki Declaration. Institutional Review Boards from 11 hospitals approved the protocol and National Regulatory Authority (CECMED) was notified for this postmarketing study.

All patients included signed the informed consent. The protocol was submitted on the National Register for clinical trials (RPCEC00000087) which is a primary register, approved by the World Health Organization (WHO) (http://registroclinico.sld.cu/ensayos).
http://registroclinico.sld.cu/en/trials/RPCEC00000087-En

RESULTS

Patient's characteristics

Between September 2008 and September 2011, 241 patients were screened, 127 of them were included in the study (52.7 %), and 114 (47.3 %) excluded because of diverse causes (Fig. 1). The cut-off date for evaluation was set at September 2013.

Average age was 49.5 years, with rate1:1.5 between male and female and skin color as Caucasian prevailed. Most patients (96%) had a good performance status, but in 39.4 % of cases some co-morbidities were presented, mainly cardiovascular (23%) metabolic (6.3%) and neurologic disorders (6.2%). Glioblastoma histology was the most common (73.2%), followed by Anaplastic Astrocytoma (19.7%) and Anaplastic Oligoastrocytoma (7.1%). Frontal and Parietal tumor

localizations were more frequent, however one fourth of patients had tumor lesion in more than one site.

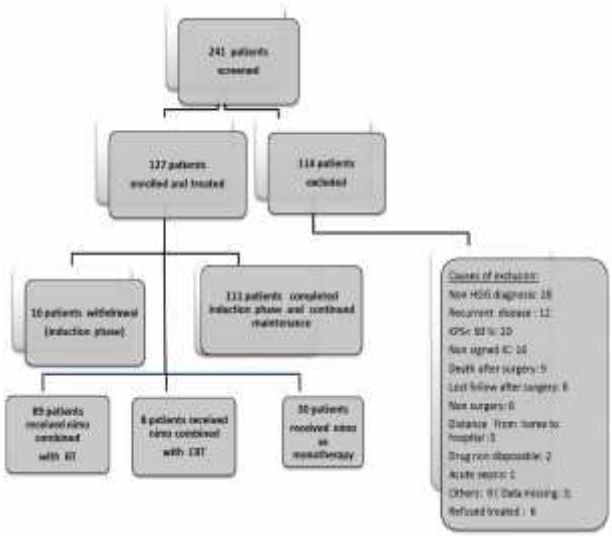

Figure 1 Diagram of patients

Legend: CRT: Chemoradiation; HGG: High Grade Glioma; KPS: Karnofsky Performance Status; RT: Radiotherapy.

All patients underwent surgery as initial treatment, although complete tumor resection was possible only in 7.9 % of patients, the rest received either partial resection (57.5%) or just biopsy (34.7%).

Table 1 Baseline patient characteristics of full population included

Variables	Patients N= 127/%
Age (mean, min- max)	49. 5 (17-82)
< 50 years	67/52.8
≥ 50 years	60/47.2
Gender	
Male	76/ 59.8
Female	51/40.1
Skin color	
Caucasian	86/67.7
Black	14/11.0
Mestizo	27/21.3
KPS (mean, min-max)	90.1 (50-100)
KPS grouped	
≥ 70 %	122 /96.1
< 70 %	5/3.9
Comorbidities	50/39.4
Histology	
GBM	93/73.2
AA	25/19.7
AOA	9/7.1
Tumor localization	
Frontal	46/36.2
Parietal	20/15.8
Temporal	16/12.6
Occipital	8/6.3
Corpus Callosum	2/1.6
III Ventricle	1/0.8
Protuberance	1/0.8
Other (more than 1 localization)	33/26.0
Prior Surgery	
Biopsy	44/34.7
Partial resection	73/57.5
Total resection	10/7.9
EGFR expression (N = 50 pts/%) **	
0	7/14.0
1+	5/10.0
2+	12/24.0
3+	26/52.0

Legend: AA: Anaplastic Astrocytoma; AOA: Anaplastic Oligoastrocytoma, GBM Glioblastoma multiforme. ** Only 50 patients were available for outcome EGFR

Immunohistochemistry staining (IHC) was performed in 50 patients, showing that most of tumors over express EGFR (Table 1).

Treatment and compliance

Nimotuzumab was used in all patients. In most of them (54.3%) the MoAb was given concurrently with RT. In 15.7% following the criteria of the treating physician, the MoAb treatment was given sequentially after completion of radiotherapy. A small group of 8 patients (6.3%) received TMZ chemotherapy concurrently with radiation. In 30 cases (23.6%) RT or chemotherapy was not possible and these received only nimotuzumab as monotherapy after surgery.

Maintenance antibody treatment was given used biweekly in most patients (more than 6 doses, 87.4%), although a small group of 16 patients (12.6%) received less than 6 doses.

Average number of nimotuzumab doses was 28.6 implying a median duration of 9 months of antibody treatment. In 14 patients biweekly nimotuzumab treatment continued beyond 2 years. The extension of treatment was not different between patients receiving the concurrent or the sequential schedule (Table2).

Table 2 Nimotuzumab treatment and compliance

Modality	N= 127/%
nimo + RT concurrently	69/54.3
nimo + RT sequentially	20/15.7
CRT+ nimo concurrently	8/6.3
nimotuzumab (monotherapy)	30/23.6
nimotuzumab doses received	
Mean doses	28.6
(SD; min. -max.)	(2.26; 1-119)
Less than 6 doses	16/12.6
Between 6 to 30 doses	67/52.8
More than 31 to 60 doses	30/23.6
More than 60 doses	14/11.0

SD: standard deviation

Progressive disease (38.5%), worsening KPS (15%) and death by progression (7.8%) were the most common causes of interruption of nimotuzumab treatment, over the 2 years of follow-up.

In no case treatment had to be stopped as a consequence of antibody toxicity.

Safety

The majority of patients presented some adverse events (92/127 patients, 72.4 %). In total were 749 events, classified as mild (47.5%) and moderate (34.6%).

Only 79 events (10.5 %) were classified as ADR to nimotuzumab. These were mainly headache (16.5 %), transaminase increased (11.4 %), fever (10.1%) and skin rash (6.3%). Adverse events related to the drug were also mild (65%) and moderate (29%), (Table 3).Among ADR, four were recognized as Serious Adverse Events (SAEs); three of them in the same patient who suffered fever, chills and tremors, summarized as anaphylactic reaction; the second, presented severe seizures. Both patients required hospitalization and had complete resolution.

Table 3 Most common adverse drug reactions to nimotuzumab

ADR	No.	%
Headache	13	16.5
Transaminase alterations (ALAT)	9	11.4
Fever	8	10.1
Rash	5	6.3
Alkaline phosphatase alteration	4	5.1
Pain (chest/ limbs)	4	5.1
Tremors	4	5.1
Chills	3	3.8
Thrombocytosis	3	3.8
Arthralgia	2	2.5
Hypotension	2	2.5
Infection (respiratory/other)	2	2.5
Nauseas	2	2.5
Seizures	2	2.5
Vomiting	2	2.5
Others	14	17.8
Total	79	100

Legend: Others ADR were notified one each: Anorexia, Appetite augmentation, Asthenia, Bleeding uterine, Blurred vision, Dermatitis, Dizziness, Eosinophilia, Hyperglycemia, Hypertension, Insomnia, Lactate desgydrogenase augmentation(LDH), Pruritus and Pyrosis.

There was no association between incidence of adverse events and treatment modality, neither nimotuzumab doses received (Figure 2a, 2b).

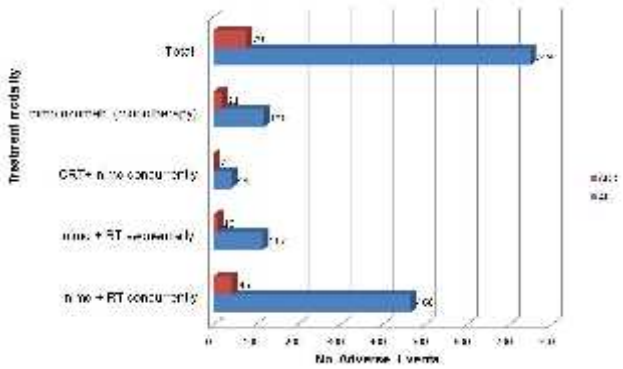

Figure 2a Adverse events according treatment modality.

Legend: ADR: Adverse drug reactions to nimotuzumab; AEs: Adverse events.

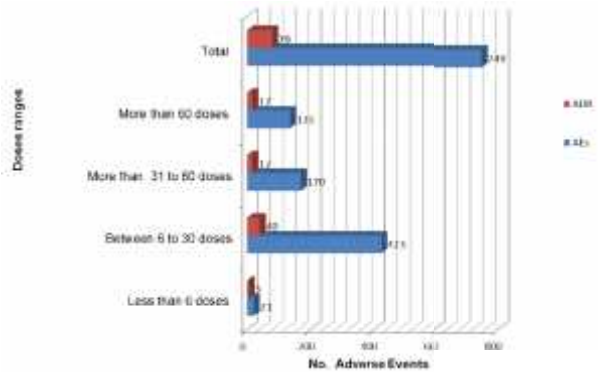

Figure 2b Adverse events according number doses received

Legend: ADR: Adverse drug reactions to nimotuzumab; AEs: Adverse events.

Survival Analysis

The median progression-free survival (PFS) for the all patients was 10.05 months (95% confidence interval, 8.40 to 14.27). Overall survival (SV) showed a median of 12.23 months (95% CI, 9.87 to 15.80). At the time of analysis, after 2 years of follow-up, 30 of the 127 patients (23.6%) were still alive. According histology grade, the median PFS in GBM stratum patients was 8.97 months (95% CI, 7.83 - 10.87) and survival of 10.57 months (95% CI, 8.43 - 13.50). The two year PFS rate was 17.39% and SV rate was 18.57%.

In patients with AA histology, the median PFS was 21.77 months (95% CI; 10.20 - 45.83) and SV of 28.27 months (95% CI, 8.87 -.). Two year PFS rate was 43.64 % and SV rate was 52%.

The small group of 9 patients classified as Anaplastic Oligoastrocytoma (AOA), only 2 deaths occurred. Therefore median PFS and SV data could not be calculated. Two year PFS and SV rates were respectively 57.14 % and 77.78% (Figure 3a, 3b).

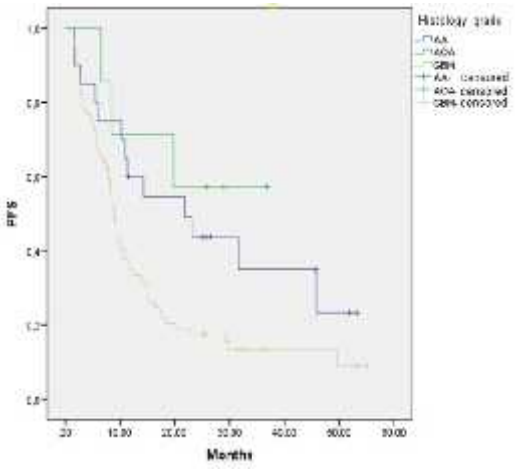

Figure 3a Kaplan–Meier Estimates of progression-free survival

Legend: AA: Anaplastic Astrocytoma; AOA: Anaplastic Oligoastrocytoma; GBM: Glioblastoma multiforme; PFS: Progression-free survival.

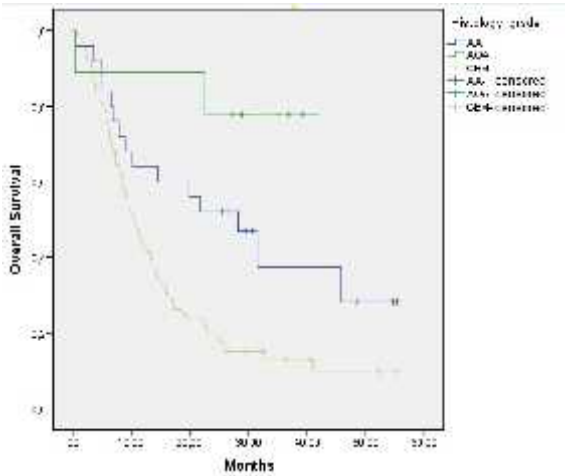

Figure 3b Kaplan–Meier Estimates of overall survival.

Legend: AA: Anaplastic Astrocytoma; AOA: Anaplastic Oligoastrocytoma; GBM: Glioblastoma multiforme.

Subgroup analysis showed survival advantage for patients younger than 50 years old as compared with older patients and also for patients who have non GBM diagnosis. Additionally patients receiving any combined modality (nimo plus radiotherapy or chemotherapy or both) performed better than patients receiving only antibody as monotherapy (Table 4).

In this series 96% of patients were included with good performance status and therefore the influence of this factor

was not considered. Other factors as surgery extension and EGFR expression no shown effect over survival.

Table 4 Regression analysis

			Univariate		Multivariate	
Subgroup	**No. pts**	**Median Overall Survival (mo.)**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age (years)						
Younger than 50	67	22.33	2.79 (1.85 to 4.22)	< 0.0001	2.25 (1.47 to 3.44)	0.0002
Equal or older than 50	60	8.16				
Surgery extension						
Complete resection	10	18.61	1.18 (0.54 to 2.54)	0.6796	-	-
Residual tumor (biopsy and partial resection)	117	12.10				
Histology						
No GBM (AA and AOA)	34	31.57	2.78 (1.63 to 4.72)	0.0002	2.32 (1.35 to 3.99)	0.0022
GBM	93	10.57				
EGFR expression**						
2-3+	38	9.93	0.78 (0.37 to 1.65)	0.5217	-	-
0-1	12	8.30				
Modality of treatment						
Combination therapy	97	14.50	2.04 (1.29 to 3.23)	0.0024	1.73 (1.09 to 2.76)	0.0211
Monotherapy	30	5.63				

** Only patients available for EGFR by IHC.

DISCUSION

The results presented here reinforces the safety profile of good tolerability for nimotuzumab, even in long term use and also reproduce the survival data of the preceding clinical trials, this time in an open patient population, closely to the real world context.

Despite treatment compliance was coherent to indication and posology recommended in package insert, nimotuzumab combined to RT concurrently, a notable proportion of them received nimotuzumab after ended RT as sequential, even as monotherapy. This deviation treatment also was described in prior observational study (16) and could be as consequence of organizational issues as distance from radiotherapy department and department destined to receive nimotuzumab or chemotherapy, waiting time of radiotherapy or just preference of parents and patients.

With independence of treatment combination modality, the majority of patients received maintenance with nimotuzumab even as long lasting 2 years or more. Actually the maintenance treatment specifically with biological becomes as usual practice in the oncology attributable to more clinical benefit (17-22); but many patients withdrawal treatment and fails as consequence of intolerance and deleterious effects (23-25).

Remarkably none patients discontinued treatment as consequence of toxicity directly related to nimotuzumab treatment, even there were no cases of infusion-related toxicities, skin rash, diarrhea, electrolyte of magnesium and potassium imbalances, substantial cause of interruptions of treatment, and therefore limited in maintenance with others anti EGFR drugs(26).

Many experimental assays explain how this MoAb has optimal affinity to tumor cell specifically with high EGFR expression and can discriminate tumor cell between normal cells to focuses antitumor effect, with a minimum of adverse events(11, 27). To differences of those anti EGFR MoAb, nimotuzumab has an intermediate affinity, which facilitates binding to cells with high density of EGFR as tumor cells, to those of lower density of EGFR as normal epithelial cells located primarily in skin epithelial and mucosae.

This distinctive mechanism, explains their differentiation from the point of view of safety without detriment to the efficacy. Likewise, nimotuzumab safety profile allows to use in vulnerable population as child and elderly patients, even with comorbidities to require concomitant medication for other disease and also, to continuing immunotherapy for long exposition time (28-32). All of them are advantages for a good adherence treatment to warranty efficacy.

Consequently, this report provides reliable evidence to safety profile described in prior studies (6, 7, 9, 10); albeit the majority of patients included had several comorbidities as representative of patients of real word, in contrast to restrictive inclusion criteria of patients who participated from RCT(9, 10).

Other interesting finding related to nimotuzumab safety is how the combination therapy with RT even CRT, no exacerbate the toxicities for this conventional therapy, either not found evidence of cumulative toxicity by a treatment continued beyond of the year, even at 2 years.

As far as effectiveness, PFS and SV reported for all patients treated in this study (median 10.05 and 12.23 months) were lower to describe in RCT, which evaluated nimotuzumab + RT, (median 15.73 and 17.76 months) and some differences data from control arms (median PFS 6.5 and SV 12.63 months)(9).

However, survival analyses by histology strata separately could be better illustrated the benefit of nimotuzumab in addition to irradiation. Here, outcome to median survival was remarkable for GBM patients (10.57 months), in contrast to all GBM patients treated in RCT refereed above (8.40 nimotuzumab arms vs. 8.36 months in control arm)(9).

Additional postmarketing studies (PMS) which assessed nimotuzumab describe similar results for GBM patients with a median SV between 14.8 and 12.4 months (16, 33) . For AA patients results were not reproducing to data from RCT (median SV 28.3 and median SV 44.56 month respectively); however it was improved than control arm from same RCT (17.57 months)(9). Similarly, in AA patients from others PMS with nimotuzumab, results were wide different, median survival 27 and 45 months (16, 33).

Many factors could be explained the dispersal of data. In our opinion, besides of heterogeneity of HGG, it was also important therapeutic schedule received. Nimotuzumab with RT, concurrently as sequentially, absolutely was better than monotherapy, even some patients received CRT based TMZ, exhibited a longer lasting survival.

As mentioned above, this outcome is in line with Westphal´s Phase III trial that compared nimotuzumab in combination

with CRT (TMZ+RT) vs. CRT where the differences on survival was in more than 3 months in favor to nimotuzumab arm; however did not reach statistical significance(10). It is not doubt the benefit to CRT based TMZ, however the combination with nimotuzumab could provide a greater benefit, but we need explore in a major sample. Specifically in Cuba is not possible evaluate the ample use of TMZ due to restrictions imposed by the United States.

To best understanding regards sensible factors to improve survival, regression analyses discriminated those patients who have younger 50 years and histology grade non GBM were the subgroup more beneficed to this drug refers with multimodal treatment added nimotuzumab. This find is rational to describe as the most important prognosis factors for HGG with independent to treatment (34, 35). Even so, it is well known as a poor KPS and incomplete surgical resection or only biopsy, impedes the survival improvement (35-38). In this study those variables have a similar behavior to literature ready described on.

Moreover EGFR status was not correlated with nimotuzumab response. Same notice is described byYang *et al*., in GBM patients treated with CRT and nimotuzumab (39). We consider it could be influenced for the very limited sample tested or due to heterogeneity of HGG tumor patients. On the other hand, Westphal´s study evaluated EGFR amplified and do not found differences with regard to this marker expression and response to this MoAb in GBM patients. Nevertheless, authors noted a subset of patients characterized by residual tumor and non-methylated MGMT promoter with greatest benefit to nimotuzumab (19.0 vs. 13.8 months, P = 0.3648)(10). The biology of responsiveness is still unclear for nimotuzumab, so those finds suggest a differentiate evaluation of efficacy-predicting tumor parameters for nimotuzumab in the treatment of GBM.

CONCLUSION

Results of this Phase IV trial is consistent to safety profile and adherence as maintenance prolonged treatment, in HGG patients treated with nimotuzumab below RCT. Although survival benefit could be marginal with respect to CRT based TMZ, it is no doubt that nimotuzumab might improve survival time over RT alone and may have promising value in the combination treatment. Furthermore those approaches must be evaluated in patients selected on the basis of having predictor biomarkers.

The results of this PMS provide further information about drugs´ s safety, efficacy or optimal use to take account for multimodal treatment in HGG patients.

Nimotuzumab treatment can be currently recommended as standard treatment for adults newly diagnosis with HGG, in combination with radiotherapy, including maintenance long term treatment. The combination with chemo-radiotherapy could be also beneficial. On the other hand, this MoAb as monotherapy produced poor results and is not to be recommended.

Funding

This Phase IV trial was funded and undertaken by Center of Molecular Immunology (CIM) and Cuban government in accordance with the conditions for approval. CIM was responsible for design, development of the protocol and for the analysis of the data in contract agreement with CENCEC who was responsible for monitoring, data management and statically analysis for this trial mostly.

Conflict of Interest

GS, PP, and ALare employees of the Center of Molecular Immunology (CIM), the research institution that patented and manufactures nimotuzumab. RU, MAM, and LP are employees of the National Coordinating Center of Clinical Trials, clinical research coordinator (CRO) who was hired by CIM.

Rests of authors have no competing interests.

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