# Prescription Practices for Temozolimide

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# 21 medical centers involved !!

| | | | |
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| 11- | P. Leynia De La Jarrige | CLNCC | Angers |

# = 21 medical centers involved !
# + 1 coordinators group + 1 guidelines group

| | | | |
|---|---|---|---|
| 15- | V. André - C. Mabillais | CHU | Tours |
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| 17- | F. Pinguet - M. Fabbro | CLNCC | Montpellier |
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**Coordinators group :**

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**Guidelines Group :**

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# Temodal® (TMZ) : introduction

- Oral alkylating agent (Antineoplasic drug)
- Well tolerated
- Crossing the blood brain barrier
- Marketing Authorization (M.A.):
  - Treatment of patients with newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and subsequently as monotherapy treatment.
  - Treatment of malignant glioma, such as glioblastoma multiforme and anaplastic astrocytoma (AA), showing recurrence or progression after standard therapy.

# Specificity of TMZ ?

Market Authorization very precise : indications, dosages and schemes of administration

Numerous off labeled prescriptions

Due in part to the lack of available treatment

Hospital dispensing procedure.

- Make the recruitement and follow-up by colleagues easier
- Allow exhaustive data collection

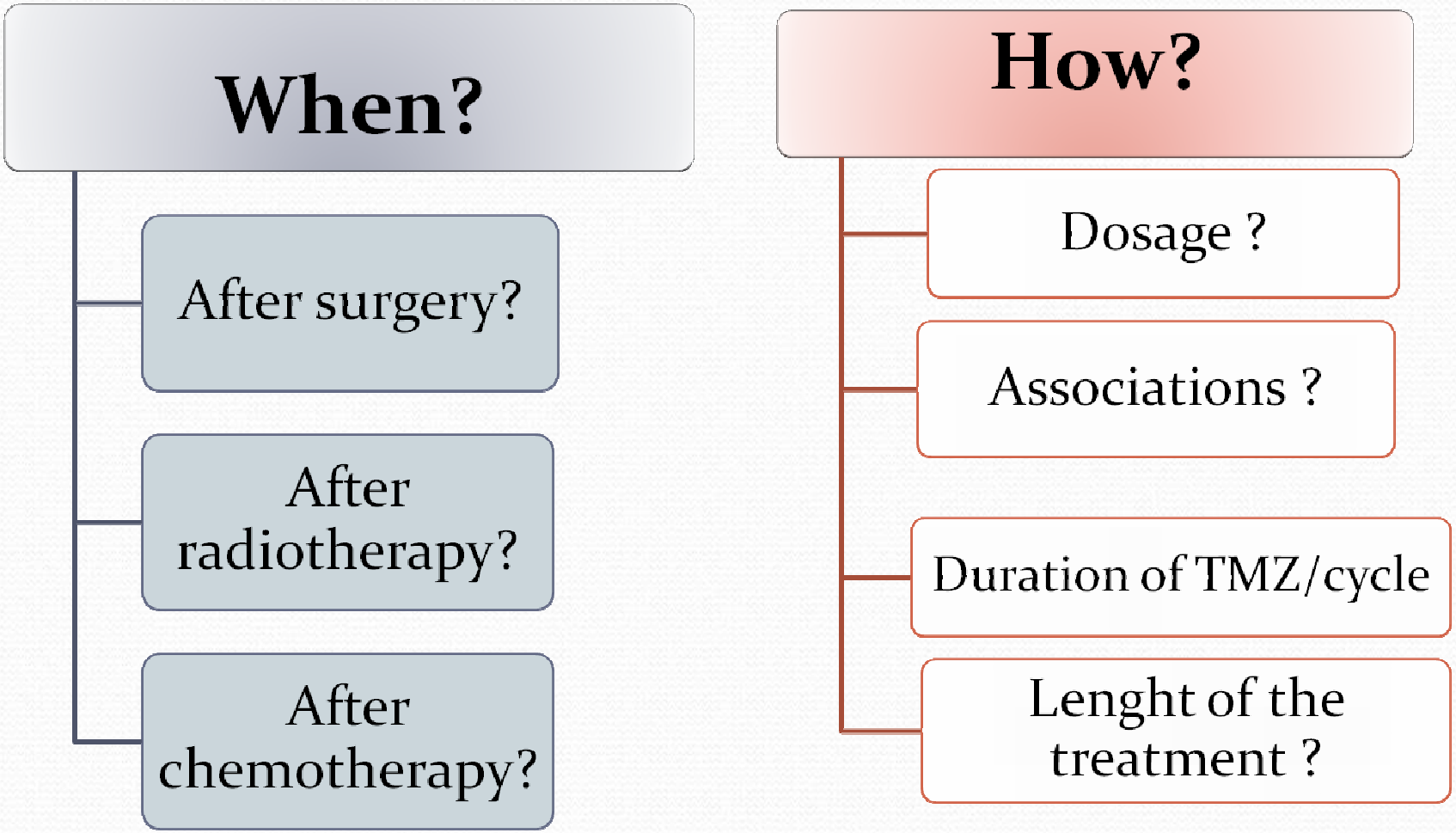
# Study Objectives (1)

To identify patients treated in daily current clinical practice

For which indications ?

- Marketing authorization ?
- Prescribed in referred indications?

# Study Objectives (2)



# Important questions concerning TMZ in clinical practice

% of 1st line of treatment

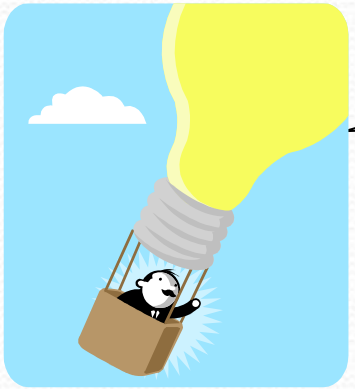
What kind of side effects and what incidence ?

Is the TMZ prescribed in conformity to the science knowledge ?

(no guideline identified for prescription –dispensing process)

# Methodology

# Logistic organisation (1)



One idea

Some meetings

Brain-storming

- To conceive and write a protocol
- Integrating a clear and simple sheet for collecting data

# Logistic organization (2)

**At the center level**

- Discussion with medical staff
- Data collection– validation
- To group and to send data

**At the coordinator center level.**

- To conceive ad to create a specific program with SAS
- Entering the data
- Analyzing the data

# Data Analysis

Creating guideline

- From literature data
- By an expert group associating neuro-oncologists (ANOCEF*) and pharmacists (SFPO)
  - * = ***A**ssociation des **N**euro **O**ncologues d'**E**xpression **F**rançaise*

Creating the export From datasheet→ SAS software

Many hours to program the requests

…To automatize and validate the safety of this process

# Guideline conception (2)

- To analyse all the literature available on TMZ
- Level of evidence established from 40 published studies

| Studies | Levels of evidence |
|---|---|
| Meta-analysis of randomised controlled trials (RCT) or several RCT with high methodological quality | **A** |
| Randomized trials, prospective ($B_1$) or retrospective studies ($B_2$) with same | **B** |
| Studies characterized by a low methodological quality with variable results and conclusions | **C** |
| Retrospective studies, case studies | **D** |
| No data - Experts approval | **E** |

# Main Results

# Demographic Datas (1)

- 21 centers involved (11 university hospitals + 9 cancer centers + 1 private)
  - Representing 62 % of the selected centers !
  - Representing 39 % of the national prescriptions of TMZ in France *(source Schering-Plough)*
- 834 adults patients, mean 7,2 ± 4,7 datasheets/patient
- In average, 38 patients / center ± 33 [3-133]
- 5982 datasheets,

# Patient Characteristics (2)

- Mean Age : 54 years ± 14 [18 – 95]
- Sex ratio M/F: 57% / 43%
- Lenght of follow-up during the study: 8,1 months ± 7,2

# Previous therapy

- No prior treatment = 215 patients (25.9%)
- 616 patients have received prior treatment
  - Surgery alone for 336 patients (**40,4%**)
  - Radiotherapy + surgery for 92 patients (**11,1 %**)
  - Radiotherapy alone for 35 patients (**4.2%**)
  - Radiotherapy + surgery + chemotherapy for 62 patients (7,5 %)
  - Surgery + chemotherapy for 57 patients (6,9%)
  - Radiotherapy + chemotherapy for 23 patients (2.8%)
  - Chemotherapy alone for 11 patients (1.3%)

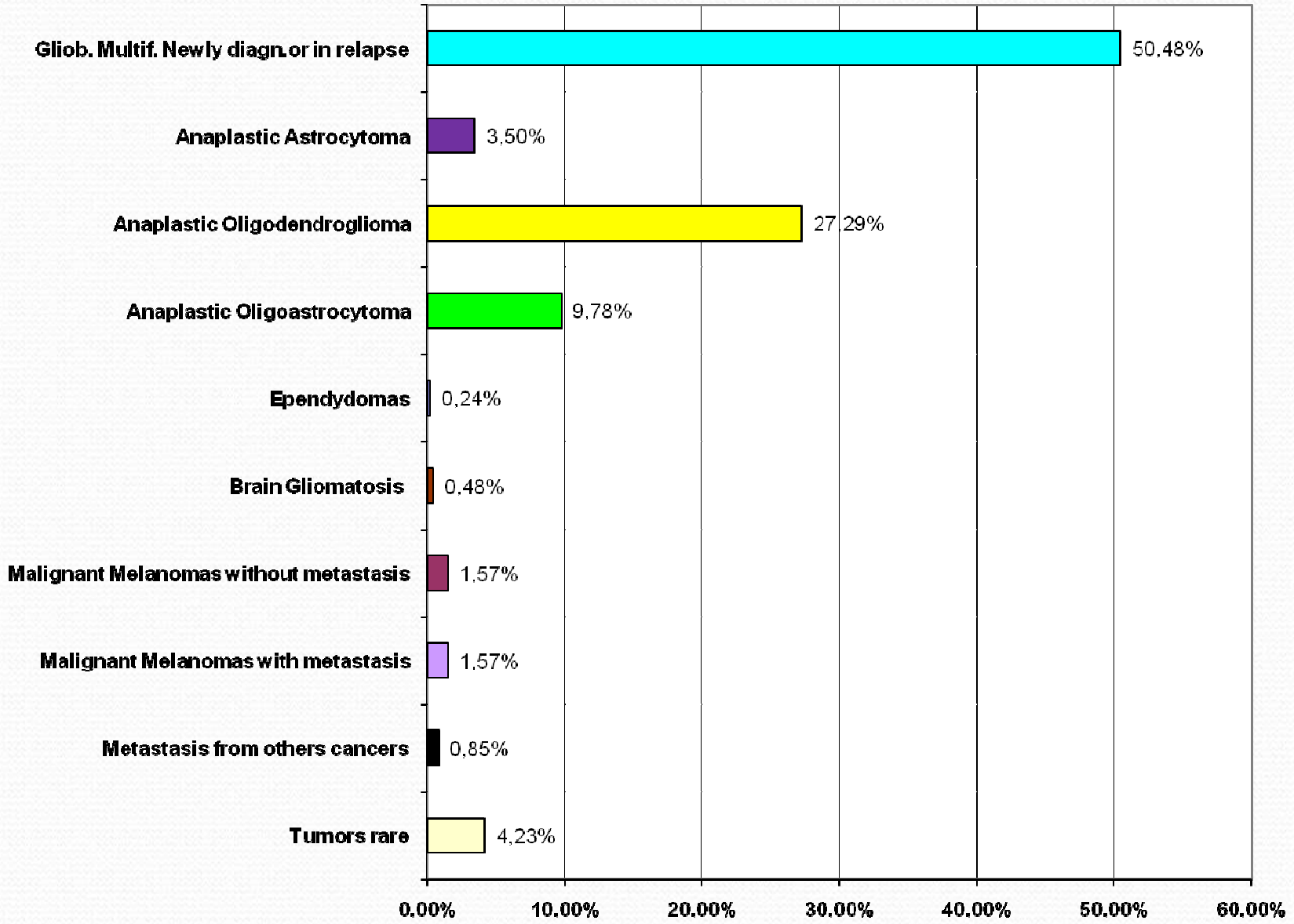
# Line of treatment (including all cures)

- 1st line of chemotherapy = no prior chemotherapy before intiating TMZ
  - 81,6 % of the patients
  - 81,6 % of the cures
- 2nd line of chemotherapy 18,4 % of the patients
  - 18,4 % of the cures

# Indications : global approach

- 795 of the patients (96 %) treated for primary brain tumor
- 26 of the patients (3,1 %) treated for melanoma (including 50% of metastatic melanoma)
- 7 of the patients (0,8 %) treated for brain metastasis from other tumour type
- 3 not identified

# Indications : Patient profile observed

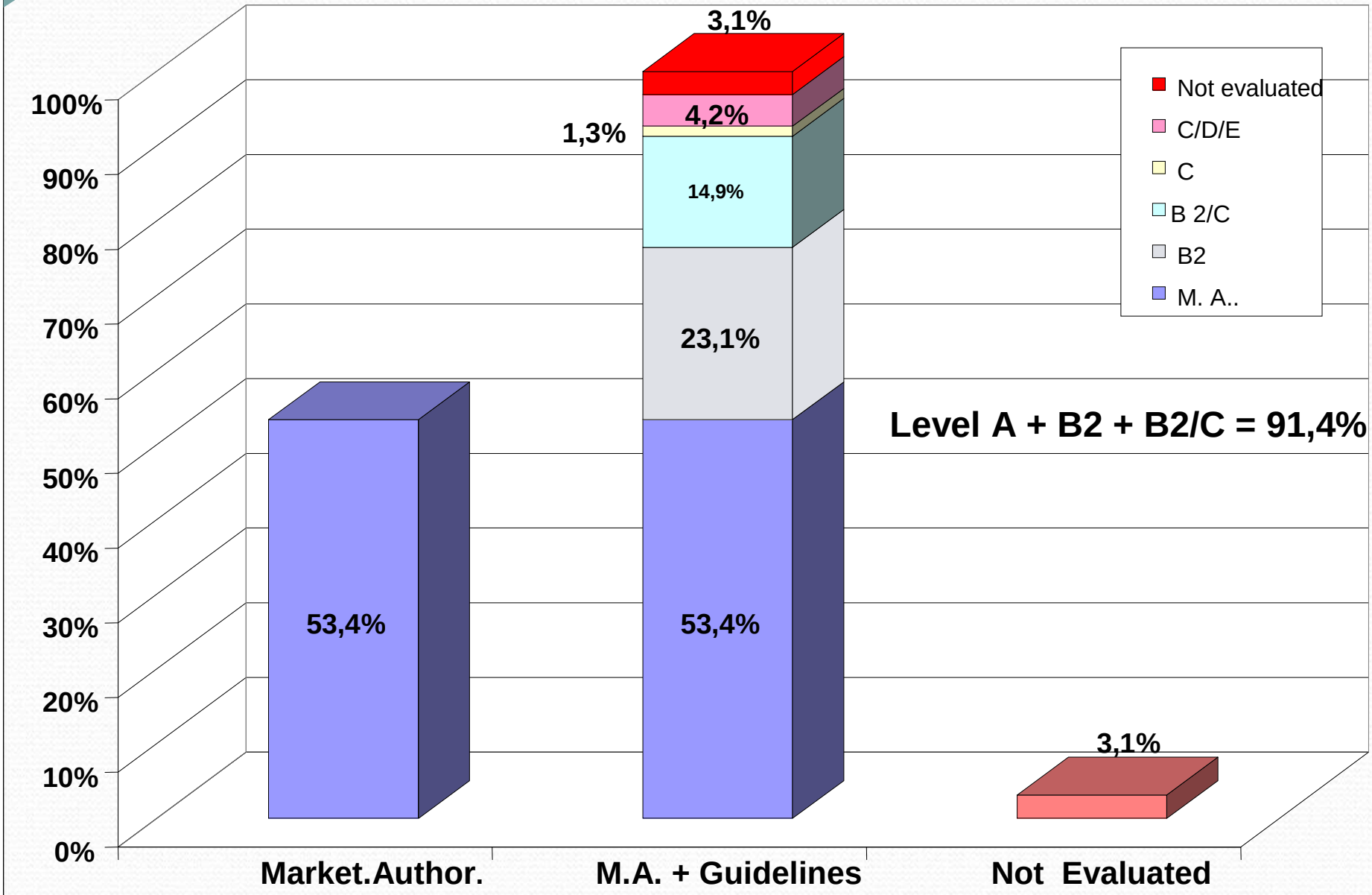


# Guidelines for« indications »

- Beyond the market authorization
- From the analysis of the available literature

| TYPE OF TUMORS | LEVEL OF EVIDENCE |
|---|---|
| High grade | Level B2 |
| Low grade | Level B2 |
| Rare tumors | Level C, D et E |
| Brain metastasis from other cancers | **Not conform** |
| Metastatic Melanoma or not | Not evaluated |

# Conformity with indications (% of number of cures)



# Conformity analysis in the marketing authorization

1. Dosage
2. Combination of treatments
3. Duration of TMZ cycles
4. Lenght of treatment
5. Number of cycles

# Newly diagnosed glioblastoma multiforme (GBM)

## Concomitant Phase

Temozolomide **75mg/m2**
radiotherapy 60Gy
**- 42 days -**

**4 Weeks off**

## Adjuvant Phase

Until **6 cycles** of monotherapy during **28 days**

5 consecutive days

followed by 23 days without treatment

### 1st Cycle

Temozolomide
**150 mg/m²**

### 2 to 6 cycles

Toxicity during the 1st cycle ?
(hematologic toxic effects ?)

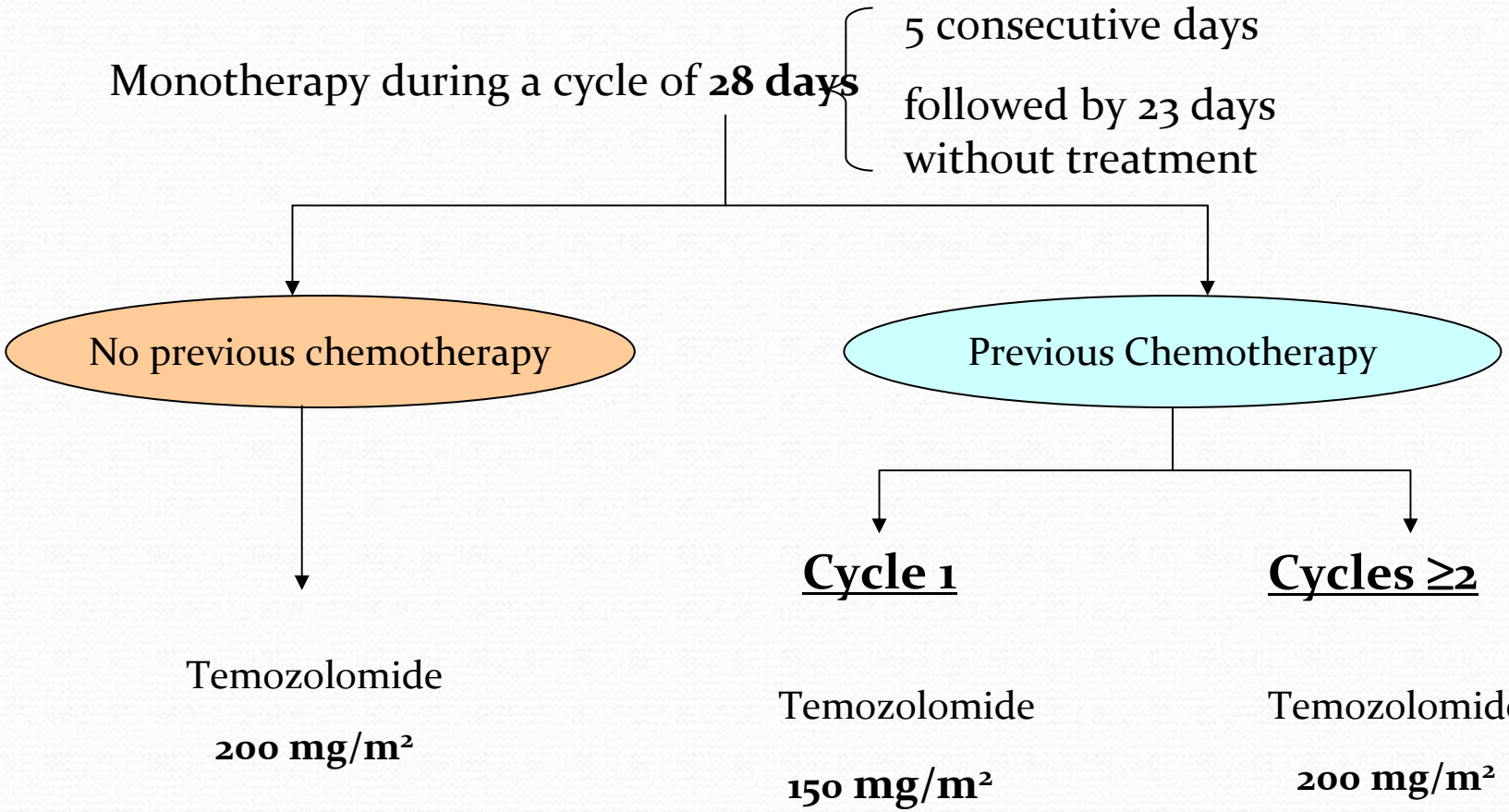
Yes

Temozolomide
**100 mg/m²**

No

Temozolomide
**200 mg/m²**

# Malignant glioma in recurrence or progression



# Dosages(1)

- No previous study suporting dosage variation, except for toxicity problems.
  - Mean posology in mg/m² during concomitant phase : 100 mg ± 42 (as a reminder, dosage M.A.=75mg/m²)
  - Mean posology in mg/m² during monotherapy : 173 mg ± 35 (dosage M.A.=150-200 mg/m²)

# Combination of treatments

- Many combinations :
  - TMZ - nitroso-urea (The most explored)
  - TMZ - cisplatine
  - TMZ - thalidomide
- Level C- of evidence
  - Many clinical datas published with no incremental effect as compared to monotherapy
  - No further development of these combinations
- Identified in **11,7%** of the cures
- Classified as not conform

# Intensity of TMZ Treatment

- Duration of TMZ / cycle
  - 84% received the planned duration of TMZ / cycle
  - If not, mean lenght of TMZ / cycle < 5 days ± 24 as compared to M.A.
- Duration of cycles
  - 90% received the planned duration of cycles
  - If not, mean lenght of cycles < 4 days ± 12 as compared to M.A.

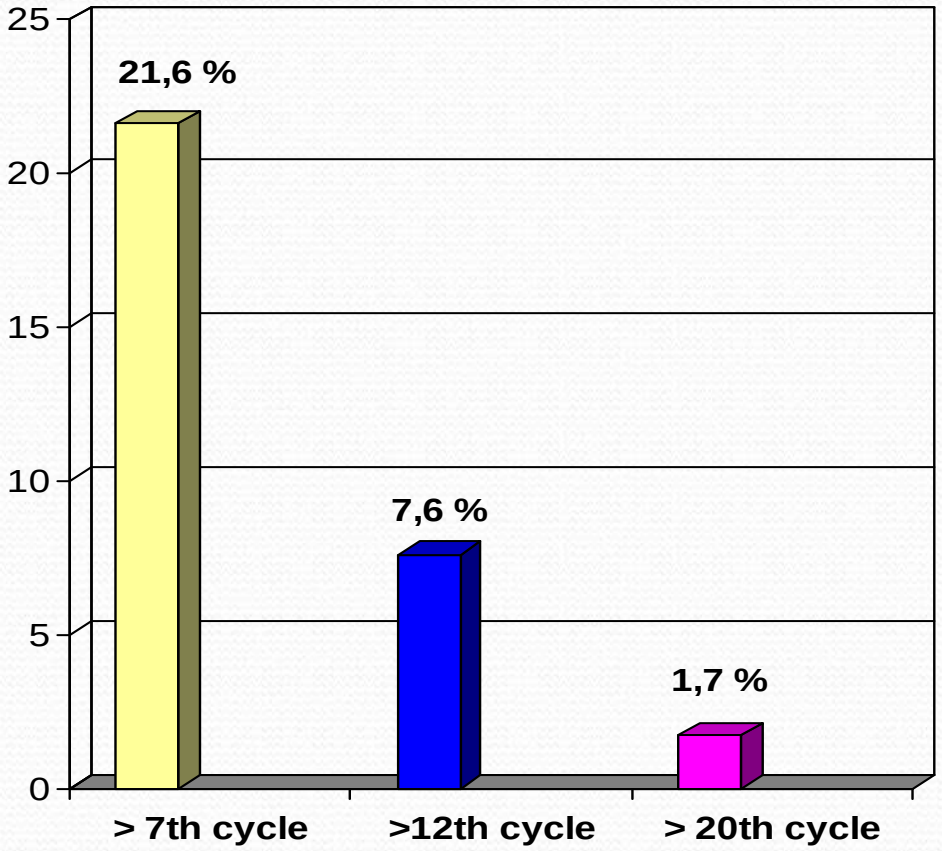
# Total lenght of treatment = Number of cycles (M.A.)

**Maintenance treatment**

(> 7th cycle) :

- 10% of the cures
- 21,6% of the cycles corresponding to M.A.
- 27% in newly diagnosed GBM

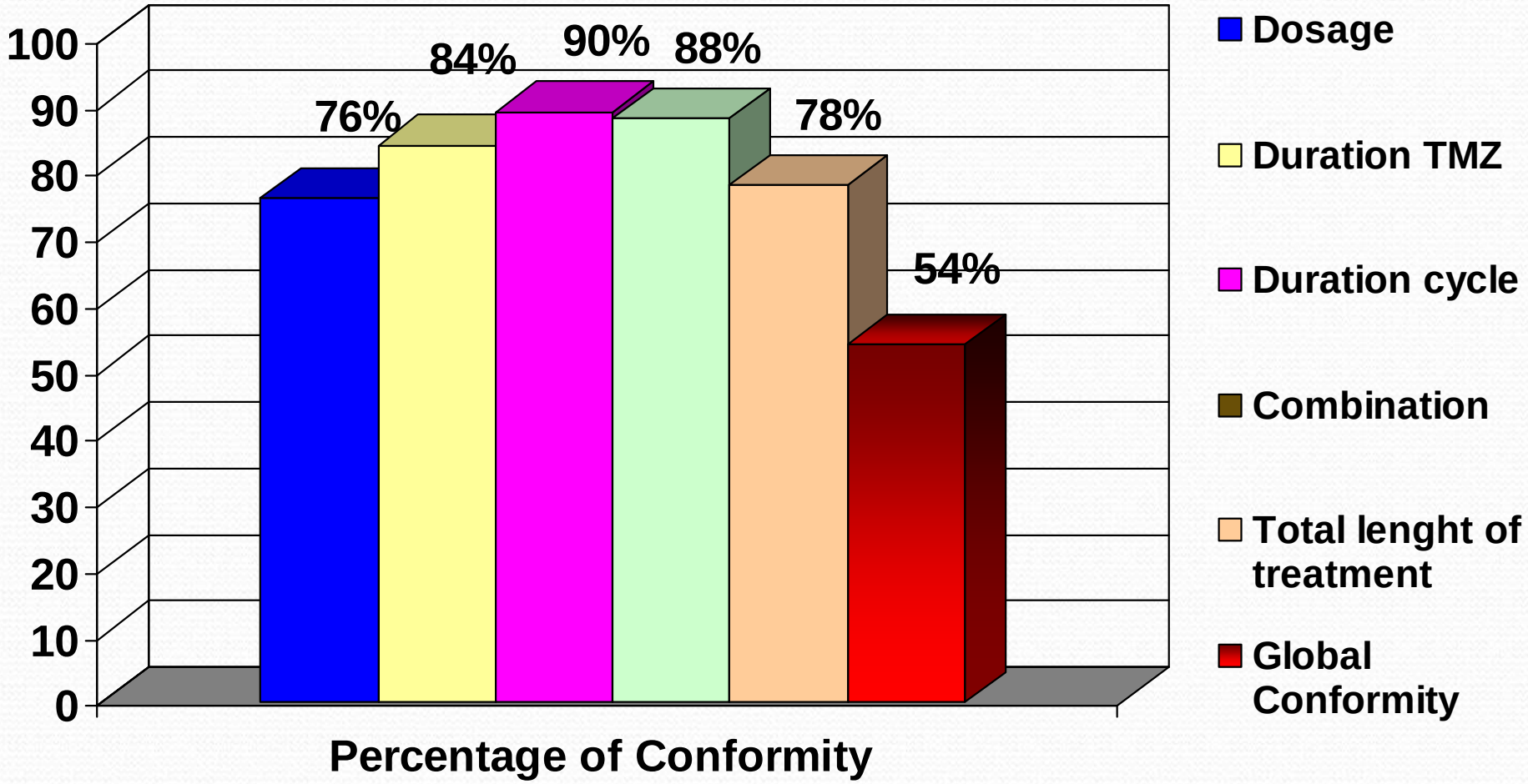
  (Only in this indication, the total lenght of treatment is exactly defined in the M.A.)



# Conformity to M.A.

## (Dosage + duration TMZ/cycle/treatment + combinations)

### (in % of number of cycles)



# Response to treatment

- Study not designed for this goal
- 729 patients (88%) with at least a documented answer to the treatment, during the first 7 cures
- Global lenght of treatment for patients achieving their treatment at the end of the study : 7,7 months ± 6,9
- 157 deaths (18,8%) registered at the end of data collection

# TMZ discontinuation treatment

- 46,6 % patients still under treatment at the end of data collection
- Reasons for discontinuation of temozolomide
  - End of the cycles (36 patients - 4,3%)
  - Side effects (31 patients - 3,7%)
  - Relapse = progression under treatment (167 patients - 20,1%)
  - Death (80 patients - 9,6%)
  - Other (128 patients -15,4%)

# Toxicity (1)

- Side effects registered in 33 % of cures
- Among them
  - Hematologic toxicity : 9%
  - Nausea : 8% / vomiting : 4% + combined : 2%
  - Constipation : 5%
  - Headache : 5%
  - Asthenia : 18%

# Prophylactic Therapy

- % of patients receiving prophylactic therapy :
  - Antiepileptics: 63%
  - Corticoïds : 42%
  - Antiemetics : 86%
  - Antibiotics : 8%

# Conclusion (1)

- This analysis give us some precious and until now not well known informations :
  - Most of the patients (96 %) treated for neurologic primary tumors
  - Modest conformity regarding the M.A. (53,4 %)
  - …. But a better compliance (91,4 %) in comparing these daily practices to guidelines elaborated by experts in this objective (Level A, B2 and B2/C)
  - …Resulting of an accurate analysis of the available literature on this topic.

# Conclusion (2)

- Some limitations
  - Few private centers included
  - Hypothesis of a different conformity to clinical practice in these centers :
    - Less patients treated
    - Refusal to participate ?
- Higher non compliance for the schedule of administration (dosage, lenght of treatment) than for the indications
  - Highlights the importance of guidelines in these prescription parameters