Survey of the treatment of neuro-oncology patients by temozolomide through a partnership between physicians and pharmacists

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Data analysis: G. Ezeque, Y. Hassani

Introduction

1. **Development of a pharmacoepidemiologic survey of temozolomide practices in neuro-oncology**
    1. Protocols of survey created by pharmacists validated by neurooncologists concerning the prescription's parameters (Indications, dosage, lenght of prescription..)
    2. Development of guidelines from a subgroup with both pharmacists and neuro-oncologists
    3. Analysis of conformity of 6000 prescriptions concerning 835 patients
2. **Analysis of our practices and organizations**

Neuro-oncology medical specifications: issues

- 3% of cancers
- Poor prognosis
  - Grade II-III versus IV
- Functional impact:
  - Cognitive
  - Motor

- Socio-familial impact
  - Patients
  - Family

Neuro-oncology medical specifications: therapies

- Surgery
  - Progress for grade II
- Radiotherapy
- Chemotherapy
  - Limited number of agents
  - Monotherapy (Nitrosourea (Nu), Temozolomide (TMZ) exceptions (procarbazine, lomustine and vincristine (PCV))
  - Risk-Benefit: TMZ, Nu
- "Target" treatments
  - Anti-angiogenics
  - Agents in development ++
- Prognostic/predictive molecular markers
  - Not strictly decision-making, but in development

Specificity of pharmaceutical treatment for patients treated in Neuro-oncology

- The person involved is less often the patient than in other pathologies
- His/her level of understanding needs to be clearly evaluated before any explanations are provided
- Different therapeutic regimens (whether or not in combination with radiotherapy) need to be the target of specific training for pharmacy staff dispensing the drug

Temodal® (TMZ): summary

- Alkylating antineoplastic agent
- Good penetration into the Cerebrospinal fluid
- MA indications:
  - Newly diagnosed glioblastoma multiforme in association with RT, followed by monotherapy treatment
  - Malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, presenting with a relapse or progression after standard treatment.

Specificity of Temodal®?

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

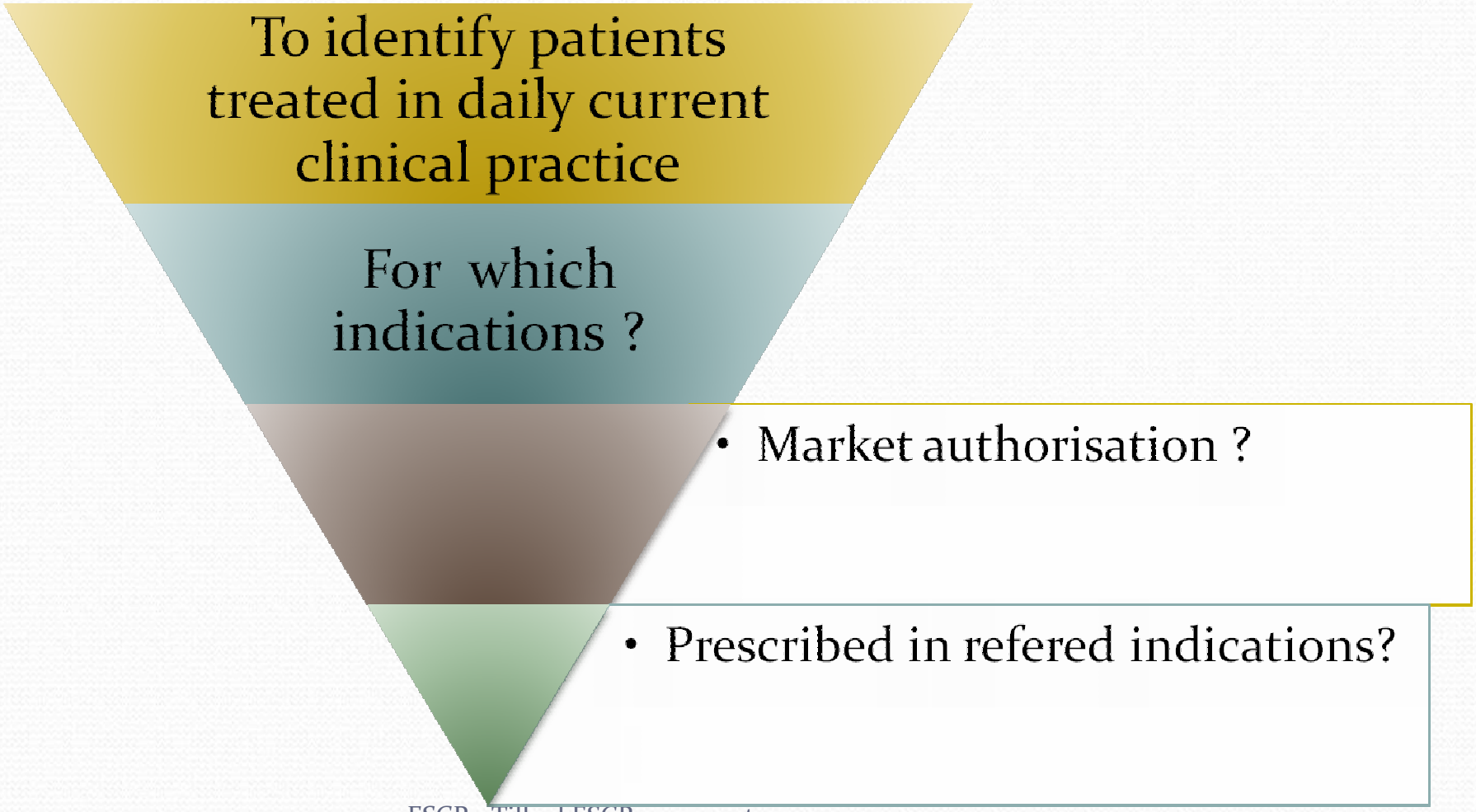
Numerous off labeled prescriptions

Due in part to the lack of available treatment

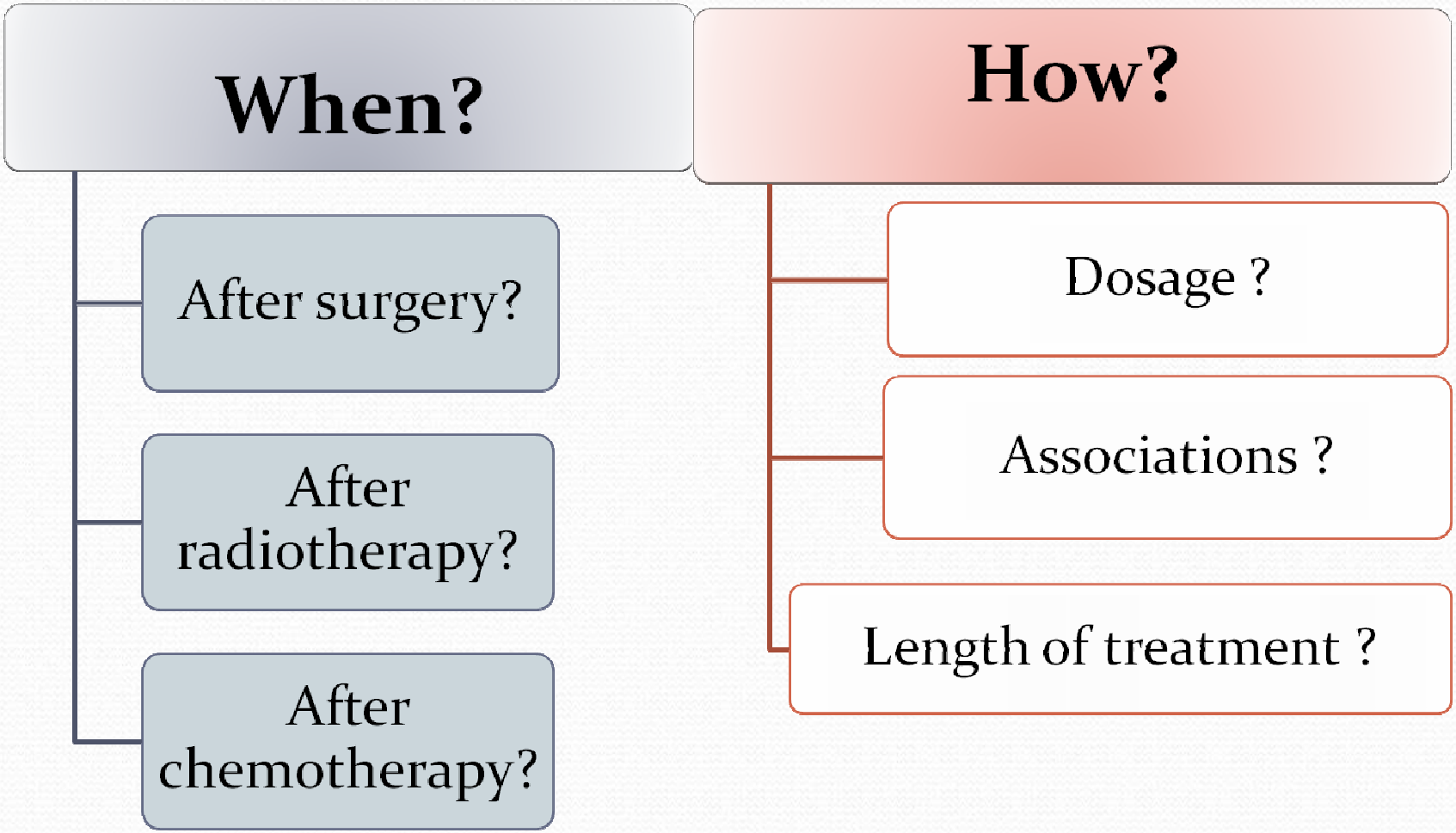
Hospital dispensing procedure.

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

Objective of the study (1)



Main objectives of the study(2)



Important questions concerning Temozolomide® in clinical practice

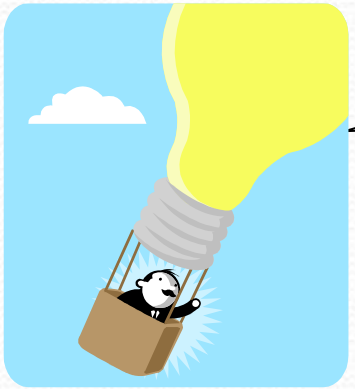
% of 1st line of treatment

What kind of side effects and what incidence ?

Is the temozolomide 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 protocole
- 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
- Submission to ethical comittee

Data Analysis

Creating guideline

- From literature data
- By an expert group associating neuro-oncologists (ANOCEF*) and pharmacists (SFPO)
  - * = *Association des Neuro Oncologues d'Expression Française*

Creating the export From datasheet→ SAS software

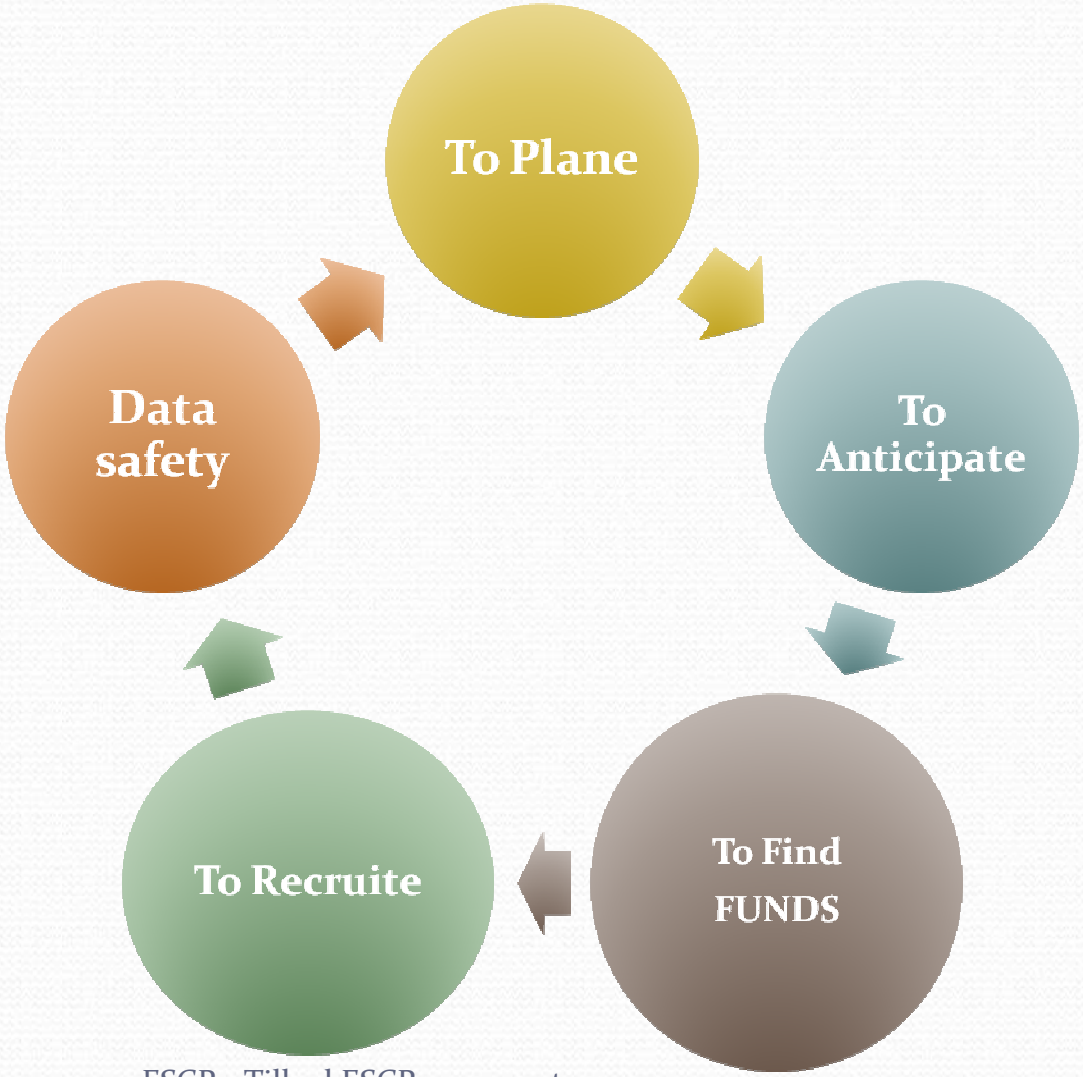
Many hours to program the requests

…To automatize and validate the safety of this process

Bulding a guideline

- Level of evidence established regarding methodology quality from published studies
- 5 level of evidence defined by the French health authority (HAS), in accordance with international rules
  - **Level A**
  - **Level B**
  - **Level C**
  - **Level D**
  - **Level E**

Beyond this organisation….



Results

Demographic Data(1)

- 21 centres recruited (11 university hospitals + 9 cancer centers +1 private)
- Representing 62 % of the selected centres !
- Representing 39 % of the national prescriptions of the temozolomide drug
- 834 adults patients, mean 7,2 ± 4,7 datasheets/patient
- 5982 prescriptions

Demographic Data(2)

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

Previous treatment

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

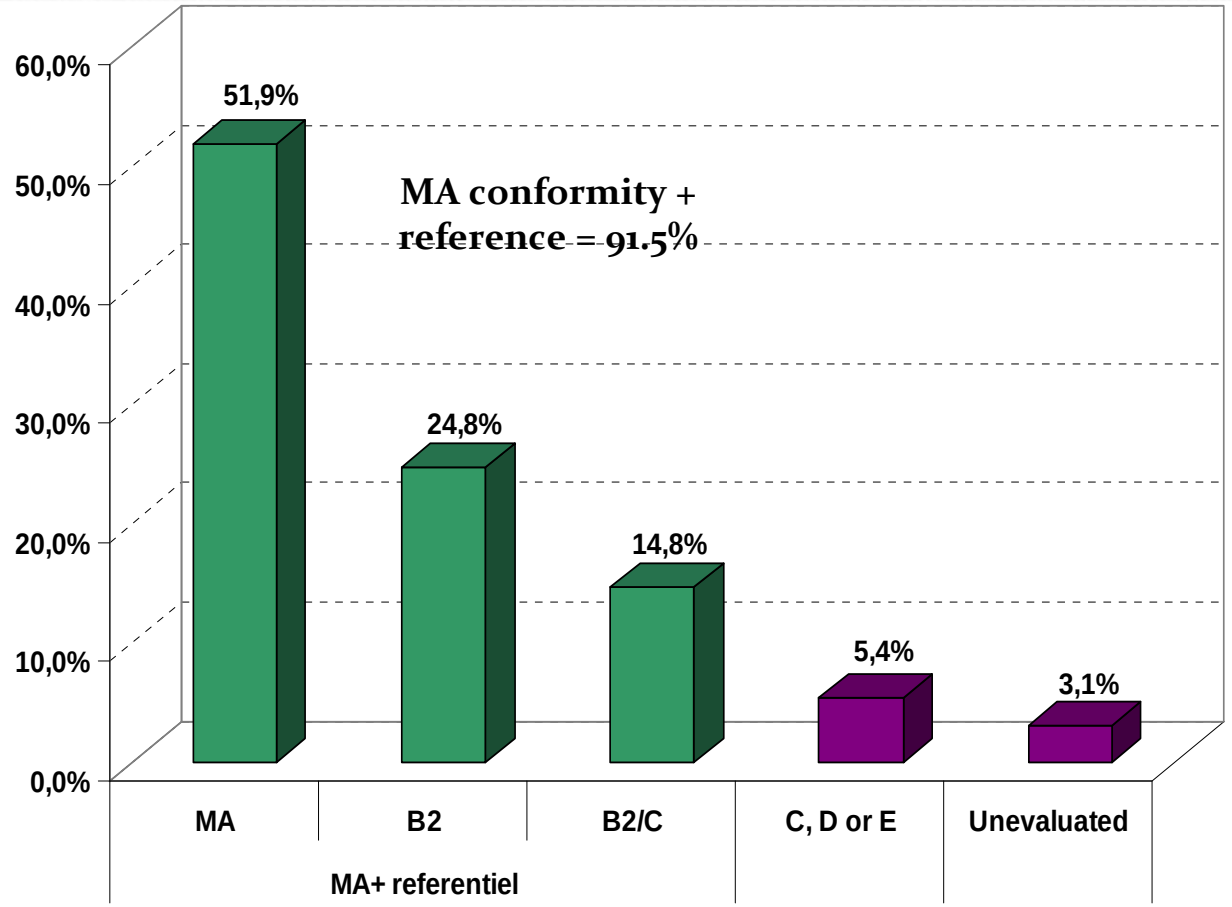
Guidelines for« indication »

- Beyond the market authorization
- From the analysis of 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
Melanoma metastatic or not	Not evaluated

1st finding: indications

- Relative conformity with indications
- When adding the B2 and C reference data > 91.5% of prescriptions



2nd finding: dosage regimens

- Level of conformity in terms of dosage
  - Newly diagnosed GBM (1st cycle): 69%
  - Newly diagnosed GBM (maintenance): 100%
  - GBM or AA in progression/relapse: 100%
- Level of conformity with the dosage regimen
  - Newly diagnosed GBM (1st cycle): 53%
  - Newly diagnosed GBM (maintenance): 91%
  - GBM or AA in progression/relapse: 80%

➢ "Pre-concomitant" regimen in certain centres

3rd finding: Associations and treatment combinations

All combinations:

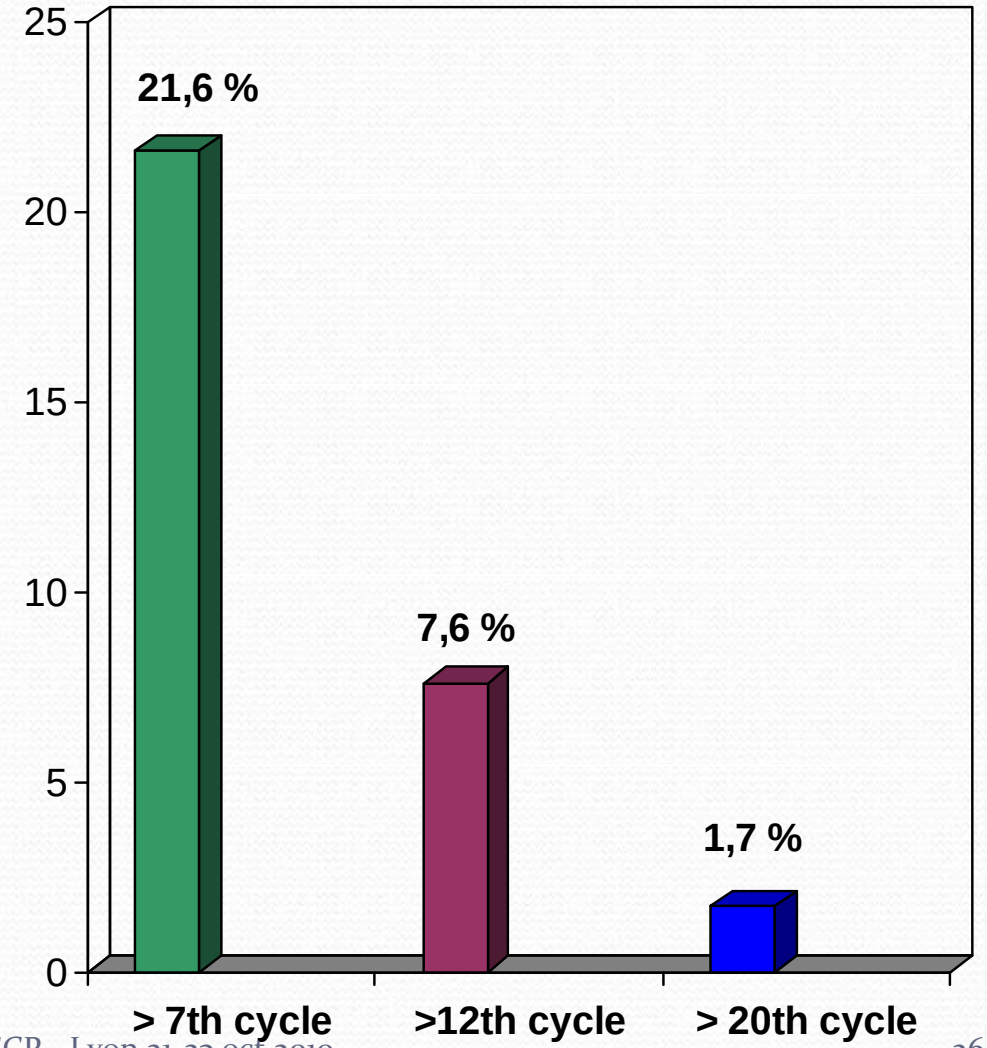
- TMZ - nitrosoureas (SLE + exploratory)
- TMZ - cisplatin
- TMZ - thalidomide

- Level C - evidence
  - consecutive series published and no further development of these combinations
- Found in 11.7% of treatments

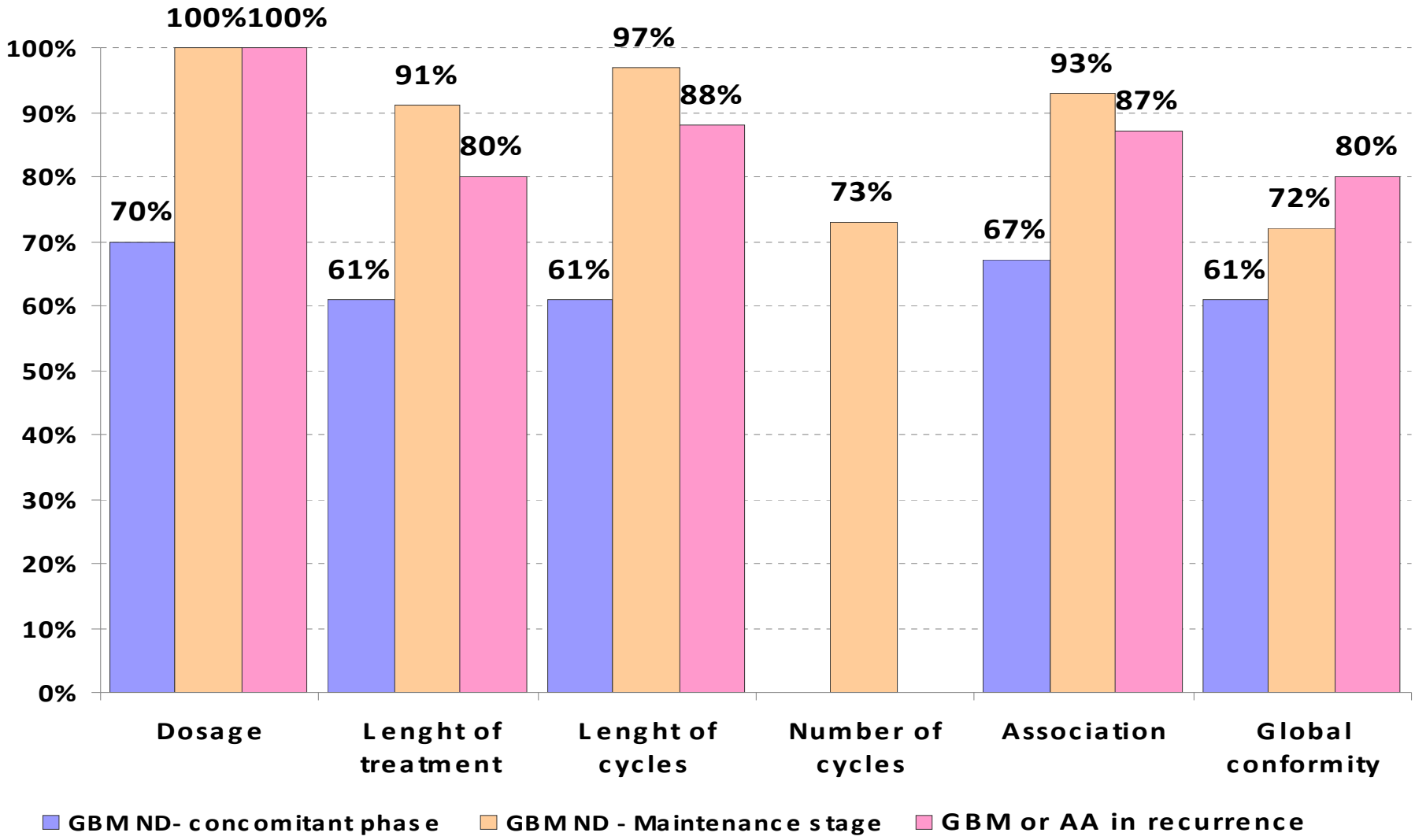
4th finding: Total duration of treatment = number of cycles

Maintenance treatment
(after the 7th cycle):

- 10% of all treatments
- 21.6% among treatments with MA indication
- 27% with newly diagnosed GMB indication (only indication with standardized duration)



Conformity in M.A. indications (Dosage + Lenght of cycle/cure/treatment + combinations – expressed as % /number of cures)



Response to the treatment

- Study not designed at this aim
- 729 (88%) patients 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 period: 7,7 months ± 6,9
- 157 death registered at the end of the data collection (18,8%).

Delay between diagnostic and initiation of the TMZ treatement

- Delay diagnostic – initiation TMZ : taking into account previous treatment
- For all prescriptions: 17 months ± 40
  - For well defined indications :
    - GBM newly diagnosed: 2 months
    - GBM in relapse: 43 mois

Stopping treatment by TMZ

- 46,6 % patients still under treatement when stopping data collection
- Reason for stopping treatments
  - End of the cycle (36 patients - 4,3%)
  - Side effects (31 patients - 3,7%)
  - Relapse = progression under treatment(167 patients - 20,1%)
  - Death (80 patients - 9,6%)
  - Others (128 patients -15,4%)

Tolerance (1)

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

Tolérance (2)

- **General side effect**
  - Dizziness : 31%
  - Weight loss : 19%, Appetite loss : 25%, anorexia : 10%
  - Apathy : 8%
  - Drowsiness : 8%
- **Digestive :**
  - Epigastric pain : 10%
  - Gastro-enteritis : 8%
- **Neurologic :** 8% (épilepsia)
- **Hépatic :** Elévation des enzymes hépatiques : 10%
- **Génito-urinary :** Urinary infections : 10%
- **Dermatologic :** cutaneous allergic reactions : 8%

5th finding: tolerance

- Treatment discontinued for intolerance in only 31 (3.7%) of the patients being monitored
- However, adverse effects reported in 33% of treatments
- Prophylactic treatments widely prescribed for patients:
  - Antiepileptics 63%
  - Corticosteroids 42%
  - Antiemetics 86%
  - Antibiotics 8%

In addition to these results, what about our organizations?

Defining these organizations from specific questions (1)

1. Who is the prescriber? Neuro-oncologist - Oncologist?
2. Who is responsible for dispensing the treatment?
3. Who controls this treatment?
4. How do we communicate with our patients?
    1. Procedures
    2. Supporting documents

Defining these organizations from specific questions (2)

5. Who is involved during treatment?
    1. Patient
    2. Accompanied patient
    3. Family
    4. Hospital representative

    .....
6. How do we communicate with our prescribing physicians?
    1. Regular meetings
    2. If there are problems
    3. Contact or monitoring record

Defining these organizations from specific questions (3)

7. How do we provide prescriptions?
    1. By computer
    2. By paper 's prescription
        1. Free format
        2. Pre-formatted
8. How long is the treatment provided (radiochemotherapy phase)?
    1. Full treatment
    2. Partial treatment

Defining these organizations from specific questions (4)

9. Is there a system for collecting unused forms in place at the pharmacy?
10. Did we check if is there a discrepancy between the doses effectively administered during the previous treatment and the prescribed dosage?

Based on the results of a survey

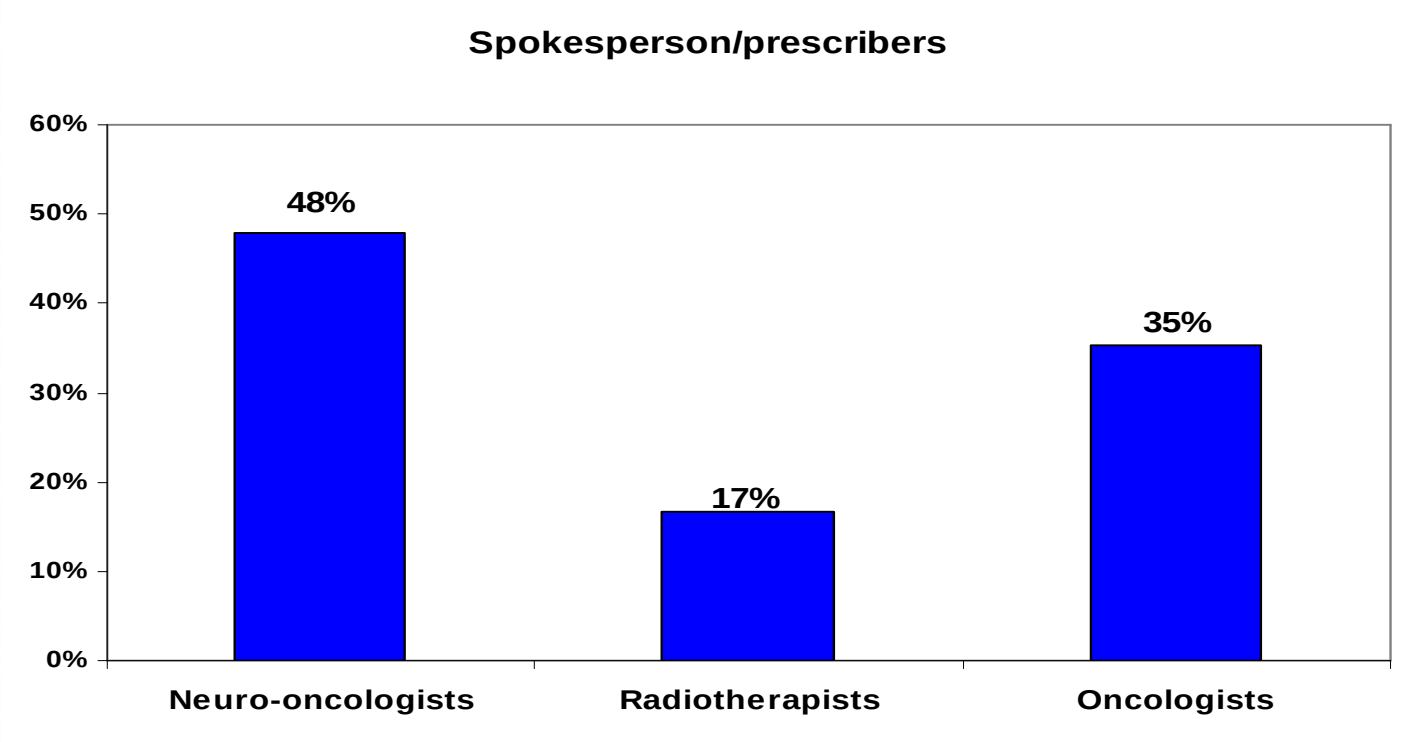
Number of participants in the survey and profile

- 17 centers, including:
  - 6 University Hospital Centers (UH)
  - 8 Regional Cancer Centers (RCC)
  - 8 Private Centers
  - 1 General Hospital Center
- Total of approximately 800 treatments/month

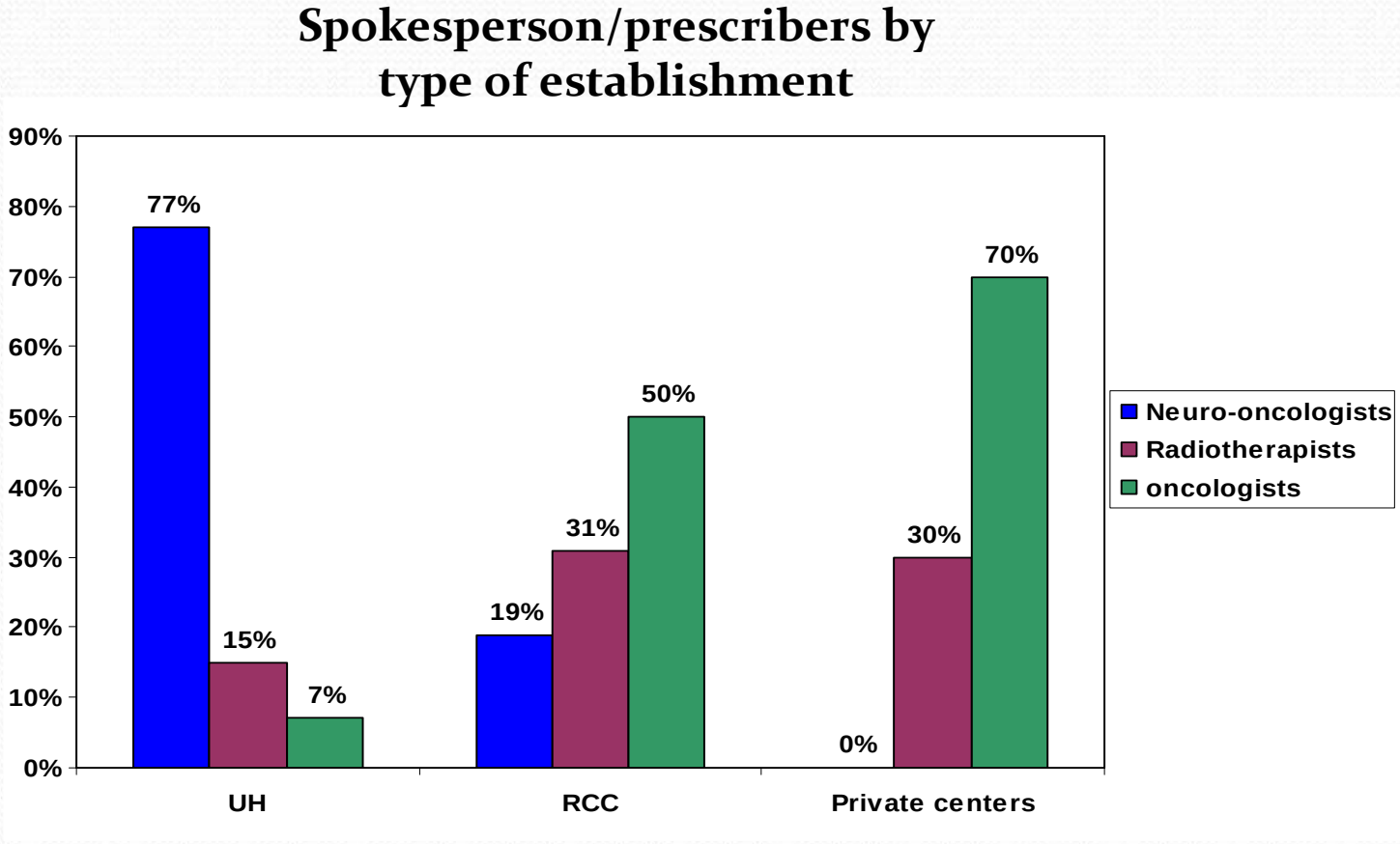
Methodology

- Questionnaires sent to **34** centers
- Follow-up telephone calls
- Creation of analysis plans for the overall evaluation of number of items

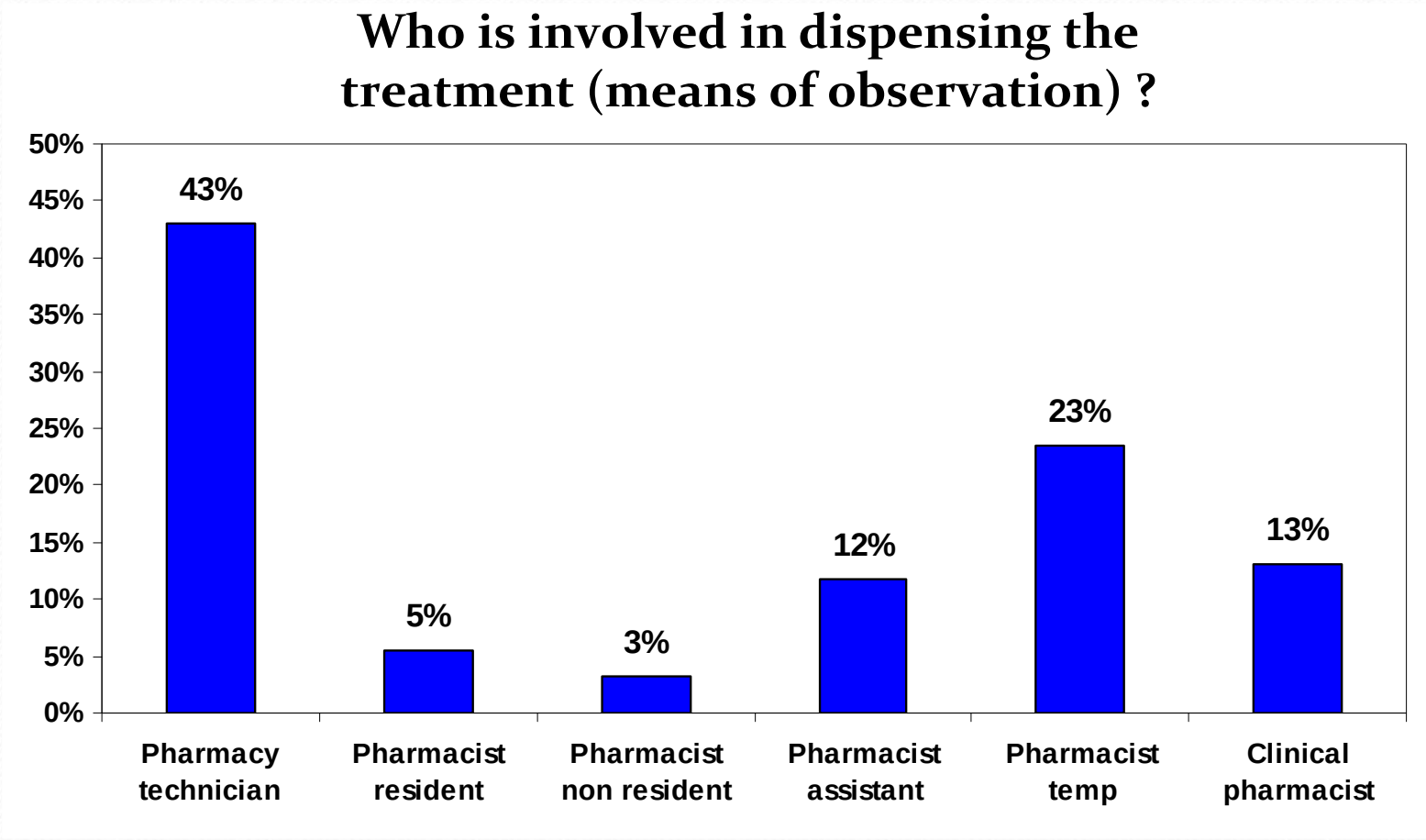
1- Prescriber profile (1)



1- Prescriber profile (2)

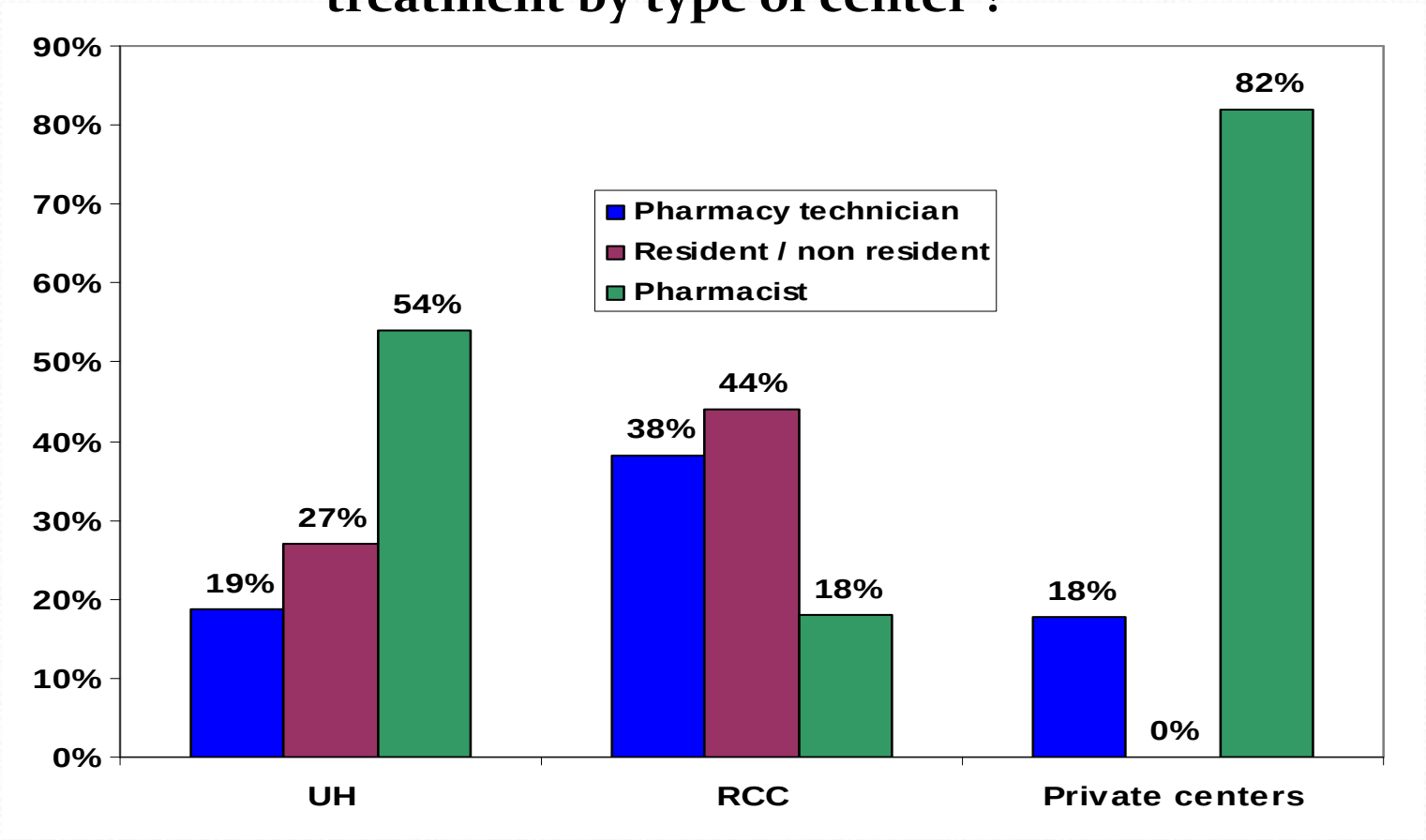


2- Dispensing organization (1)



2- Dispensing organization (2)

Who is involved in dispensing treatment by type of center ?

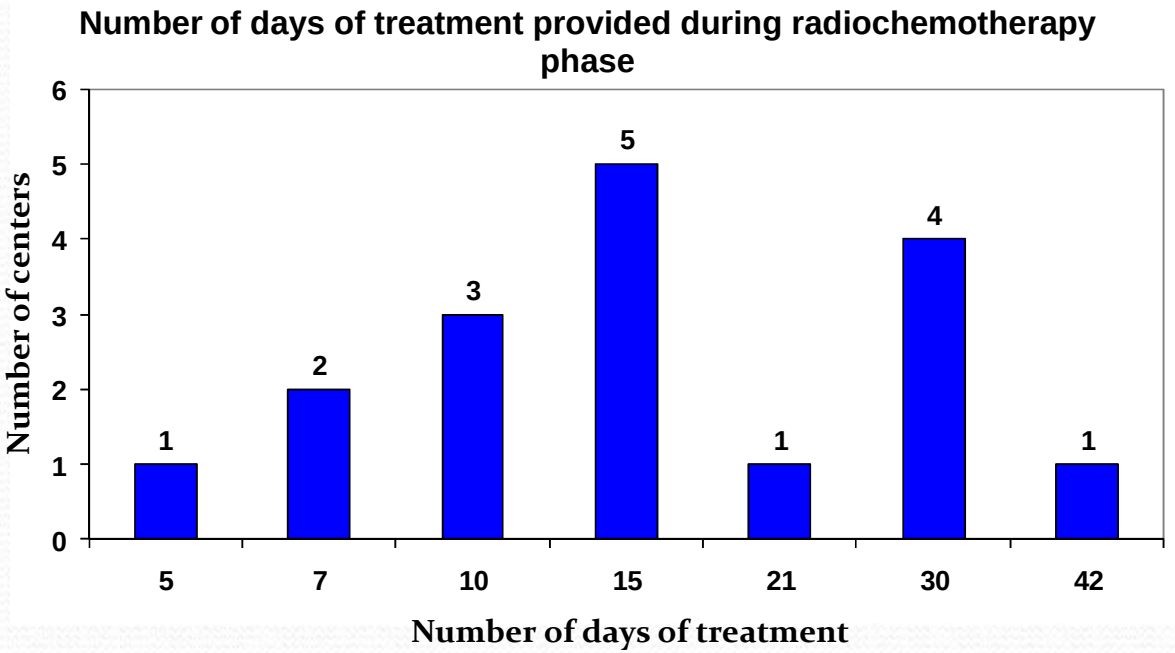


4- Dispensing organization (3)

- Specific procedures for TMZ treatment: 9 centers
- Specific explanations for patients: 11 centers
- Specific support documentation for patients: 11 centers

4- Dispensing organization (4)

- During the radiochemotherapy phase (42-47 days of treatment) the TMZ treatment provided is:
  - Full: 1 center
  - Partial: 16 centers; average = 17 days



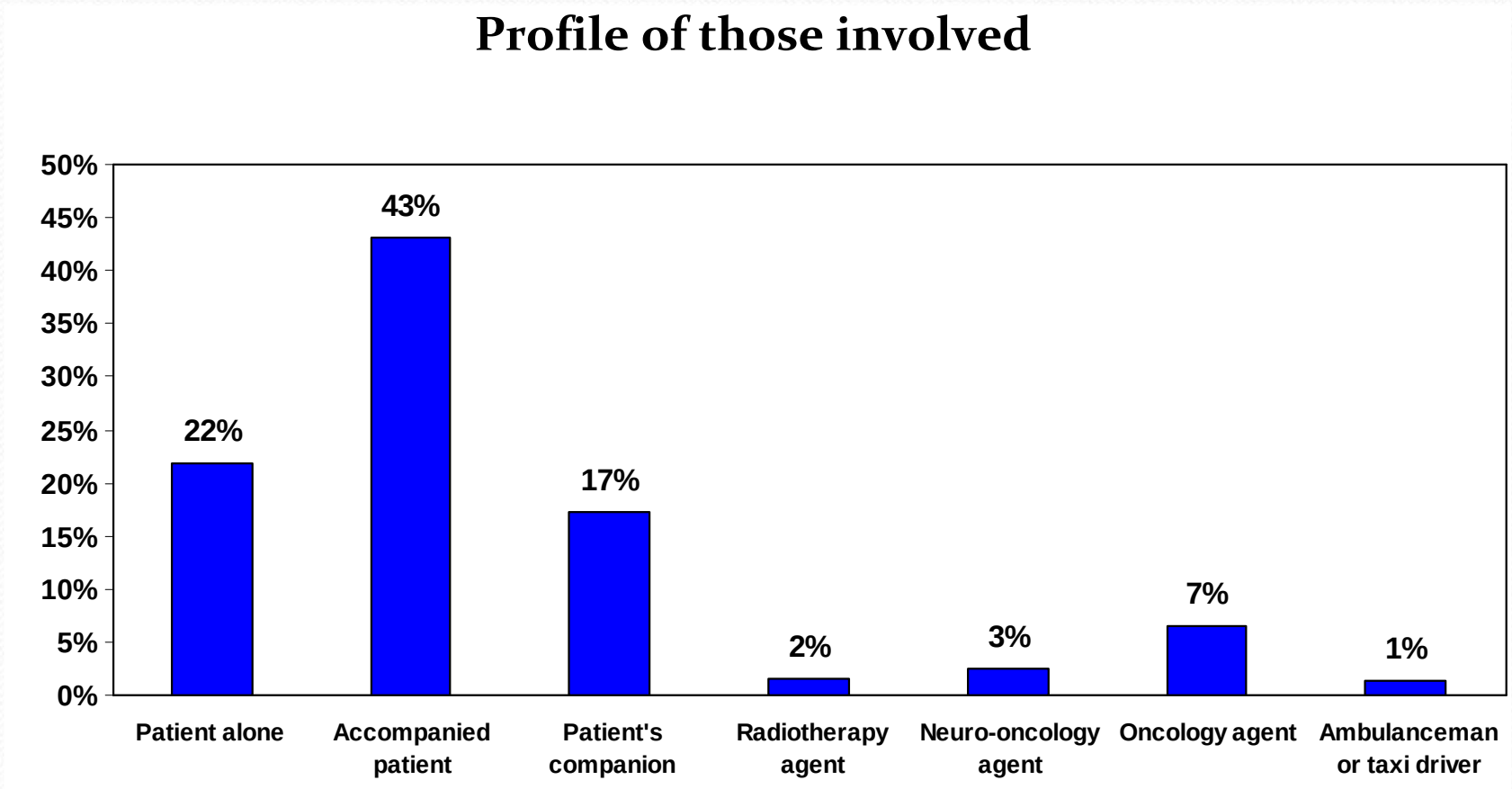
4- **Dispensing organization** (5)

- **Is there a system for the return/collection of unused capsules?**
  - 11 centers have a system
  - Recovery/destruction if returned
  - At one center (Paul Strauss Strasbourg), treatment for 15 days
  - ….Then, during the next treatment, → speak to the patient about compliance → medical contact if Pb detected
  - 5- or 7-day treatment using a pill box (Dijon CGFL) with the pillbox returned after each treatment

4- Treatment organization (6)

- **Comparison between administered and prescribed doses**
  - Systematic:10 centers
  - Not systematic (timing issues): 3 centers
  - Not performed: 4 centers

Pharmaceutical communication with patients in relation to the drug (1)



Pharmaceutical communication with patients in relation to the drug (2)

- **Content of some support documents provided by colleagues**:
  - Proposal of detailed treatment plans, indicating the complete regimen and means of drug treatment for a prescribed dosage
  - Regimens for taking the drug include:
    - Storage conditions
    - Instructions for taking the capsules (do not open, break, etc.)
    - Instructions for return in the event that treatment is interrupted

Pharmaceutical communication with patients regarding the drug (3)

- **At one center (Pitié Salpêtrière), the information pamphlet includes**
  - The necessity to take the drug on an empty stomach and a significant time after or before mealtimes and other treatments
  - A change in the regimen between the quantity provided according to the form and the number of times the drug should be taken, once in the morning
  - Warning for pregnant women who handle the drug
  - Practical advice in the event of inhalation or contact with the eyes

Physician-pharmacist communication

- Organization:
  - Regular meetings (that can cover other topics): 2 centers
  - Direct telephone contact in the event of problems: 17 centers
  - Contact or follow-up record: 1 center

How do you send the prescription to the pharmacy?

- Prescription on unformatted paper: 13 centers
- Prescription on pre-formatted paper: 9 centers
- Computerized prescription system: 4 centers
  - Chimio®, SHS santé® 400, other internal software applications
- Presence of a dual use for computerized/paper prescriptions: 3/17 centers
  - Using multiple prescription systems (unformatted/pre-formatted/computerized) at 6 centers

Conclusion (1)

- **Numerous local initiatives to optimize treatment**
- **Very specific situation for this oral form in oncology**:
  - Exclusive hospital outpatient treatment
  - → Investment of centers in terms of resources, support, and physician-pharmacist collaborations
- **In order to prevent iatrogenic risks related to:**
  - The complexity of the dosage regimen
  - The management of orders, patient treatment
  - New conditions which limit certain components of this risk

Conclusion (2)

- **Justification of:**
  - Implementing specific programs and support to accompany treatment
  - Maintain treatment at the hospital
- **Physician-pharmacist collaborations**
  - Reinforced by an evaluative research project
  - Original process:

Practice → Applied research → Analysis of practice