19. Studiensynopsis (Englisch)

<table>
<thead>
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<th>Protocol Concept Sheet</th>
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</table>
| **Study Title**        | Randomized phase III study of a one week on/one week off schedule of temozolomide versus involved-field radiotherapy in elderly (>65 years) patients with newly diagnosed anaplastic glioma and glioblastoma (Methvalem)  
Investigator-initiated study |
| **Indication**         | Newly diagnosed anaplastic glioma and glioblastoma in patients older than 65 |
| **Rationale**          | To compare the efficacy and safety of standard radiotherapy and a novel schedule of temozolomide (one week on/one week off) in the primary treatment of elderly (>65 years) patients with anaplastic glioma and glioblastoma |
| **Project Phase**      | Phase III |
| **Protocol Status**    | Planned  
Recruitment duration: 15/05/2005 - 12/2008  
Treatment and observation period: until 01/2010 |
| **Investigator and Sponsor according to GCP guidelines** | Professor Dr. med. Michael Weller  
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Prof. Dr. med. M. Bamberg, Prof. Dr. U. Bogdahn, Prof. Dr. Engenhartz-Cabillic, Prof. Dr. G.G. Grabenbauer, Prof. Dr. B. Kaina, Prof. Dr. Schackert, Prof. Dr. U. Schlegel, Prof. Dr. Ton, Prof. Dr. M. Westphal |
| **Study coordinator**  | Prof. Dr. med. Wolfgang Wick  
Department of Neurooncology  
University of Heidelberg  
Im Neuenheimer Feld 400  
69120 Heidelberg |
| **Study Committee**    | Prof. Dr. med. M. Bamberg, Prof. Dr. U. Bogdahn, Prof. Dr. Engenhartz-Cabillic, Prof. Dr. G.G. Grabenbauer, Prof. Dr. B. Kaina, Prof. Dr. Schackert, Prof. Dr. U. Schlegel, Prof. Dr. Ton, Prof. Dr. M. Westphal |
| **Biometry**           | PD Dr. C. Meisner, M.A., Corinna Engel  
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72070 Tübingen |
| **Study centers**      | Multicenter |
| **Rationale**          | The standard treatment of malignant gliomas (WHO grades III and IV) includes tumor resection, involved-field radiotherapy and possibly nitrosourea-based chemotherapy. A modest benefit of adjuvant nitrosourea-based chemotherapy has been confirmed across all age and risk groups (Glioma Meta-analysis Trialists Group 2002, NOA 2003). Yet,  
Temozolomid (one week on/one week off) versus Strahlentherapie in der Primärtherapie anaplastischer Astrozytome und Glioblastome bei älteren Patienten: eine randomisierte Phase III-Studie  
(Methvalem)  
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young age and good Karnofsky performance score are the most potent therapy-independent favorable prognostic factors, and nitrosourea-based chemotherapy is less well tolerated in elderly patients (> 65 years). Therefore, the role, if any, of chemotherapy in this patient population has remained controversial (Weller and Thomas 2003). Temozolomide is an alkylating agent which has shown activity in recurrent malignant glioma (Yung et al. 1999, 2000, Wick et al. 2004). The drug has also been explored in the first-line treatment of glioblastoma, with favorable results (Stupp et al. 2002) which gave rise to the current randomized EORTC trial 26981 which compares radiotherapy plus temozolomide chemotherapy with radiotherapy alone in the first-line treatment of glioblastoma. The safety profile of temozolomide is superior to that of nitrosoureas, both in terms of cumulative myelotoxicity and pulmonary toxicity. The median survival time for elderly malignant glioma patients is in the range of a few months. The benefit derived from surgery and radiotherapy is modest, and both treatments are less well tolerated in elderly patients than in the young (Meckling et al. 1996). The availability of a potentially effective pharmacological agent for malignant glioma, which exhibits a rather favorable safety profile, necessitates a reconsideration of the widespread therapeutic nihilism in the face of malignant glioma in the elderly. However, most elder glioblastoma patients are probably not candidates for combined modality treatment. Therefore, the present study proposal seeks to compare the standard postsurgical treatment of malignant glioma in elderly patients with a Karnofsky performance score > 60, involved-field radiotherapy to a dose of 54-60 Gy, with temozolomide alone. Temozolomide shall be used in a novel one week on/one week off schedule which allows a dose intensification of up to 2 compared with the standard regime of 150-200 mg/m² x 5 days and which has shown efficacy in recurrent glioblastoma in a small phase II study (Wick et al. 2004). At progression or recurrence, a cross-over to the alternative treatment modality is recommended if the patient is considered eligible for further treatment. The activity of the DNA repair enzyme, O6-methyl-guanine-DNA methyltransferase (MGMT) is likely to affect the response to temozolomide. The protocol will therefore include the pretreatment determination of MGMT levels in the tumor tissue and in peripheral blood cells as well a monitoring of MGMT in peripheral blood cells during chemotherapy and radiotherapy.

References


Temozolomid (one week on/one week off) versus Strahlentherapie in der Primärtherapie anaplastischer Astrozytome und Glioblastome bei älteren Patienten: eine randomisierte Phase III-Studie

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<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Median overall survival</th>
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<tr>
<td>Secondary Endpoints</td>
<td>Response rate for patients with measurable disease</td>
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<tr>
<td></td>
<td>Median progression-free survival</td>
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<tr>
<td></td>
<td>Toxicity</td>
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<td>QoL/MMSE</td>
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<td>Prognostic molecular markers (add. subprotocol)</td>
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<td>Modulation of MGMT activity (add. subprotocol)</td>
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<tr>
<td>Study Design</td>
<td>Prospective, open, randomized</td>
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<tr>
<td>Patient number</td>
<td>340 patients</td>
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<tr>
<td>Treatment plan</td>
<td>Radiotherapy, 54-60 Gy, 1,8-2 Gy fractions</td>
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<tr>
<td></td>
<td>versus</td>
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<td>Temozolomide 100 mg/m² d1-d7 of a 14 day cycle</td>
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<td>Treatment duration for temozolomide: until disease progression or unacceptable toxicities</td>
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**Inclusion / Exclusion criteria**

**Inclusion criteria**

- Patients with newly diagnosed anaplastic glioma or glioblastoma
- Karnofsky performance score ≥ 60%
- Age > 65
- Appropriate hematological and liver function according to the following definitions:
  - absolute neutrophil count (ANC) ≥ 1.5 x 10⁹/l
  - platelets ≥ 100 x 10⁹/l
  - ASAT, ALAT < 3 x upper limit of normal
- Written informed consent
- CCT or MRI scan with and without contrast

**Temozolomide (one week on/one week off)**

Strahlen-Therapie in der Primärtherapie von anaplastischen Astrozytomen und Glioblastomen bei älteren Patienten: eine randomisierte Phase III-Studie


Exclusion criteria

- Patients with anaplastic glioma or glioblastoma who have had previous radiotherapy for glioma or chemotherapy for any other type of cancer
- Karnofsky performance score < 60%
- Patients unable or unwilling to cooperate
- Serious infection or any other condition which would be a risk for the patient or interfere with the aim of the study at the discretion of the treating physician

Statistical considerations

General
The sample size is calculated with the primary objective to demonstrate the therapeutic equivalence (non-inferiority) of first-line chemotherapy (compared with first-line radiotherapy) with regard to the endpoint of overall survival. Formally this is a one-sided test for superiority with shifted hypothesis border: $H_0: \theta \leq \theta_0 - \varepsilon$ vs. $H_1: \theta > \theta_0 - \varepsilon$, with $\theta_0$ as the median survival time in the group of patients treated with radiotherapy and $\varepsilon$ as the maximum difference in survival between the two groups to be considered compatible with non-inferiority of the underlying true survivor functions. The usual sample size estimation methods for one-sided tests of difference in survival can be used.

The design is based additional on the following conditions:
- Exponential distributed survivor functions
- Alpha-error (significance level), one-sided 0,050. Beta-error: 0,2 (power: 80%)
- Median survival time in patients treated with radiotherapy: 7 months
- Maximum difference in survival to be considered compatible with non-inferiority: 25% = 1,75 months
- Accrual period: 24 months, maximum follow-up time: 36 months, 5% drop outs

Sample size
According to the above mentioned parameters, $n = 170$ evaluable patients are needed in each group. The software nQuery Advisor 4.0 was used for the sample size estimation.

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