NON-SURGICAL STRATEGY FOR ADULT EPENDYMOMA

Roberta Rudà

Department of Neuro-Oncology
University and City of Health and Science Hospital of Turin, Italy

EORTC EANO ESMO Conference 2015
Istanbul, March 27-28 2015
OUTLINE

• Natural history and patterns of relapse
• Role of radiotherapy
• Role of chemotherapy/targeted therapies
• Post-surgical management of spinal cord ependymomas
• Leptomeningeal spread
Intracranial ependymomas: patterns of relapse

• The vast majority of tumor recurrences (up to 90%) occurs as a result of lack of local tumor control
• Supratentorial tumors seem to have a higher risk of relapse
• Cerebrospinal fluid dissemination occurs in up to 15% of patients and is traditionally considered more frequent in anaplastic and infratentorial tumors.
• However, at presentation the incidence of leptomeningeal spread is less than 5%
• The occurrence of extraneural metastases is extremely rare (<1%).

Intracranial ependymomas: need for staging

- Craniospinal MRI and CSF cytology are mandatory following surgery.
- Regular surveillance with MRI may discover asymptomatic recurrences (43%) and impact subsequent treatment and survival (Good et al, 2001).
- Open questions: how often and for how long the surveillance with MRI? When CSF cytology is needed in the follow-up?
Post-surgical treatments: limitations of the studies

- The retrospective nature of most studies with small number of patients, the lack of randomized clinical studies, the heterogeneity in terms of age and location as well as the long time period analyzed in most series, explain the lack of evidence-based treatment strategies (aside from surgical resection).
Role of radiation therapy: general consensus

- For patients with anaplastic (gr.III) ependymoma postoperative radiotherapy is the standard of care and conformal techniques are used to deliver to presurgical tumor bed (margin of 1-2 cm) total doses up to 60 Gy in conventional fractionation.

- Craniospinal irradiation, considered for many years the standard of care, nowadays is reserved for patients with disseminated disease at presentation (or later in the course of the disease).

Role of radiation therapy: state of art and controversies in gr. II ependymomas

• Post-operative radiotherapy is used for treatment of patients with subtotal resection with total doses of 54-55 Gy

• The role of post-operative radiotherapy after complete resection is controversial due to lack of evidence of a clear survival benefit

Armstrong et al, 2010; Metellus et al, 2010; Vera-Bolanos 2015
Stereotactic radiosurgery for patients with recurrent intracranial ependymomas

Michael C. Stauder · Nadia NI Laack · Kamran A. Ahmed · Michael J. Link · Paula J. Schomberg · Bruce E. Pollock

Received: 13 January 2012/Accepted: 12 March 2012/Published online: 23 March 2012
© Springer Science+Business Media, LLC. 2012
A multi-center retrospective analysis of treatment effects and quality of life in adult patients with cranial ependymomas

Stephan Düttmann · Bawarjan Schatlo · Alexander Lobrinus · Michael Murek · Maria Wostrack · Carolin Weiss · Karl Schaller · Andreas Raabe · Bernhard Meyer · Roland Goldbrunner · Kea Franz · Volker Seifert · Christian Senft

Received: 6 March 2013 / Accepted: 22 June 2013 / Published online: 29 June 2013
© Springer Science+Business Media New York 2013
**Fig. 6** The QLQ-C30 results of ependymoma patients compared to EORTC Reference values in brain cancer patients. QoL Overall QoL, PF physical functioning, RF role functioning, EF emotional functioning, CF cognitive functioning, SF social functioning, FA fatigue, NV nausea and vomiting, PA pain, DY dyspnoea, SL insomnia, AP appetite loss, CO constipation, DI diarrhoea, FI financial difficulties. Values were significantly worse for the ependymoma population in the items “RF” (*p* = 0.02, Student’s *t* test), “EF” (*p* = 0.02), “FA” (*p* = 0.0006) and “PA” (*p* = 0.02) (*Asterisks*). General Quality of Life was also slightly worse, but this missed statistical significance (*p* = 0.06).
Role of chemotherapy in ependymomas
Table 1.
Summary of chemotherapy in advanced/recurrent ependymomas in adults

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>Number responding (%)</th>
<th>Number stable (%)</th>
<th>Median time to progression (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[45] Platinum-based regimens (cisplatin + etoposide and</td>
<td>6</td>
<td>4 (67%)</td>
<td>2 (33%)</td>
<td>6</td>
</tr>
<tr>
<td>cisplatin + etoposide + cyclophosphamide)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[45] Nitrosurea-based regimens (various combinations of</td>
<td>8</td>
<td>2 (25%)</td>
<td>4 (50%)</td>
<td>10</td>
</tr>
<tr>
<td>lomustine, carmustine, procarbazine, vincristine, l-aspartate,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dianhydrogalactitol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[46] Cisplatin-based chemotherapy</td>
<td>13</td>
<td>4 (31%)</td>
<td>7 (53.8%)</td>
<td>9.9</td>
</tr>
<tr>
<td>(cisplatin + etoposide + cyclophosphamide;</td>
<td>including 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cisplatin + temozolomide; carboptin + etoposide)</td>
<td>(15.4%) CR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cisplatin-based chemotherapy (PCV, CEV, temozolomide, MOPP)</td>
<td>15 No CR</td>
<td>2 (13.3%)</td>
<td>11 (73.3%)</td>
<td>10.9</td>
</tr>
<tr>
<td>[47] Chronic oral etoposide (for recurrent spinal cord ependymoma)</td>
<td>10 No CR</td>
<td>2 (20%)</td>
<td>5 (50%)</td>
<td>15</td>
</tr>
<tr>
<td>[48] Temozolomide (platinum-refractory ependymoma)</td>
<td>25</td>
<td>1 (4%)</td>
<td>9 (36%)</td>
<td>5.5</td>
</tr>
<tr>
<td>[18] Bevacizumab-containing chemotherapy (bevacizumab alone 2,</td>
<td>8</td>
<td>6 (75%)</td>
<td>1 (12.5%)</td>
<td>6.4</td>
</tr>
<tr>
<td>with irinotecan 3, carboplatin 2 and temozolomide 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCV, procarbazine, Lomustine (CCNU) and vincristine; CEV, cyclophosphamide, etoposide and vincristine; MOPP, mechlorethamine, vincristine, prednisolone and procarbazine; CR, complete response.

Shahid and Lewis, Clinical Oncology, 2013
Temozolomide chemotherapy in ependymomas of the adult

- Xenograft models have documented activity of temozolomide against ependymoma (Friedman et al, 1995).
- A retrospective series of 25 patients treated with temozolomide standard schedule in pts failing platinum-based chemotherapy demonstrated modest efficacy: PR 4%, SD 36%, PD 60% with PFS of 2 months and OS of 3 months (Chamberlain et al, 2009).
- Many ependymomas express high levels of MGMT which confers resistance to alkylating agents (Buccoliero et al, 2008).
Temozolomide as salvage treatment for recurrent intracranial ependymomas of the adult: a retrospective study

PATIENTS CHARACTERISTICS

18 patients (1999-2011)
6 female 12 male

Median age: 42 yrs (range: 18-61)
Tumor histology: 10 grade III
8 grade II
Tumor site: 11 supratentorial
7 infratentorial
8 with associated leptomeningeal spread
Karnofsky: 70 median KPS (range: 60-90)
MRI: 18 enhancing lesions

Rudà et al, submitted
## Results

<table>
<thead>
<tr>
<th>Responses</th>
<th>Histological types</th>
<th>TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>1/18</td>
<td>1 grade III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>153 (13 yrs)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>3/18</td>
<td>1 grade III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 grade II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 mo – 9 yrs+</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>7/18</td>
<td>4 grade II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 grade III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mo – 5 yrs+</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>7/18</td>
<td>5 grade III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 grade II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - 6</td>
</tr>
</tbody>
</table>

MGMT promoter methylation present in 5 patients and absent in 6 patients; no correlation was found with the response, PFS and OS

Rudà et al, submitted
Table 2.
Survey results

<table>
<thead>
<tr>
<th>Regimen</th>
<th>First line</th>
<th>Second line</th>
<th>Third line</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum-based regimen</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>PCV</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Oral etoposide</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

PCV, procarbazine, Lomustine (CCNU) and vincristine.

*Shahid and Lewis, Clinical Oncology, 2013*
About CERN

The CERN Foundation has one ultimate goal – curing ependymoma. We choose CERN Foundation members both for their scholarly excellence and their commitment to cooperatively working to cure ependymoma. Together, CERN Members collaborate by sharing research findings, responses to new treatment regimens and other new developments in a comprehensive effort against this brain cancer.

Through our team members’ collaboration, and work with our external and scientific advisory boards, the CERN Foundation comes closer to a cure every day. Our efforts are only made possible by another group dedicated to fighting ependymoma – our supporters. Their generous donations fund 100 percent of the CERN Foundation’s work.
A phase II study of lapatinib and dose-dense temozolomide for adults with recurrent ependymomas: a CERN trial

- **Treatment:** TMZ 125-150 mg/m²/d 7 days on/7 days off + Lapatinib (targeting Erb B1, Erb B2) 1250 mg/qd continuous dosing
- **Results:** 50 patients enrolled (gr I, II, III WHO) 19 intracranial, 25 spinal cord, 6 multiple tumors
- **Response:** 1 CR, 3 PR, 33 SD, 12 PD
- Positive correlation between response and high Erb B2 mRNA expression

M. Gilbert et al, SNO Meeting, Miami Beach, November 2014
Bevacizumab for recurrent ependymoma

ABSTRACT

Background: Ependymoma is a rare type of glioma, representing 5% of all CNS malignancies. Radiotherapy (RT) is commonly administered, but there is no standard chemotherapy. At recurrence, ependymoma is notoriously refractory to therapy and the prognosis is poor. In recurrent glioblastoma, encouraging responses with bevacizumab have been observed.

Methods: In this Institutional Review Board-approved study, we retrospectively analyzed the records of 8 adult patients treated for recurrent ependymoma and anaplastic ependymoma with bevacizumab containing chemotherapy regimens. We determined radiographic response (Macdonald criteria), median time to progression (TTP), and median overall survival (OS; Kaplan-Meier method).

Results: There were 4 men and 4 women with a median age of 40 years (range, 20–65). Prior treatment included surgery (n = 8), RT (8), temozolomide (5), and carboplatin (4). Bevacizumab (5–15 mg/kg every 2–3 weeks) was administered alone (2) or concurrently with cytotoxic chemotherapy including irinotecan (3), carboplatin (2), or temozolomide (1). Six patients achieved a partial response (75%) and 1 remained stable for over 8 months. Median TTP was 6.4 months (95% confidence interval 1.4–7.4) and median OS was 9.4 months (95% confidence interval 7.0–not reached), with a median follow-up of 5.2 months among 5 surviving patients (63%).

Conclusions: The radiographic response rate to bevacizumab-containing regimens is high. A prospective study is warranted. Neurology® 2009;73:1677–1680

GLOSSARY

CI = confidence interval; OS = overall survival; RT = radiotherapy; TTP = time to progression; VEGF = vascular endothelial growth factor.
Spinal cord ependymomas: general concepts

- Histologic subtypes: myxopapillary ependymoma (grade I) arising in the cauda equina and classic ependymoma (grade II or III) arising most commonly in the cervical and thoracic spinal cord.

- Relatively low risk of dissemination.

Boström et al 2011; Tarapore et al, 2013
Spinal cord ependymomas: non-surgical management

- Post-operative local radiotherapy prolongs PFS and OS survival in gr.III tumors (rare)
- Post-operative local radiotherapy prolongs PFS after subtotal resection in gr.II tumors
  → risk of radiation-induced myelopathy unknown
- Reirradiation (cyberknife) for local recurrences.
- Few data available on chemotherapy (oral etoposide, TMZ, other combinations) or target therapies (lapatinib, imatinib)

Oh et al, 2013; Chao et al, 2011; Chamberlain et al, 2001; Nokamura et al, 2009
Spinal myxopapillary ependymomas: a challenging entity

- The prognosis after surgery for some myxopapillary ependymomas seems worse than generally believed (Boström et al, 2011); some series reported a better prognosis for gr.II ependymomas compared to gr.I myxopapillary ependymomas (Tapore et al 2013)

- The pattern of relapse has been reported commonly as local (Shaw et al, 1987; Pica et al, 2009; Tsai et al, 2014) supporting the use of local RT; however, with a more extensive use of MRI screening, an increase risk of tumor dissemination has been observed (Weber et al 2015)
Spinal myxopapillary ependymomas: a challenging entity

• Radiotherapy is commonly reserved for patients with recurrent tumors

• Two recent series (Tsai et al, 2014; Weber et al, 2015) have reported that post-operative radiotherapy may improve local control and PFS in newly diagnosed patients

• These data must be confirmed in prospective studies with central review of pathology and extent of resection
CONCLUSIONS

• Post-operative radiotherapy following maximal safe resection is used in most patients with intracranial ependymomas
• Still unknown the value of post-operative radiotherapy after gross total resection in gr II tumors
• Chemotherapy with temozolomide has some role as salvage treatment
• Despite the increasing knowledge of molecular pathways in ependymomas, there is still a lack of druggable targets
• Prospective and randomized mulinational studies are needed