RADIATION DOSE ESCALATION AND COMBINED THERAPIES IN POSTOPERATIVE TREATMENT OF MALIGNANT GLIOMAS. EXPERIMENTAL AND CLINICAL RESULTS.

Ph.D. thesis
by
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Semmelweis University, Budapest, 2002

“In memoriam Bőlcsházy András”
INTRODUCTION:

The evolution of neuroradiology and radiotherapy has brought about significant theoretical and practical changes in the radiotherapy of malignant gliomas. The follow-up of patients with CT and MRI proves that the relapses are mostly found in the vicinity of primary tumours. The development of radiotherapy techniques made possible the use of focused irradiation, therefore the focal radiotherapy methods became routine-like in most centres, contrary to the previously applied extended field irradiation techniques.

More intensive focal radiotherapy than the conventional methods is necessary to reach local control of locally aggressive malignant gliomas. To increase the effectiveness of irradiation and prevent the remote brain manifestations, it is recommended that systemic treatment modalities also be applied. The image based treatment planning and the conformal radiotherapy techniques provide increased protection of normal brain tissues, creating the opportunity for dose escalation and the application of systemic modalities, like chemotherapy and immunotherapy. The purposes of our experimental and clinical investigations were to elaborate the optimal dose escalation forms in focal radiotherapy, to demonstrate the evidence of the effectiveness of combined therapies, and to develop a method ensuring the increased control of therapeutic side effects.

The ultimate purpose of our experiments was the determination of a novel therapeutic strategy with high biological dose radiotherapy which ensures local control, and with combined chemotherapy and immunotherapy which ensure the whole brain control. Hopefully, this kind of new therapy will enhance the curability of a disease with a very poor prognosis.

OBJECTIVES:

1. To elaborate a novel, combined and focally intensified treatment strategy as the alternative for whole brain irradiation of malignant gliomas characterised by local aggressiveness and a potential to infiltrate the whole central nervous system.

2. To elaborate optimal focal irradiation methods, and to prove the experimental and clinical effectiveness of combined modality treatments.
3. To analyse the favourable interactions between X-ray irradiation and chemotherapy for glial tumours in “in vivo” experimental conditions in order to prove the theoretical basis of radiochemotherapy in malignant gliomas.

4. To demonstrate the radiosensitizer effect of dibromodulcitol, and to analyse the role of “timing” between X-ray irradiation and dibromodulcitol treatment.

5. To examine the simultaneous application of X-ray irradiation and nitrosoureas, which are often employed as citostatic drugs in neuro-oncology.

6. To examine the effectiveness of the combination of X-ray irradiation with procarbazine (the active metabolite of temozolomide, the most active drug against gliomas) in mice with brain tumour.

7. To analyse the tumour growth inhibition effect of the transfer of the cytokine-producing gene, as an active immunotherapy, combined with brain radiotherapy.

8. To develop a three-dimensional radiobiological isoeffect model for elaborating biological dose escalation forms which is suitable for the comparison of different treatment plans and altered fractionations.

9. To elaborate optimal focal dose escalation methods via computer modelling, in order to establish individual radiotherapy in glioblastoma patients, based on the knowledge of individual tumour and normal tissue radiosensitivity.

10. To examine the normal tissue complication probability during biological dose escalation with hypofractionation and without total dose reduction.

11. To analyse the effect of practical methods and clinical application of focal dose escalation on survival in glioblastoma patients.

12. To examine the feasibility of high dose rate after-loading boost irradiation following conventional external beam radiotherapy.

13. To assess the effectiveness and side-effects of the novel intensified hypofractionated focal radiotherapy.

14. To compare the effectiveness of the conventional and dose escalated radiotherapy on survival in glioblastoma patients.

15. To examine the impact of adjuvant chemotherapy on survival after intensified focal radiotherapy.

16. To develop an easy-to-use CT-densitometric method, which is suitable for preventing acute therapeutic toxicity and for the follow-up of irradiation induced brain oedema.

17. To elaborate the optimal adjuvant neurological medication and to establish a feasible alternative oedema medication strategy during radiotherapy of brain tumours, contrary to the routine use of steroids.

18. To explore the aetiology of performance state deterioration observed during radiotherapy course.
METHODS:

**Laboratory methods:**
We used ependymoblastoma and G1 glioma murine tumour strains (NCI, Bethesda) during our laboratory experiments. $2 \times 10^5 - 10^6$ viable cells were transplanted intracranially in suspension, then the animals were irradiated locally with 6 Gy and injected with DBD of 25-50 mg/kg, BCNU of 1-2.5 mg/kg and procarbazine of 25 mg/kg. In the combined therapy the chemotherapeutic treatments preceded the X-ray irradiation by 1 hour. However, in examining the effect of DBD, we introduced few-hour and few-day intervals between the different treatments.

In the immunotherapy experiments, we transduced G1 glioma cells with viral vectors coding cytokine producing genes. After the local X-ray therapy of brain tumour animals, auto-vaccination was executed with encoded glioma cells sterilised by cobalt irradiation.

The mean survival time (MST) in days, the increased life span (ILS) in percentage and the number of living animals on the 90th day after transplantation were determined for the purpose of detailed evaluation.

**The method of 3-dimensional radiobiological dose calculation:**
For a biological dose distribution system, the physical dose values were converted into biological, isoeffect values by the use of the BED (biological effective dose) equivalency equation based on the LQ formula. With the use of the isoeffect maps and the biological dose volume histograms, we were able to compare different treatment plans and altered fractionation regimens. During the detailed comparison, we analysed the effect of the conventional 2-dimensional (2D-2 Gy) and the novel 3-dimensional conformal hypofractionated (3D-2.5 Gy) radiotherapy regimens. To examine the dose to the normal brain tissues, we determined the integral biological effective dose (IBED), the volumes in ccm that received 54 Gy biological equivalent dose (V-BED54) and the minimal dose of the critical volume fractions (CVF-MD) of the midline structures (upper and lower brain stem, hypophysis and chiasma).

**The possibilities of dose escalation:**
We retrospectively analysed the effect of conventional and novel dose escalated radiotherapy on glioblastoma patients treated in the last 4 years. 26 patients were treated with 60 Gy / 2 Gy conventional radiotherapy, and 23 were treated with dose escalation. For 8 patients with T1 tumour we applied HDR AL boost irradiation of 10-12 Gy, and for 15 patients with T2-4 tumour we executed the novel hypofractionated intensified conformal external beam radiotherapy of 2.25-2.5 Gy daily and 60
Gy total dose. In the dose escalation study we also analysed the effect of adjuvant chemotherapy on survival.

The method of CT-densitometry for controlling side-effects:
To evaluate the acute side effects and to follow-up irradiation induced brain oedema we elaborated a densitometric computer program with “High-Lighting” CT method. For the enhanced visualisation, we colour-coded the brain tissues, with the definition of normal brain (29-36 HU), mild oedema (21-28 HU) and advanced oedema (10-20 HU). On the oedema maps we were able to visualise the changes in time. During the radiotherapy course we carried out neurological examinations and CT-densitometry weekly in order to observe the clinical and densitometric changes and the effectiveness of the applied oedema therapies (diuretics, steroids, osmotic diuretics). Based on the detailed examination of 50 patients with solitary brain tumours, we also determined the factors which were responsible for increased oedema generation.

RESULTS:

The effect of X-ray irradiation combined with chemotherapy and immunotherapy on the survival of glioma bearing mice:
On ependymoblastoma tumour the chemotherapeutic drugs alone showed a significant dose-dependent cytotoxic effect alone, and with the application of lower doses, they unambiguously improved the effect of irradiation, resulting in better mean survival and a higher percent of cured animals (Table I-II.). However, the G1 glioma proved to be a less radio- and chemosensitive tumour (ILS:36-14-24 %), nevertheless, the combined treatments with both DBD and BCNU resulted in supra-additive advantageous interactions, (ILS:113-179 %) (Table III.). With the application of fractionated treatments with higher dose, the G1 glioma bearing animals were also cured.
According to the experiments that analysed the role of time factor, the application of chemotherapeutic drug (DBD) was optimal 1 hour prior to irradiation, however we also observed favourable interactions in combined treatments performed with interval of 1-4 days.
In the immunotherapeutic investigations, both the auto-vaccination and the X-ray irradiation of the skull showed only a moderate effect (ILS:27-55-33 %), however by combining the modalities it was demonstrated that all the animals became cured (Table IV.).
I. Table: The effect of X-ray irradiation combined with DBD and procarbazine treatment on the survival of rodents with ependymoblastoma tumour

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MST +/- SD</th>
<th>ILS (%)</th>
<th>Living on 90. day</th>
<th>P values**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated controls</td>
<td>17.0 +/- 5.6</td>
<td>0/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ray irradiation</td>
<td>27.7 +/- 8.5</td>
<td>63</td>
<td>0/10</td>
<td>0.0018</td>
</tr>
<tr>
<td>DBD 25 mg/kg</td>
<td>29.2 +/- 22.9</td>
<td>72</td>
<td>0/10</td>
<td>0.0896</td>
</tr>
<tr>
<td>DBD 25 mg/kg + X-ray</td>
<td>75.0 +/- 25.7</td>
<td>341</td>
<td>7/10</td>
<td>0.0001-0.0003</td>
</tr>
<tr>
<td>Procarbazin (25 mg/kg)</td>
<td>49.3 +/- 22.6</td>
<td>190</td>
<td>3/11</td>
<td>0.0001</td>
</tr>
<tr>
<td>Procarbazin + X-ray</td>
<td>77.0 +/- 25.9</td>
<td>352</td>
<td>9/11</td>
<td>0.0005-0.0473</td>
</tr>
</tbody>
</table>

**The p values were calculated to untreated controls in case of monotherapies, and to the two monotherapies in case of combined modality treatments (first to X-ray irradiation)

II. Table: The effect of X-ray irradiation combined with BCNU treatment on the survival of rodents with ependymoblastoma tumour

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MST +/- SD</th>
<th>ILS (%)</th>
<th>Living on 90. day</th>
<th>p values**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated control</td>
<td>16.3 +/- 3.3</td>
<td>0/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ray irradiation</td>
<td>30.4 +/- 28.2</td>
<td>87</td>
<td>0/10</td>
<td>0.0827</td>
</tr>
<tr>
<td>BCNU 2.5mg/kg</td>
<td>41.1 +/- 22.1</td>
<td>152</td>
<td>1/10</td>
<td>0.0001</td>
</tr>
<tr>
<td>BCNU 2.5mg + X-ray</td>
<td>66.6 +/- 30.3</td>
<td>309</td>
<td>6/10</td>
<td>0.0006-0.0266</td>
</tr>
</tbody>
</table>

III. Table: The effect of X-ray irradiation combined with DBD and BCNU treatment on the survival of rodents with G1 glioma tumour

<table>
<thead>
<tr>
<th>Treatments</th>
<th>MST +/- SD</th>
<th>ILS (%)</th>
<th>Living on 90. day</th>
<th>p values**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated control</td>
<td>18.9 +/- 2.7</td>
<td>0/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ray irradiation</td>
<td>25.7 +/- 8.2</td>
<td>36</td>
<td>1/10</td>
<td>0.0191</td>
</tr>
<tr>
<td>DBD 50 mg/kg</td>
<td>21.6 +/- 5.1</td>
<td>14</td>
<td>0/10</td>
<td>0.1082</td>
</tr>
<tr>
<td>DBD 50 mg/kg + X-ray</td>
<td>40.3 +/- 30.6</td>
<td>113</td>
<td>2/12</td>
<td>0.5911-0.0767</td>
</tr>
<tr>
<td>BCNU 2.5 mg/kg</td>
<td>23.4 +/- 8.7</td>
<td>24</td>
<td>1/10</td>
<td>0.1300</td>
</tr>
<tr>
<td>BCNU 2.5 mg/kg + X-ray</td>
<td>52.7 +/- 34.0</td>
<td>179</td>
<td>4/10</td>
<td>0.1057-0.0697</td>
</tr>
</tbody>
</table>
IV. Table: The effect of combined X-ray irradiation and auto-vaccination with GM-CSF producing cells on the survival of rodents with G1 glioma tumour

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MST +/- SD</th>
<th>ILS (%)</th>
<th>Living on 90. day</th>
<th>p values**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated control</td>
<td>21.4 +/- 4.8</td>
<td>0/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ray irradiation</td>
<td>33.2 +/- 13.4</td>
<td>55</td>
<td>0/6</td>
<td>0.0357</td>
</tr>
<tr>
<td>GM-CSF-</td>
<td>21.0 +/- 3.5</td>
<td>-2</td>
<td>0/4</td>
<td>0.7481</td>
</tr>
<tr>
<td>X-ray + GM-CSF-</td>
<td>28.4 +/- 11.9</td>
<td>33</td>
<td>0/5</td>
<td>0.5528-0.2520</td>
</tr>
<tr>
<td>GM-CSF+</td>
<td>27.2 +/- 11.7</td>
<td>27</td>
<td>0/5</td>
<td>0.3091</td>
</tr>
<tr>
<td>X-ray + GM-CSF+</td>
<td>90.0 +/- 0.0</td>
<td>321</td>
<td>5/5</td>
<td>0.0014-0.0018</td>
</tr>
</tbody>
</table>

The analysis of biological dose on normal tissues that determines the possibilities of dose escalation at conventional and modern irradiation techniques:

With the examination of biological dose distribution, we concluded that with 3D conformal irradiation methods, the integral (IBED) and the focal dose (V-BED54 and CVF-MD) to normal brain structures are more favourable even at higher daily fractions (2.5 Gy), than with conventional treatment planning and fractionation (2 Gy) (Table V.). Only the mean value of minimal dose for critical volume fractions in the upper brain stem was higher for the novel treatment method, indicating that high doses could occur in the neighbourhood of the target volume when hypofractionation is applied. Nevertheless, for each tumour, the detailed analysis of different treatment plans and fractionation schemes is necessary to determine the optimal treatment for the patients. A biological treatment planning system like ours may be further developed into an individual, biological based radiotherapy.

V. Table: The biological dose impact of midline structures with conventional (2D-2 Gy) and the novel intensified, hypofractionated conformal (3D-2.5 Gy) radiotherapy regimens

<table>
<thead>
<tr>
<th></th>
<th>Lower brain stem</th>
<th>Upper brain stem</th>
<th>Hypophysis-chiasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBED (Gy)</td>
<td>27.1 ± 13.4 and</td>
<td>53.1 ± 8.0 and</td>
<td>44.5 ± 19.1 and</td>
</tr>
<tr>
<td></td>
<td>11.7 ± 8.1 (p&lt;0.0001)</td>
<td>38.8 ± 14.9 (p=0.0021)</td>
<td>24.9 ± 18.7 (p=0.0004)</td>
</tr>
<tr>
<td>V-BED54 (ccm)</td>
<td>6.18 ± 8.44 and</td>
<td>15.21 ± 14.97 and</td>
<td>0.78 ± 0.93 and</td>
</tr>
<tr>
<td></td>
<td>0.46 ± 0.98 (p=0.0463)</td>
<td>8.19 ± 6.06 (p=0.1355)</td>
<td>0.09 ± 0.19 (p=0.0417)</td>
</tr>
<tr>
<td>CVF-MD (Gy)</td>
<td>54.3 ± 6.6 and</td>
<td>57.8 ± 4.2 and</td>
<td>50.9 ± 16.3 and</td>
</tr>
<tr>
<td></td>
<td>32.9 ± 21.7 (p=0.0045)</td>
<td>61.0 ± 6.2 (p=0.0675)</td>
<td>35.3 ± 25.1 (p=0.0185)</td>
</tr>
</tbody>
</table>

The impact of interstitial boost irradiation, intensified hypofractionated radiotherapy and adjuvant chemotherapy on the survival of glioblastoma patients:
Our glioblastoma patients tolerated well the more intensive radiotherapy courses. We observed transient performance state deterioration in 1 and 2 cases, prolonged steroid medication was necessary in 2 and 6 cases, and necrectomy was executed in 1 and 2 patients. The median survival time after histological diagnosis was 17 (9-25) months at the interstitial boost irradiation and 12 (6-38) months at the intensified external beam radiotherapy (p=0.2472). In regard to the drugs (Temodal and BCNU) these values were 15.5 (11-38) months with chemotherapy (10 patients), and 12 (6-17) months without chemotherapy (13 patients) (p=0.0118). The median survival time for all the dose escalated treatments was 13 (6-38) months, in contrast to the 10 (4-36) months of the conventional therapy (p=0.3080) (see Figure). Nevertheless, these results suggest that both focal dose escalation and adjuvant chemotherapy could play a role in prolonging survival.

![Figure: The impact of dose escalated vs. conventional radiotherapy on the survival of glioblastoma patients](image)

The results of prevention of early radiotherapy complications:
In the densitometric patient follow-up procedure we concluded that the changes in oedema maps correlated with the clinical symptoms, moreover the densitometric deterioration always preceded the decrease of performance state. During the detailed observation we noticed no oedema changes in 14 cases, increased oedema declination with no clinical changes in 30 patients, and neurological deterioration in 6 cases, where in one case we were not able to complete the radiotherapy course. Overviewing the oedema therapies, we succeeded in avoiding the unnecessary application of steroids in the majority of our patients. (Table VI.). The spironolactone based preventive and the densitometry adapted oedema therapies proved efficacious. In the background of increased oedema declination we
noticed the following factors as aetiology: ineffective oedema therapy, patient incompliance in medication, intratumoural bleeding and cyst evolution, the impact of previous interstitial irradiation and advanced disease with the infiltration of midline structures.

VI. Table: Oedema medications based on densitometric and clinical observations in 50 patients receiving radiotherapy.

<table>
<thead>
<tr>
<th>With no densitometric and no clinical changes</th>
<th>Densitometric changes with no clinical deterioration</th>
<th>Unambiguous densitometric and clinical deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusively with diuretics</td>
<td>9 Exclusively with diuretics</td>
<td>17 Exclusively with osmotic diuretics</td>
</tr>
<tr>
<td>With previously indicated steroids and diuretics</td>
<td>5 With previously / in radiotherapy course indicated steroids</td>
<td>4/9 With previously / in radiotherapy course indicated steroids</td>
</tr>
<tr>
<td>No. of cases</td>
<td>14 No. of cases</td>
<td>30 No. of cases</td>
</tr>
</tbody>
</table>

CONCLUSIONS:

1. Based upon the data found in the literature and the results of our investigations, to reach both local and whole brain control in malignant gliomas, a therapeutic strategy consisting of intensive focal radiotherapy and combined systemic modalities could be more appropriate than the previously applied extended beam irradiation.

2. Utilising information technology and clinical modelling we elaborated two types of dose escalation method. Based on our clinical observations, the intensive focal radiotherapy and adjunctive chemotherapy increase the survival of glioblastoma patients, and our experimental results suggest that beside the modern conformal radiotherapy methods, the radiochemotherapy and radioimmunotherapy will become an effective mode of treatment in the future.

3. The combination of X-ray irradiation and chemotherapy results in significant increase in survival of glioma-bearing animals in laboratory, moreover a great proportion of them can be cured. Examining different types of drugs we can conclude that supra-additive advantageous interactions could happen.

4. The dibromodulcitol increases the effectiveness of X-ray irradiation in different doses. The optimal treatment combination occured when the drug was administered 1 hour prior to the irradiation, however we also
observed advantageous interaction in a few day interval. Based on our investigations both interactive and non-
interactive mutual effects could develop between the modalities.

5. The BCNU can also be successfully combined with X-ray irradiation.

6. We also observed supra-additive favourable interaction between procarbazine and X-ray treatment by
examining the life span of brain tumour bearing laboratory animals.

7. By combining auto-vaccination glioma cells transduced with GM-CSF cytokine producing gene and local
irradiation, the glioma bearing mice could be cured, which phenomenon suggests the favourable mutual effect
of active immunisation and radiotherapy.

8. With computer modelling, we succeeded in developing a radiobiological treatment planning system which is
suitable for the comparison of different treatment plans and altered fractionation schemes.

9. Alternative and biologically optimised dose escalation methods in glioblastoma brain tumours can be
developed.

10. By applying conformal radiotherapy techniques, the hypofractionation without total dose reduction does not
    go with the increased risk of neurotoxicity.

11. According to last year’s clinical experience, our novel dose escalation methods are feasible procedures.

12. With the application of single HDR-AL interstitial boost irradiation, we succeeded in reaching an increase in
    life expectancy of T1 glioblastoma patients with no serious complications.

13. Based on our observations, the hypofractionated intensified external beam irradiation for advanced disease
does not coincide with more complications, shorten the treatment course and could be the alternative to the
conventional fractionated radiotherapy.

14. In our series, the focal dose escalation results in an increase of median life expectancy by 30 percent
    compared to the conventional teletherapy.

15. The adjuvant or salvage chemotherapy significantly increased the median survival time of glioblastoma
    patients after dose escalated focal radiotherapy.

16. Our CT-densitometric follow-up method verified that the colour-coded oedema maps exactly indicate the
existence of oedema conditions, and with adoptive oedema therapies, the oedema-generated neurological state
deterioration can be prevented in the great majority of brain tumour patients.

17. We succeeded in avoiding the unnecessary usage of steroids in more than half of our patients and we
    managed to develop an oedema therapeutic strategy based on diuretics (spironolactone and furosemide) which
    follows the clinical and CT changes.

18. In our clinical series the increased inclination of oedema generation and the consequent performance state
deterioration was expected more in higher histological grade and advanced tumour stage, in case of ineffective
oedema therapy, previous irradiation, liquor passage disturbance and intra-tumoural events.
Bibliography of original articles and congress lectures in the topic:


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