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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Combination Therapy for the Treatment of Central Nervous System Malignancies: Clinical Effectiveness and Guidelines

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Research Questions

1. What is the clinical effectiveness of combination therapy for the treatment of patients with central nervous system malignancies?
2. What are the evidence-based guidelines associated with the use of combination therapy for the treatment of patients with central nervous system malignancies?

Key Findings

Three non-randomized studies were identified regarding combination therapy for the treatment of central nervous system malignancies.

Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and January 25, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (adults and children) with a CNS malignancy (e.g., gliomatosis cerebri, meningioma, glioblastoma, glioma, astrocytoma, neuroblastoma)
Intervention	Either combined with each other (in groups of two or more) or with standard of care (e.g., conventional chemotherapy). • Dimethyl sulfoxide (DMSO); • Hyperthermia (any variant, including electric and magnetic); • Sonodynamic therapy; • Laser therapy; • Rife therapy; • Biomagnetic therapy
Comparator	Q1: Any comparator; No comparator Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., progression-free survival, response rate, change in tumour size, overall survival, quality of life) and safety (e.g., toxicity, adverse events, discontinuation) Q2: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Three non-randomized studies were identified regarding combination therapies for central nervous system malignancies. No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, or evidence-based guidelines were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Three non-randomized studies were identified regarding combination therapies for central nervous system (CNS) malignancies.[1-3] Each study utilized a varying combination of therapies for CNS cancers. The authors of the first study investigated the safety of using radiation and laser therapy in patients with brain tumours.[1] They observed that laser interstitial thermal therapy in combination with radiation therapy can induce cerebral edema (a safety issue) and thus prolong cancer treatment.[1] In a minority of cases, patients may require more aggressive treatment such as drug therapy.[1] The authors of the second study[2] investigated the efficacy of radiation therapy with hyperthermia for patients with high grade gliomas and observed that combination therapy of radiation and hyperthermia was safe and well-tolerated. In the third study[3] the authors investigated the efficacy and cost-effectiveness of modulated electrohyperthermia in combination with chemotherapy treatment. Their effect-to-treatment analysis found that patient survival significantly improved after receiving the combination therapy in a regimen of 21 out of 28 days.[3]

No evidence-based guidelines were identified; therefore, no summary can be provided.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

Radiation and Laser Therapy

1. Maraka S, Asmaro K, Walbert T, Lee I. Cerebral edema induced by laser interstitial thermal therapy and radiotherapy in close succession in patients with brain tumor. *Lasers Surg Med*. 2018 Sep;50(9):917-923.
   PubMed: PM29799137

Radiation and Hyperthermia

2. Heo J, Kim SH, Oh YT, Chun M, Noh OK. Concurrent hyperthermia and re-irradiation for recurrent high-grade gliomas. *Neoplasma*. 2017;64(5):803-808.
   PubMed: PM28592133

Chemotherapy and Hyperthermia

3. Roussakow SV. Clinical and economic evaluation of modulated electrohyperthermia concurrent to dose-dense temozolomide 21/28 days regimen in the treatment of recurrent glioblastoma: a retrospective analysis of a two-centre German cohort trial with systematic comparison and effect-to-treatment analysis. *BMJ open*. 2017 Nov 3;7(11):e017387.
   PubMed: PM29102988

Guidelines and Recommendations

No literature identified.

Appendix — Further Information

Previous CADTH Reports

4. Alternating electric fields (“tumour-treating fields”) for the treatment of glioblastoma. *(CADTH issues in emerging health technologies; issue 165)*. Ottawa (ON): CADTH; 2018: https://www.cadth.ca/dv/ieht/alternating-electric-fields-tumour-treating-fields-treatment-glioblastoma. Accessed 2019 Feb 6.

Non-Randomized Studies

Radiation and Hyperthermia

Case Series

5. Grauer O, Jaber M, Hess K, et al. Combined intracavitary thermotherapy with iron oxide nanoparticles and radiotherapy as local treatment modality in recurrent glioblastoma patients. *J Neurooncol*. 2019 Jan;141(1):83-94. PubMed: PM30506500

Chemotherapy and Laser Therapy

Case Series

6. Ali SC, Basil GW, Diaz RJ, Komotar RJ. The safety of bevacizumab administered shortly after laser interstitial thermal therapy in glioblastoma: a case series. *World Neurosurg*. 2018 Sep;117:e588-e594. PubMed: PM29933086

High Intensity Focused Ultrasound – Uncertain if Combined with Another Therapy

Alternative Population – Mixture of Cancer Types

7. Shim J, Staruch RM, Koral K, Xie XJ, Chopra R, Laetsch TW. Pediatric sarcomas are targetable by MR-guided high intensity focused ultrasound (MR-HIFU): anatomical distribution and radiological characteristics. *Pediatr Blood Cancer*. 2016 Oct;63(10):1753-1760. PubMed: PM27199087

Alternative Outcome

8. Leuthardt EC, Duan C, Kim MJ, et al. Hyperthermic laser ablation of recurrent glioblastoma leads to temporary disruption of the peritumoral blood brain barrier. *PLoS One*. 2016;11(2):e0148613. PubMed: PM26910903

Review Articles

9. Paolillo M, Boselli C, Schinelli S. Glioblastoma under siege: an overview of current therapeutic strategies. *Brain Sci.* 2018;8(1). https://www.mdpi.com/2076-3425/8/1/15/htm Accessed 2019 Feb

10. Mahmoudi K, Bouras A, Bozec D, Ivkov R, Hadjipanayis C. Magnetic hyperthermia therapy for the treatment of glioblastoma: a review of the therapy's history, efficacy and application in humans. *Int J Hyperthermia*. 2018 Dec;34(8):1316-1328. PubMed: PM29353516

11. Borasi G, Nahum A. A new glioblastoma treatment, potentially highly effective, combining focused ultrasound generated hyperthermia and radiations. *JSM Brain Sci.* 2017;2(1). https://pdfs.semanticscholar.org/0b6b/da66b13491284fc21f2ad5715f7dc4573031.pdf Accessed 2019 Feb 6

12. Wang X, Jia Y, Wang P, Liu Q, Zheng H. Current status and future perspectives of sonodynamic therapy in glioma treatment. *Ultrason Sonochem*. 2017 Jul;37:592-599. PubMed: PM28427672

13. Bredlau AL, McCrackin MA, Motamarry A, et al. Thermal therapy approaches for treatment of brain tumors in animals and humans. *Crit Rev Biomed Eng*. 2016;44(6):443-457. PubMed: PM29431091

14. Lee Titsworth W, Murad GJ, Hoh BL, Rahman M. Fighting fire with fire: the revival of thermotherapy for gliomas. *Anticancer Res*. 2014 Feb;34(2):565-574. PubMed: PM24510985

Additional References

Laser Therapy – Uncertain if Combined with Another Therapy Modality

15. Mohammadi AM, Schroeder JL. Laser interstitial thermal therapy in treatment of brain tumors--the NeuroBlate System. *Expert Rev Med Devices*. 2014 Mar;11(2):109-119. PubMed: PM24471476

Radiation and Hyperthermia

Mathematical Models

16. Borasi G, Nahum A, Paulides MM, et al. Fast and high temperature hyperthermia coupled with radiotherapy as a possible new treatment for glioblastoma. *Journal of therapeutic ultrasound*. 2016;4:32. PubMed: PM27980785