CNS MALIGNANCIES

Educational session
FPON
Muhammad Zulfiqar, MD
January 2021
Conflict of Interest

- Nothing to declare
Objectives

- Recognize early signs and symptoms
- Describe current management
- Discuss supportive care and the role of the family physician.

- Discussion of questions and comments
What is estimated in Canada

• In 2020, an estimated:
  • 3,000 Canadians will be diagnosed with brain and spinal cord cancer.
  • 2,500 Canadians will die from brain and spinal cord cancer.
  • 1,700 men will be diagnosed with brain and spinal cord cancer and 1,400 will die from it.
  • 1,350 women will be diagnosed with brain and spinal cord cancer and 1,050 will die from it.

Canadian cancer statistics
Incidence

RELATIVE FREQUENCIES OF GLIOMAS

Roman numerals denote World Health Organisation (WHO) tumour grades.
Looks can be deceiving
How does it look?
Vs
How it behaves?
How it looks?

- Prominent anaplasia, vascular proliferation and palisading of tumor cells around necrosis
How it Behaves?

- **IDH** wild-type
- glioma with **TERT** mutations and polysomy of chromosome 7
- plus loss of heterozygosity of chromosome 10q have similar
- outcomes compared with those with GBM


Current WHO Classification

WHO CLASSIFICATION

- Histology:
  - Astrocytoma
  - Oligoastrocytoma
  - Oligodendroglioma

- IDH status:
  - IDH mutant
  - IDH wild-type

- 1p/19q and other genetic parameters:
  - ATRX loss*
  - TP53 mutation*
  - 1p/19q codeletion
  - Diffuse astrocytoma, IDH mutant
  - Oligodendroglioma, IDH mutant and 1p/19q codeleted
  - After exclusion of other entities: Diffuse astrocytoma, IDH wild-type Oligodendroglioma, NOS

- Glioblastoma:
  - IDH mutant
  - IDH wild-type
  - Genetic testing not done or inconclusive
  - Diffuse astrocytoma, NOS Oligodendroglioma, NOS Oligoastrocytoma, NOS

*Characteristic but not required for diagnosis.

How do these malignancies present?

- Headache
- Seizure
- Focal neurological symptoms
- Cognitive issues
How do these malignancies present?

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Spectrum:

Target Angiogenesis
Bevacizumab

Radiation Therapy and Alkylating agents
STUPP

Check point Inhibitors
PD-1
PDL-1
CTLA-4

T-Cell Therapy
DC Therapy
Oncolytic Viral

Peptide Vaccines

Combination Immune Strategies
Nivolumab and DC vaccine

Tumor Treating Fields
PHASE III TRIAL OF CONCOMITANT AND ADJUVANT TEMOZOLOMIDE AND RADIOTHERAPY FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

Roger Stupp, WP Mason, MJ Van Den Bent, M Weller, B Fisher, M Taphoorn, AA Brandes, G Cairncross, D Lacombe, RO Mirimanoff

On behalf of the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and National Cancer Institute of Canada Clinical Trials Group

ASCO Plenary Session / June 7, 2004

EORTC 26981-22981 and NCIC CE.3
Temozolomide 75 mg/m² po qd for 6 weeks, then 150–200 mg/m² po qd d1–5 every 28 days for 6 cycles.

Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.
• 85 institutions, 14 countries, 573 patients

**Patient Accrual**

Accrual of Study 26981

![Accrual Graph]

- Theoretical
- Study

Number of Patients

Year

- 28/12/2000
- 28/09/2001
- 28/06/2002
- 28/03/2003
Progression Free Survival

- Median PFS, mo: 5.0 for RT, 6.9 for TMZ/RT
- 1-yr PFS: 9% for RT, 27% for TMZ/RT
- 2-yr PFS: 2% for RT, 11% for TMZ/RT
- HR [95% C.I.]: 0.54 [0.45-0.64]

Number of patients at risk:

<table>
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<tr>
<th></th>
<th>RT</th>
<th>TMZ/RT</th>
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<tr>
<td>N</td>
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<td>286</td>
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<tr>
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Number of patients at risk:

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Overall Survival

- Median OS, mo: RT 12.1, TMZ/RT 14.6
- 2-yr survival: RT 10%, TMZ/RT 26%
- HR [95% C.I.]: RT 0.63 [0.52-0.75], TMZ/RT $p < 0.0001$

Number of patients at risk:

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<tr>
<th>Months</th>
<th>RT 219</th>
<th>N 286</th>
<th>TMZ/RT 246</th>
<th>N 174</th>
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<td>24</td>
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45 years old gentleman

- Glioblastoma
- Treated with STUPP protocol.
Images

Before surgery

Before RCT

1 month after RCT

[Images of brain scans showing changes before and after surgery and RCT.]
Appropriate next step:

1. Disease progression. Move to second line treatment
2. Options are limited. Continue same treatment.
3. Re-image in 8 weeks
4. Continue same treatment as it falls into the right timeframe of pseudo progression
Bavacizumab at Progression

- Phase 2
- 6 month PFS of 40% to 50%
- Median OS of 8 to 9 months.

Pseudo improvement
Course of Events

RT+TMZ → TMZ → Bev

CCNU Etoposide Trials?

What about DCA?
Fusion Protein? CTV, CNN, Global News?
How is it possible in this day and age?
Checkpoint Inhibitors
Checkpoint inhibitors gliomas

1. Have game changing effect
2. Are under investigation
3. Not as promising as they are in other solid tumors
### FDA Approval of Checkpoint Agents

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Mode of Action</th>
<th>Cancers Treated</th>
<th>Year approved</th>
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<td>Opdivo/Nivolumab</td>
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<td>Anti-PD-1</td>
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<td>Head and Neck</td>
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<td>Lung (first line)</td>
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<td>Nivolumab + Ipilimumab</td>
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Ongoing Experience with Checkpoint Blockade in Glioblastoma

- **CheckMate-143**: randomized trial of Nivolumab (anti-PD-1) compared to Bevacizumab in recurrent GBM (N = 369 patients)
  - No difference in OS-12 (42%) or median OS (9.8 vs 10 months)

- **CheckMate-498** *(Methylated)*: An Investigational Immuno-therapy Study of Nivolumab Compared to Temozolomide, Each Given With Radiation Therapy, for Newly-diagnosed Patients With Glioblastoma

- **CheckMate-548** *(Unmethylated)*: An Investigational Immuno-therapy Study of Temozolomide Plus Radiation Therapy With Nivolumab or Placebo, for Newly Diagnosed Patients With Glioblastoma
Window of Opportunity Clinical Trials to Monitor Immune Responses in GBM patients

Presented By John De Groot at 2018 ASCO Annual Meeting
Data in Context of Biomarker Predictors for Response to Immune Checkpoint Inhibitors

Hodges, Neuro-Oncology, 2017; Garber, Neuro-Oncology, 2016; Nduom, Neuro-Oncology, 2015
Objectives

• Recognize early signs and symptoms
• Describe current management
• Discuss supportive care and the role of the family physician.

• Discussion of questions and comments
CURE FOR CANCER
DCA’s Promise at two levels

- Electrical
  - High mitochondrial membrane potential
  - Low expression of K+ channels

- Metabolic
  - Aerobic glycolysis
DCA
LACK OF CLINICAL STUDIES
Tumor Treating Fields

- Mitotic arrest and apoptosis
- Increased sensitivity to chemotherapy in the presence of TTF
Tumor-treating fields 100 to 300 kHz
- 150 kHz: Pancreatic, non-small cell lung cancers
- 200 kHz: Glioblastoma, ovarian cancer

Optune uses low-level electrical fields that alternate 100,000 to 300,000 times per second. Electromagnetic frequencies are on the lower end of the spectrum and range from 100 to 300 kHz, depending on the tumor type.
Tumor Treating Fields

EF-14 phase 3 pivotal trial—TTF + TMZ vs TMZ alone in newly diagnosed GBM

Newly diagnosed GBM 315
Biopsy/debulking
Radiation + TMZ

Enrollment window (4-7 weeks after RT + TMZ)

RANDOMIZED 2:1

TTF + TMZ x 6 cycles

Optune + 2L chemotherapy, surgery, SRS, or combination

1st progression

24 months or 2nd progression

TMZ x 6 cycles

2L chemotherapy, surgery, SRS, or combination
Findings

• 210 patients randomized to TTFields plus temozolomide
• 105 randomized to temozolomide alone
• Stopped early due to ongoing benefit.
• median follow-up of 38 months (range, 18-60 months)
• PFS 7.1 months vs 4.0 months.
• OS 20.5 months vs 15.6 months.
• No increase in toxicity
• Main side effects from TTF was skin irritation, rash, ulceration and infection.
Sham Device?
Clinician training and certification
Shaved scalp with portable battery
Continuously for 18 hours per day
20,000 US$ per month
Functional status
Caregiver support
Mind body medicine

1. Is a new age popular term with no scientific merits
2. Field of neuro-immunology supports evidence that mind plays pivotal role in healing
3. If there is any role, it is very limited at its best.
Mind Body Medicine: Guiding Patients to Health & Happiness

Oct 19-21, 2017
Boston, MA

Featuring Mind Body Medicine Pioneers
Herbert Benson, MD
and Jon Kabat-Zinn, PhD
MBSR (Mindfulness based stress reduction)

Does increased stress promote cancer growth?

- Thaker et al (MD Anderson)
- Nude mice model (inoculation with ovarian cancer cells)
- Stressed out mice (growth rate 275% more than non stressed)
- Beta adrenergic receptor expression on tumor cells.
- Transcriptional upregulation of VEGF

Can decreasing stress have improvement in cancer outcome?

- Cancer. 2008;113:3450–3458. OSU and Walther Cancer Institute and NCI.
- Adjuvant Breast cancer (N=212)
  - Randomization between intervention (26 sessions teaching strategies to reduce stress, improve mood and alter health behaviors vs assessment only)
  - 11 yrs of follow up
  - Median survival 6.1 vs 4.8 yrs.
  - Multivariate analysis HR 0.44; p=0.016)
Exercise

Melanoma B16F10

In 4 weeks
Increase NK cells
61% ; \( p < 0.01 \) reduction of cancer cells in exercising mice

Exercise in high grade Glioma

- 243 patients with high grade glioma
- KPS 70 or higher
- Self administered questionnaire on exercise behavior
- 6 minute walk to assess functional capacity.
- Exercise was better predictor of survival than KPS, age, sex, grade and number of prior progressin
- Adjusted HR 0.64 (95% CI 0.46-0.91)
- Strenuous exercise was independent predictor of survival.

Nutrition

- Joint Study at PMH and Harvard Medical School.

- Breast cancer patients
  - randomized to daily intake of either a 25 g flaxseed containing muffin (n = 19) or a control (placebo, n=13) muffin

- Reductions in Ki-67 labeling index (34.2%; P = 0.001) and in c-erbB2 expression (71.0%; P = 0.003) and an increase in apoptosis (30.7%; P = 0.007) were observed in the flaxseed, but not in the placebo group.

- Potential to reduce tumor growth.
Summary

- STUPP protocol remains standard of care
- Unique microenvironment of GBM does not allow immune check point inhibitors to work most effectively.
- There are no available clinical trial evidence for DCA
- In right situation, TTF is reasonable option to try as first line treatment.
- Several innovative combination immunomodulatory treatments are under active investigation
- Think about open clinical trial.
- Mind body medicine needs more attention going forward in an ever increasing field of expensive targeted interventions.
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Questions and Comments