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Anticonvulsant prophylaxis and steroid use in adults with metastatic brain tumors: summary of SNO and ASCO endorsement of the Congress of Neurological Surgeons guidelines*

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Abstract

Background. The Congress of Neurological Surgeons (CNS) has developed a series of guidelines on the treatment of adults with metastatic brain tumors, including systemic therapy and supportive care topics. ASCO has a policy and set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations.

Methods. Two CNS Guidelines were reviewed for developmental rigor by methodologists and an independent multi-disciplinary Expert Panel was formed to review the content and assess agreement with the recommendations. The expert panel voted to endorse the two guidelines and ASCO and SNO independently reviewed and approved the ASCO/SNO guideline endorsement.

Results. The ASCO/SNO Expert Panel determined that the recommendations from the CNS anticonvulsants and steroids guidelines, published January 9, 2019, are clear, thorough, and based upon the most relevant scientific evidence. ASCO/SNO endorsed these two CNS guidelines, with minor alterations.

Conclusions. Key recommendations include: prophylactic anti-epileptic drugs were not recommended for routine use; corticosteroids (specifically dexamethasone) were recommended for temporary symptomatic relief in patients with neurologic symptoms and signs related to mass effect from brain metastases.

The Congress of Neurological Surgeons (CNS) has published a series of eight guidelines[1–9] covering multiple aspects of the treatment of adults with metastatic brain tumors. Prior to publication, the CNS requested that the American Society of Clinical Oncology (ASCO) provide feedback on and consider endorsing the guideline series. As the care of the target population of these guidelines is an important issue for the members of both ASCO and the Society for

Neuro-Oncology (SNO), ASCO and SNO conducted a joint guideline endorsement process on these guidelines. This article is a summary; for complete details of the endorsement process see the full endorsement statement[10] and at www.asco.org/neurooncology-guidelines.

Of the eight CNS guidelines, four addressed radiation and surgery related topics (see below) and four addressed systemic therapy and supportive care for these patients. Of the four guidelines that covered systemic therapy and supportive care two were selected for endorsement: "The Role of Prophylactic Anticonvulsants in the treatment of Adults with Metastatic Brain Tumors"[2]; and "The Role of Steroids in the Treatment of Adults with Metastatic Brain Tumors".[5] Because these two guidelines cover the same target population (adults with metastatic brain tumors) and because their recommendations have substantial interaction between the guidelines, ASCO and SNO conducted a common review of both guidelines.

Methods

Summary of Methods for CNS Guideline Development

The CNS guideline series was developed by a multidisciplinary author expert panel, the Metastatic Brain Tumor Guidelines Task Force that included medical oncologists, radiation oncologists, neurological surgeons, neuro-oncologists, and others. It built upon a previous guideline series published in 2010. The risk of bias and overall quality of the evidence, as well as the strength of the recommendations, were determined using CNS's published methods (https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology).

Summary of ASCO/SNO Endorsement Methods

An initial methodology evaluation of the CNS guideline series was completed using the Rigor of Development subscale from the AGREE II instrument. Each guideline in the series was also initially assessed by two content evaluators, members of the SNO guideline committee, who conducted a structured evaluation of the clinical content of the guideline series. Based on the AGREE II and clinical evaluations, the Clinical Practice Guideline Committee (CPGC) of ASCO determined that the guideline series warranted detailed review by an ASCO expert panel to determine which guidelines/recommendations could be endorsed. A multi-disciplinary Expert Panel (ASCO/SNO Expert Panel, Box 1) was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc).

An updated literature search was conducted by the ASCO/SNO expert panel. Pubmed was searched from December 2015 (the end of the search conducted by CNS) to March 20, 2018. In addition, the abstracts of the ASCO and American Society for Radiation Oncology (ASTRO) annual meetings from 2016–2017 were searched for relevant randomized controlled trials. The updated search yielded 31 new articles, the details of which can be found in the full endorsement statement.

Box 1 Guideline Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Susan M. Chang	University of California San Francisco, San Francisco, CA, USA	Co-Chair, Medical Oncology
Michael A. Vogelbaum	Cleveland Clinic, Cleveland, OH, USA	Co-Chair, Surgical Oncology
Manmeet Ahluwalia	Cleveland Clinic, Cleveland, OH, USA	Medical Oncology
David Andrews	Thomas Jefferson University, Philadelphia, PA, USA	Surgical Oncology
Priscilla K. Brastianos	Massachusetts General Hospital, Boston, MA, USA	Medical Oncology
Laurie E. Gaspar	University of Colorado School of Medicine, Denver, CO, USA	Radiation Oncology
NaTosha N. Gatson	Geisinger, Neuroscience & Cancer Institutes, Danville, PA, USA	Neuro-oncology
Justin T. Jordan	Massachusetts General Hospital, Boston, MA, USA	Neuro-oncology
Mustafa Khasraw	The University of Sydney, NSW, Australia	Medical Oncology
Andrew B. Lassman	Columbia University Irving Medical Center, New York, NY, USA	Neuro-oncology
Julia Maues	Georgetown Breast Cancer Advocates, Washington, DC, USA	Patient Representative
Maciej Mrugala	Mayo Clinic Phoenix, Phoenix, AZ, USA	Neuro-oncology
Jeffrey Raizer	Northwestern University, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA	Neuro-oncology
David Schiff	University of Virginia Medical Center, Charlottesville, VA, USA	Neuro-oncology
Glen Stevens	Cleveland Clinic, Cleveland, OH, USA	Neuro-oncology
Ashley Sumrall	Levine Cancer Institute, Charlotte, NC, USA	Neuro-oncology
Martin van den Bent	Erasmus MC Cancer Institute, Rotterdam, Netherlands	Neurology
Hans Messersmith	American Society of Clinical Oncology(ASCO)	Staff/health research methodologist

Box 2 Recommendations

American Society of Clinical Oncology and Society for Neuro-Oncology Joint Endorsement of the Congress of Neurological Surgeons Guidelines on Systemic Therapy and Supportive Care of Adults with Metastatic Brain Tumors

ASCO and SNO endorse the Congress of Neurological Surgeons (CNS) Clinical Practice Guidelines "The Role of Prophylactic Anticonvulsants in the treatment of Adults with Metastatic Brain Tumors" and "The Role of Steroids in the Treatment of Adults with Metastatic Brain Tumors", with some minor alterations.

GUIDELINE QUESTIONS:

CNS Anticonvulsant Guideline: Do prophylactic anti-epileptic drugs (AEDs) decrease the risk of seizures in non-surgical patients with brain metastases who are otherwise seizure free? Do prophylactic AEDs decrease the risk of seizures in patients with brain metastases and no prior history of seizures in the postoperative setting?

CNS Steroids Guideline: Do steroids improve neurologic symptoms and/or quality of life in patients with metastatic brain tumors compared to supportive care only or other treatment options? If steroids are given, what dose should be used?

TARGET POPULATION:

Adults with metastatic brain tumors.

TARGET AUDIENCE: Medical oncologists, neurologists and others providing care for adults with metastatic brain tumors

METHODS: An ASCO/SNO Expert Panel was convened to consider endorsing the CNS guideline recommendations that were based on a systematic review of the medical literature. The ASCO/SNO Expert Panel considered the methodology employed in the CNS guidelines by considering the results from the AGREE II review instrument. The ASCO/SNO Expert Panel carefully reviewed the CNS guidelines content to determine appropriateness for ASCO/SNO endorsement.

KEY RECOMMENDATIONS: (Additions by the ASCO Expert Panel are in ***bold italics***. See note below regarding CNS recommendation levels.)

CNS Anticonvulsants Guideline[2]

- Level 3: Prophylactic anti-epileptic drugs are not recommended ***for routine use*** in patients with brain metastases who did not undergo surgical resection and are otherwise seizure free.
- Level 3: Routine post-craniotomy anti-epileptic drug use for seizure-free patients with brain metastases is not recommended.

CNS Steroids Guideline[5]

Steroid therapy versus no steroid therapy

Asymptomatic brain metastases patients without mass effect

- Insufficient evidence exists to make a treatment recommendation for this clinical scenario.

Brain metastases patients with mild symptoms related to mass effect

- Level 3: Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases. It is recommended for patients who are symptomatic from metastatic disease to the brain that a starting dose of 4–8 mg/day of dexamethasone be considered.

Brain metastases patients with moderate to severe symptoms related to mass effect

- Level 3: Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases. If patients exhibit severe symptoms consistent with increased intracranial pressure, it is recommended that higher doses such as 16 mg/day or more be considered.

Choice of Steroid

- Level 3: If corticosteroids are given, dexamethasone is the best drug choice given the available evidence.

Duration of Corticosteroid Administration

- Level 3: Corticosteroids, if given, should be tapered as rapidly as possible but no faster than clinically tolerated, based upon an individualized treatment regimen and a full understanding of the long-term sequelae of corticosteroid therapy.

ASCO/SNO Expert Panel Comment: The Panel's expert opinion is that given the important side-effects of steroids the minimum effective dose (often no more than 4 mg) should be used where possible and night-time doses of steroids should be avoided to minimize toxicity.

Note regarding CNS Level 3 recommendation classification: CNS defines a Level 3 recommendation as one based on "Evidence from case series, comparative studies with historical controls, case reports, and expert opinion, as well as significantly flawed randomized controlled trials."

Additional Resources: More information, including a the full endorsement statement, Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/gag-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net

The CNS Guideline series can be found at https://www.cns.org/guidelines/guidelines-treatment-adults-metastatic-brain-tumors

Results

The ASCO/SNO Expert Panel reviewed the recommendations of the CNS Guidelines, the details of which are available in the full endorsement statement. ASCO and SNO endorse the CNS guidelines on anticonvulsants[2] and steroids[5] in the treatment of adults with brain metastases, with a very minor alteration, as presented in the boxed statement (Box 2).

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