

Documented: Big Regulatory Barriers To Cancer Pain Relief Worldwide

BY HEATHER LINDSEY

More than half of the world's population lives in countries where regulations aiming to prevent opioid misuse leave cancer patients without access to pain medicines, according to new data from the Global Opioid Policy Initiative (GOPI) (*Ann Oncol*; Dec 2013;24, suppl 11).

Overall, the survey of 104 countries in Africa, Asia, the Middle East, Latin America and the Caribbean, and India “confirms what many of us thought when looking at opioid-consumption data,” said James F. Cleary, MD, FACHPM, one of the authors and Associate Professor of Medicine and Director of the Pain and Policy Studies Group (PPSG) at the University of Wisconsin Carbone Cancer Center. “Few opioid medicines are consumed for medical and scientific purposes.”

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ASCO Report on 2013 Advances: Progress, But Harm from Budget Cuts

BY PEGGY EASTMAN

The American Society of Clinical Oncology's year-end report on the major clinical cancer advances in 2013 documents much to celebrate, but sounds a

strong note of alarm due to budget cuts for cancer research funding.

To keep cancer research strong and counter funding cutbacks, ASCO is seeking a fiscal year 2014 appropria-



tion of \$32 billion for the National Institutes of Health, including \$5.2 billion for the National Cancer Institute.

While the recent Senate-House budget agreement is a step in the right direction of making up for what ASCO calls years of stagnant funding and cuts to NIH, the agreement falls short in protecting the nation's cancer care infrastructure, the

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Sales and Marketing of Ponatinib Resume

The U.S. Food and Drug Administration has approved a revised U.S. Prescribing Information (USPI) and Risk Evaluation and Mitigation Strategy (REMS) for the leukemia drug Iclusig (ponatinib). In addition, the agency has asked Ariad Pharmaceuticals, the drug's manufacturer, to conduct post-market investigations to further characterize ponatinib's safety and dosing.

These required safety measures include:

- Label changes to narrow the indication;
- Providing additional warnings and precautions about the risk of blood clots and severe narrowing of blood vessels;
- Revising the recommendations about the dosage and administration; and
- Updating the patient Medication Guide.

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Call to Pay More Attention to Brain Metastases Tumor Biology

BY MARK FUERST

“The number of brain tumors may be irrelevant or a poor selection variable for treatment. It is the crudest metric of tumor burden.”

NEW YORK—Clinical trials of lung cancer and melanoma patients who have brain metastases show that surgery plus radiation can extend survival, but the trials have not yet addressed one of the key components in clearing the cancer: the heterogeneity of these patients’ tumors. So said a speaker at the Chemotherapy Foundation Symposium here.

“Patients with brain metastases have differing histological make-ups,” Joshua Silverman, MD, PhD, Assistant Professor in the Department of Radiation Oncology at New York University Langone Medical Center, said in an interview after his presentation. “Clinical trials have ignored individual tumor biology. Most of what we think we know about brain metastases may be wrong. Lung cancer does not equal melanoma, which does not equal breast cancer. Triple-negative breast cancer does not equal luminal A breast cancer. Molecular subtypes behave differently in the brain.”

Clinical trials usually note the number of tumors, often including patients with one to three tumors, he explained. “But the number of brain tumors may be irrelevant or a poor selection variable for treatment. It is the crudest metric of tumor burden.”

An estimated 20 to 40 percent of cancer patients will develop brain metastases each year, and lung cancer is the most common cancer to have five or more brain metastases, according to data from the American Cancer Society.

Goals of Treatment

In his presentation, Silverman said the goals of treating brain metastases include preservation or improvement of function and memory or cognition; continued treatment of cancer in other body sites; increasing survival expectations; reduction or elimination of steroid medications; minimizing side effects; and treatment safety.

“Most tumors are moderately well circumscribed and are good targets for treatment with gamma knife radiosurgery techniques,” he said. “Resection has a role for larger tumors, but small tumors are best treated with radiosurgery.”

Prolonged survival is possible and relates to obtaining control of the brain and the body. “With no treatment, the median survival is one to two months, with steroids two to three months, and with whole brain radiation therapy

(WBRT) three to six months. Limited data show that chemotherapy leads to survival of eight to 12 months,” Silverman said.

Combinations of surgery and WBRT can extend survival time, he continued.

Surgery plus WBRT leads to survival of 10 to 16 months for patients with single brain metastases and limited extracranial disease. Radiosurgery plus WBRT extends survival up to 15 months for patients with fewer than four metastases and limited disease volume.

Survival depends greatly on the extent of extracranial disease, he said, adding that studies show that clinicians tend to overestimate early survival and underestimate long-term survival.

Silverman posed the question: What is worse, a patient who has eight small (5 mm) metastases or two large (2 cm) metastases? Modern techniques allow for treatment of multiple lesions, he noted. “In 1988, treating more than

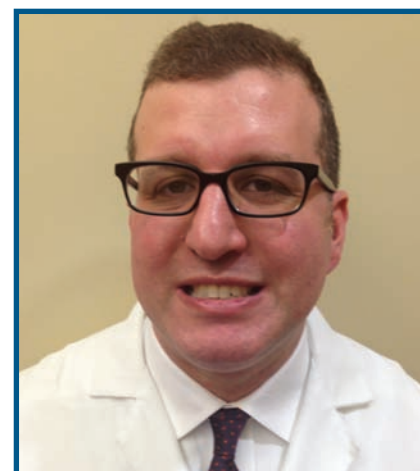
one tumor was heresy. In 2000, heresy was more than four tumors, and in 2005 it was more than 10 tumors.

Now we may be able to treat more than 20 tumors.”

He described treatment for a breast cancer patient who had a good initial response seven months after WBRT for multiple cerebellar metastases. Subsequently, the patient developed 26 new tumors. “We used gamma knife radiosurgery to treat 13 tumors at a time. Five months later, 25 of the tumors were gone, and the largest cerebellar tumor had regressed. She now has normal neurologic function.”

“Resection has a role for larger tumors, but small tumors are best treated with radiosurgery.”

The concept that brain cancer is a diffuse problem due to the presence of micrometastases is an observation from autopsy series and predates modern imaging,” Silverman said. “Current treatments for brain metastases have gone far beyond those early guidelines. How do we treat brain metastases in this era of targeted therapy?”



JOSHUA SILVERMAN, MD, PHD: “Clinical trials have ignored individual tumor biology. Most of what we think we know about brain metastases may be wrong. Molecular subtypes behave differently in the brain.”

He noted that there are many targeted therapies now available to treat melanoma, breast cancer, lung cancer, and renal cancer. “We need better information regarding pharmacokinetic, pharmacodynamic, efficacy, tolerability, and adverse effects of drugs in the central nervous system to devise targeted therapies for brain metastases.”

Surviving Metastases

Lung cancer is the leading cause of death from cancer, and the most common source of brain metastases. More than half of all lung cancer patients may develop brain metastases. Treatment is available to reduce the size and number of metastases, and patients can live a long time with brain metastases,” Silverman said.

For non-small cell lung cancer, imaging studies show a 60 percent decrease in the size of metastases, and some metastases disappear completely. About one-quarter of metastases remain about the same size without further growth. Some 16 percent eventually enlarge and may require further treatment, but about 86 percent of tumors can be locally controlled, he said. “Significant factors for higher local control, based on multivariate analyses, include smaller tumor volume and higher treatment isodose.”

Causes of death include extracranial disease progression in more than two-thirds of patients, about six percent from intracranial disease progression, and about one-quarter from unknown causes.

Several large retrospective series of patients with brain metastases treated with radiosurgery show a median survival of

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REGULATORY BARRIERS TO CANCER PAIN RELIEF *Continued from page 1*

Complete data from 104 countries and states were available, representing 67% of those contacted, including about five billion people, or 87% of the target population.

Based on the data, “it’s quite clear that there is inadequate access and education regarding prescribing of opioids,” commented Jamie H. Von Roenn, MD, Senior Director of American Society of Clinical Oncology’s Education, Science and Professional Development Department.

Overall, the survey provides a monumental series of data with in-depth analysis, said Daniel B. Carr, MD, MA, Professor of Public Health and Community Medicine and Program Director of the Pain, Research Education & Policy Program at Tufts University School of Medicine. “It’s a fabulous blueprint or roadmap for clarifying the



JAMES F. CLEARY MD, FACHPM, said that despite the problems, access to palliative care is already improving, with programs such as the UICC’s Global Access to Pain Relief Initiative and other international organizations. “These groups are all working together, but we’ve got to make sure we’re coordinated in the right way. Working with local advocates and champions is important, as well as with government authorities.”



gaps in palliative care across different areas of the world.”

Many of the barriers documented in the study are well known, noted Eduardo L. Cazap, MD, PhD, FASCO, Founding President of the Latin-American & Caribbean Society of Medical Oncology (SLACOM), which was involved with the survey. “But when you’re talking with regulators or with policymakers, it’s necessary to have documentation to support your position.”

Study Details

The European Society for Medical Oncology (ESMO) and the European Association for Palliative Care conducted the survey, with the cooperation of the Union for International Cancer Control (UICC), the PPSG, the World Health Organization (WHO), and 17 international oncology and palliative care societies.

The researchers collected information about the availability of seven “essential” opioids for cancer pain relief: codeine, immediate-release (IR) and controlled-release (CR) oral morphine, injectable morphine, IR oral oxycodone,

transdermal fentanyl, and IR oral methadone.

Additionally, investigators assessed the following factors:

- The presence of national palliative care organizations;
- Cultural and social barriers to opioid use;
- Changes in drug regulations during the past five years;
- Opioid availability to patients with prescriptions; and
- The accessibility of medication dispensers.

Complete data from 104 countries and states were available, representing 67 percent of those contacted. On a population basis, the dataset reflects 5.03 billion people, representing 87.3 percent of the target population. Overall, substantial formulary and regulatory barriers to opioid access were identified in the majority of countries surveyed.

The results showed that opioid availability in 25 African countries is “critically low,” the study authors said. Codeine and morphine were the most common pain medications available, with no country having access to all seven essential opioids.

Most African countries used regulatory restrictions to limit opioid access. For example, 16 countries required special authorization for outpatients to receive an opioid prescription, while this was the case for inpatients in 15 countries.

Opioid availability was also found to be low in Asia, except for Japan and South Korea, with a total of 20 countries surveyed. Codeine and morphine were the most commonly available formulations, and only three countries had all seven essential formulations.

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BRAIN METASTASES

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“Preserving neurological function and memory is key. Survival is dependent on getting the brain tumor and the body tumor under control.”

11 months, including patients who had lung cancer, melanoma, renal cell carcinoma, and breast cancer, he said, noting that survival depends on many factors.

“What can we learn from patients who live much longer than anyone may have expected?” he asked. About one-third of these patients had only brain disease or the brain was the primary site of cancer. About another one-quarter had brain cancer plus nodes, and another 40 percent had brain cancer plus two or more organ sites.

In summary, Silverman said, “Preserving neurological function and memory is key. Survival is dependent on getting the brain tumor and the body tumor under control. Gamma knife radiosurgery can be used for any number of brain tumors. Close imaging follow-up is needed. WBRT may be used for specific patients. Long-term survivals are possible and will continue through innovation and research to improve outcomes.”

In the future, researchers need to determine the optimal treatment for larger tumors following resection, and develop biologics and better radiotherapy for brain metastases. “We need to treat ‘radio-resistant’ histologies, such as those found among renal carcinoma and melanoma patients,” he said. Areas still under question include decreasing toxicities and neuroprotection, novel imaging technologies, disruption of the blood brain barrier, and primary systemic treatment for brain metastases, as well as possible immunotherapies.

“We need to think more about neurosurgery to treat a larger burden of metastases. If we are able to do that, then we can reduce the neurocognitive complications that often accompany WBRT,” Silverman said.

Trials are needed to compare WBRT with neurosurgery. He noted that some studies show that surgical resection plus WBRT does not necessarily im-

prove survival. “At the moment, results for these two treatments—neurosurgery and WBRT—vary from center to center,” he said, adding that in making a referral, clinicians need to look for a center that has experience in treating a large number of metastases.

Asked for her opinion, Katharine McNeill, MD, an instructor in the Departments of Medicine and Neurology at New York University Langone Medical Center, said, “It will be exciting to see more investigations into treating brain metastases in glioblastoma, which is a heterogeneous disease. Studies can identify genes from the patient that can be targeted for therapy. Then we can detail what genomic changes may be due to particular tumors, and target pathways in individual patients.”

She predicted that this type of genomic therapy will be available for treating patients with brain metastases within the next five to 10 years.