

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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Stereotactic Surgery Alone Shown as Sufficient for Some Patients with Brain Mets

BY ROBERT H. CARLSON

ATLANTA—Cancer patients age 35 to 50 with brain metastasis had increased overall survival when treated with stereotactic radiosurgery alone, compared with stereotactic radiosurgery plus whole brain radiotherapy (WBRT), in an individual-patient-data meta-analysis of three published randomized controlled trials. As reported here at the ASTRO Annual Meeting (Abstract LBA3—accessible via <http://online.myiwf.com/astro2013/Abstract.aspx>), the results showed that beyond age 50 there was no difference in the two arms of the meta-analysis.

The three randomized trials—EORTC 22952-26001, JRSOG99-1, and MDACC NCT00460395—included newly diagnosed patients who had one to four brain metastases, treated with either stereotactic radiosurgery alone or stereotactic radiosurgery plus whole brain radiotherapy.

Those trials by themselves, however, were each under-powered for overall survival comparisons, said the first author of the new meta-analysis, Arjun Sahgal, MD, Associate Professor in the Department of Radiation Oncology at the University of Toronto and Deputy Chief of Radiation Oncology at Odette Cancer Center, also in Toronto.

Analyzing the raw patient data in this new meta-analysis allowed the re-

searchers to formulate conclusions that could not be done through an aggregate meta-analysis previously performed earlier by the same group, he explained. “What we see now is that overall survival is significantly increased with radiosurgery alone in patients age 35 to 50 years, relative to an age-matched cohort treated with whole brain radiation plus radiosurgery.”

In the new meta-analysis, the risk of distant brain failure was significantly higher with radiosurgery alone, but only for patients 55 and older. The risk of new metastasis was also greater in patients with more than one metastasis.

Sahgal noted that previous research by his group showed that the addition of whole-brain radiation to radiosurgery improves distant brain control and local control but makes no difference on overall survival (Tsao et al: *Cancer* 2012; 118: 2486-2493). Therefore, he said, radiosurgery alone is a reasonable option because it spares the patient the adverse effects of whole brain radiation. In addition, the new meta-analysis expands on the results by age.

Patient Data Detailed

Sahgal reported a median time to death of 10 months for use of stereotactic radiosurgery vs. 8.2 months for



ARJUN SAHGAL, MD: “Based on our individual patient data of randomized controlled trials from three continents, we conclude that stereotactic radiosurgery alone is the preferred treatment for patients presenting with one to four brain metastases, recursive partitioning analysis score class 1 or 2, Karnofsky performance score of 70 or above, and age 50 years or younger.”

radiosurgery plus whole brain irradiation; local failure was 6.6 vs. 7.4 months, respectively; and distant brain failure was 4.5 vs. 6.5 months, respectively.

The only significant treatment effect modifier was age.

Patients with a single metastasis also had significantly longer overall survival than those with two to four

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Analyzing the raw patient data in this new meta-analysis allowed the researchers to formulate conclusions that could not be done through an aggregate meta-analysis previously performed earlier by the same group.

‘FIVE DAYS AT MEMORIAL’

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understood by oncologists, this book makes it clear that it is often not well accepted by other doctors, nurses, and health professionals, who may have strong feelings against such intervention under any circumstances.

the care of the desperately ill. Lest you think that the issue has been resolved, the Institute of Medicine in 2012 in their report on “Crisis Standards of Care” (National Academies Press) wrote, “Neither the law nor ethics sup-

“This is a very powerful book, masterfully constructed with wonderfully nuanced presentations of complex situations where systems and people are under great stress.”

The critical testimony by outside forensic pathologists and ethicists adds to the disquiet. The legal and justice systems may have very different standards generated for typical situations and applied to crisis settings.

All this has made this reader reassess what society understands about

port the intentional hastening of death even in a crisis.”

Five Days at Memorial is a wonderful book with insights on many different levels about human behavior during crises and about society’s expectations of medical care. Read it—you won’t regret it! ☐

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CLL: Can IMiDs & TKIs Replace Chemotherapy?

BY ROBERT H. CARLSON

NEW YORK—Complete response (CR) rates for patients with chronic lymphocytic leukemia (CLL) have risen from five percent in the 1960s when the alkylating agents chlorambucil and cyclophosphamide were standard, to 45 percent today with use of chemo-immunotherapy. Meanwhile, new additions to the armamentarium such as immune modulators (IMiDs), tyrosine kinase inhibitors (TKIs), and anti-CD-20 monoclonal antibodies are showing their strengths in clinical trials.

Key questions, therefore, are whether there are now enough data to eliminate chemotherapy from initial treatment for CLL; and if so, whether kinase inhibitors and IMiDs can replace chemotherapy.

Two experts debated those questions here at the Lymphoma & Myeloma International Congress. Jennifer R. Brown, MD, Director of the CLL Center at Dana-Farber Cancer Institute, said that yes, kinase inhibitors and IMiDs can replace chemotherapy. Susan O'Brien, MD, Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center, though, said that no, they can't.

Jennifer Brown: The Problem with Chemotherapy...

The problem with chemotherapy, Brown began, is continuous relapse at progres-

sively shorter intervals and progressive resistance to therapy. She started her argument citing the GCLLSG CLL8 trial of single-agent fludarabine in which about 31 percent of patients had disease progression within two years. Furthermore, she said, "elderly patients—the majority with CLL—tolerate chemotherapy poorly, and patients with 17p and/or complex cytogenetics respond poorly from the start."

Myelosuppression can be persistent with chemotherapy, leading to the risk of therapy-related myelodysplastic syndromes and acute myelogenous leukemia, she explained. Plus there is a risk of immunosuppression, also often

and T cell function but is not cytotoxic. It is effective in relapsed/refractory CLL, with an objective response rate of 35 to 50 percent.

"But it can be difficult to tolerate, with tumor flare, tumor lysis, and myelosuppression."

Brown cited one study with impressive results, of upfront therapy for elderly patients. At 24 months of follow-up, the overall survival and progression-free survival rates were 88 and 60 percent, respectively. At four years, overall survival was 82 percent, with no time to failure yet reached (*Badoux X et al: Blood 2011;118:3489-3498*).

In another study she cited, the best response for lenalidomide did not include any complete responses at 20.7 months of follow-up, but the rate was 53.2 months was 20 percent. Partial response rates were 56 and 52 percent, respectively, and the duration of response was 16.6 and 40.4 months, respectively (*Chen C et al: 2012 ASH Annual Meeting, Abstract 718*).

"Long-term follow-up of that study demonstrated that when using low doses of single-agent lenalidomide in CLL, prolonged therapy is feasible and may be required for the achievement of durable, high-quality responses," Brown said.

Those researchers also reported that maximal daily doses of 25 mg could be reached and may be needed for optimal response, although recurrent myelosuppression remained a limitation.

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persistent, as well as increased infection risks.

In addition, clonal evolution, the selection for pre-existing adverse clones vs. induction of new clones, is a concern with chemotherapy.

So what are the alternatives? Brown pointed to mature data in previously untreated patients with lenalidomide, idelalisib, and ibrutinib, and evolving data on the anti-CD-20 antibody obinutuzumab.

Lenalidomide is active in several hematological malignancies, she continued. In CLL it promotes cell activation

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"These survival results have the potential to change practice as our field moves away from whole brain radiation."

metastases. Those with more than one brain metastasis had a significantly greater risk of distant brain failure. Distant brain control and local control significantly favored the addition of whole brain irradiation, but multivariable analysis showed significant increases in distant brain failures in the radiosurgery-alone cohort only in patients older than 50.

"Therefore, based on our individual patient data of randomized controlled trials from three continents, we conclude that stereotactic radiosurgery alone is the preferred treatment for patients presenting with one to four brain metastases, recursive partitioning analysis score class 1 or 2, Karnofsky performance score of 70 or above, and age 50 years or younger," Sahgal said.

"This conclusion allows radiosurgery alone to be offered and the patient potentially spared the adverse effects of whole brain radiation."

Patient inclusion was limited to those with a recursive partitioning

analysis score of 1 or 2, and Karnofsky performance score of 70 or above. The meta-analysis was based on one-stage time-to-event individual patient data.

Among 364 patients from the three randomized controlled trials who met the inclusion criteria, 51 percent had been treated with stereotactic radiosurgery alone; 19 percent were age 50 or younger; 41 percent were recursive partitioning analysis class 1; and 60 percent had a single brain metastasis.

In total, 21 percent of patients had a local failure, 44 percent had distant brain failure, and 86 percent died during follow-up.

Sahgal said the survival advantage with radiosurgery alone in younger patients may be explained by the lack of benefit in those receiving whole brain radiation in reducing the risk of brain metastases, while still exposing patients to the toxicities of worse memory function and harming quality of life, which ultimately translated into shorter survival.

Moving Away from Whole Brain Radiation Therapy

The moderator of a news briefing at the meeting, Daphne Haas-Kogan, MD, Professor of Radiation Oncology and Neurologic Surgery and Program Director of the Department of Radiation Oncology at the University of California, San Francisco, said the strength of the study is that it identified a cohort of patients in which the risk of distant brain metastases is not great, and that those patients might not need whole brain radiotherapy on top of stereotactic radiosurgery.

"The study provides us with results we would not otherwise have had if we had examined the individual studies separately," she said. "These survival results have the potential to change practice as our field moves away from whole brain radiation."

She added that it is not understood why the younger age group has less risk of dying. Her first thought on reading

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LM-CLL

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“In summary, the mature data on lenalidomide in previously untreated elderly patients look very promising,” she said.

However, in July 2013, the industry-sponsored Phase III ORIGIN (CLL008) study of lenalidomide versus chlorambucil was closed early due to excess deaths in the lenalidomide arm in patients over age 80, and many early drop-outs in that age group.

Targeting Kinases

Idelalisib (GS-1101) targets kinases in the BCR pathway and is highly selective for PI3K delta, Brown said. She then cited a study led by her opponent in this debate, the 101-08 Phase II single-arm, open-label study of oral idelalisib plus rituximab in 64 previously untreated patients with a median age of 71 (*O’Brien S et al: ASCO 2013 Annual Meeting, Abstract 7005*).

The regimen achieved a 19 percent complete response rate but an overall response rate of 97 percent, with estimated progression-free survival (PFS) at 24 months of 93 percent.

The probability of PFS in the intent-to-treat analysis was 93 percent at 24 months for all 64 patients, and 100 percent for the nine patients with TP53 mutation/del(17p).

Adverse events in the idelalisib-rituximab trial were 55 percent for any grade of diarrhea, with 23 percent grade 3 or 4; 42 percent pyrexia, with three percent grade 3-4; nausea 38 percent with two percent grade 3-4; rash 38 percent with eight percent grade 3-4; chills 36 percent of any grade and none grade 3-4; cough three percent, with two percent grade 3 or 4; and fatigue 31 percent but no grade 3-4; pneumonia 27 percent, 17 percent grade 3-4. Transaminase elevations occurred in 23 percent of patients, and neutropenia in 23 percent.

“But all could be managed effectively, and certainly we’re used to managing

these and worse toxicities with chemotherapy,” Brown said.

Of note, she added, was that the response rate with idelalisib-rituximab was preserved in the high-risk TP53 mutation/del(17p) patients.

The other kinase inhibitor Brown discussed was the Bruton tyrosine kinase (Btk) inhibitor ibrutinib, which forms a specific and irreversible bond with cysteine-481 in the Btk to inhibit it. Once-daily dosing results in 24-hour sustained target inhibition.

Brown cited the ibrutinib Phase Ib/2 RESONATE (PCYC-1102-CA)

trial, with 31 previously untreated patients age 65 and older with CLL or small lymphocytic leukemia (*Byrd J et al, 2013 ASCO Annual Meeting, Abstract TPS8619*).

The best responses in that trial were 13 percent complete responses and 58 percent partial responses, 13 percent partial responses with lymphocytosis, and 10 percent stable disease. There was no disease progression, and immunoglobulin levels remained stable or increased.

Brown summarized the first part of her presentation, saying that mature follow-up data with lenalidomide,

idelalisib, and ibrutinib demonstrate at least comparable and possible improved PFS compared with chemo-immunotherapy.

“Can we improve further on these outcomes?” she asked rhetorically, and move on to the anti-CD-20 antibody.

That drug increases direct cell death and enhances antibody-dependent cell-mediated cytotoxicity (ADCC) and lowers complement-dependent cytotoxicity (CDC).

The ongoing CLL11 study, she noted, planned for 780 patients with previously untreated CLL with

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the abstract, she said, was that there were perhaps more breast cancer patients in the younger age group since they tend to have less risk for distant brain metastases. But in fact, more patients had lung cancer than breast cancer.

“We’re going deeper into the data to understand it better,” Sahgal said, noting that the majority of the patients were treated before the era of molecular tests, and molecular predictors such as EGFR status is not known, “but the data are there and we can make some strong inferences.”

WBRT still has a role to play, however—the majority of patients will be offered whole brain irradiation because most present with a large number of brain metastases.” ☐