Increasing Focus on the Difficult Issue of Discussing the Cost of Care with Patients

BY ERIC T. ROSENTHAL

ASCO is readying a “Guidance Statement” on the cost of cancer care, expected to be published in July in JCO. In addition, one of the seven highlighted studies the Society selected for a teleconference two weeks before the Annual Meeting showed that a “significant minority” of patients in clinical trials feel anxious or adopt coping strategies to be able to pay for supportive medications. The same study also documented that cost is rarely discussed among patients and physicians.

See Page 10
The combined use of temozolomide and lomustine (CCNU) has extended survival by more than 50% for one category of patients with glioblastoma in a small study reported in the *Journal of Clinical Oncology* now available online, published ahead of print.

“We were stunned” by the data showing 50% of the whole cohort surviving more than two years, chief investigator Ulrich Herrlinger, MD, Professor of Clinical Neuro-Oncology at the University of Bonn Medical School, said in an interview. Reflecting on the findings, however, Martin J. van den Bent, MD, of the European Organization for Research and Treatment of Cancer (EORTC) and Professor of Oncology at the Daniel Den Hoed Cancer Center at Erasmus Medical Center in Rotterdam, cautioned, however, that although the data are of interest as the first signs of clinical activity, the study is still very small: “We don’t know to what extent biases have played a role in getting this result,” he noted.

**Long-Term Survival**

The prospective study looked at long-term survival among patients newly diagnosed with glioblastoma between March 2002 and December 2003 among whom 31 received oral CCNU at 100 mg/m² on Day 1 followed by temozolomide at 100 mg/m² on Days 2 through 6 each week, continued for a maximum of six weeks.

An additional group of eight patients received an intensified regimen in which the CCNU dose was raised to 110 mg/m² and the temozolomide was given at a dose of 150 mg/m² for six courses. All patients received standard surgery plus radiotherapy (60 Gy) to the tumor site only.

The median overall survival was 23.1 months for the whole cohort, with 47% of the patients surviving for two years and 18.5% for four years. But after a median follow-up of 41.5 months the median overall survival had not been reached in the patients who had received the intensified regimen and was significantly higher than in the standard group (22.6 months).

**MGMT Methylation**

Four out of eight patients receiving the intensified regimen were alive at 56 months, two of them without any recurrence, and the investigators noted that methylation of the O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter in tumor tissue was associated with a much longer median overall survival of 34.4 months compared with only 12.5 months in patients without such methylation.

Dr. Herrlinger noted that since MGMT is an enzyme that detoxifies the DNA changes brought about by temozolomide, when it is methylated the detoxification should be low, so temozolomide is expected to have a good effect in patients who have a methylated MGMT promoter. But, on the other hand, in patients with a non-methylated MGMT promoter there should be high MGMT expression in the tumor cell and high detoxification, reducing the anti-neoplastic benefit of temozolomide.

“And that’s what we saw in our group,” Dr. Herrlinger said. “This has been demonstrated previously for standard temozolomide therapy, and we were able to show this also happens in our temozolomide-plus-lomustine therapy”.

Side effects on the therapy included thrombocytopenia, leukopenia, and risk of infection. Two patients died. And the German team reported an increase from 16% to 57% in the incidence of World Health Organization Grade 4 hemotoxicity in the intensified group compared with patients receiving the standard doses.

**Off-Study**

But the gains demonstrated in this study have prompted the investigators to launch a Phase III study comparing the combination of lomustine plus temozolomide versus temozolomide alone; and Dr. Herrlinger suggested that young patients with newly diagnosed glioblastoma without any comorbid disease could be treated off-study with this combination:

“Clinicians have to keep in mind that this still remains experimental. But we in Bonn, at least, are giving this combination therapy to some of our patients.”

**No Control Group**

He and his colleagues concluded that the combination may add a survival benefit, but with greater risk of acute toxicity. The *JCO* article states that the improvement in survival “might be the best rate ever observed in a glioblastoma analysis,” and that: “it does not appear to be bias driven.”

Furthermore, the long-term survivors in the study were not particularly young: The median age was 57. The authors acknowledged that second resections and multiple salvage therapies might also have influenced overall survival to some extent in addition to the change in therapy.

**‘Old Fashioned’**

Dr. van den Bent urged caution in assessing the value of data from such a small study, which was also less conclusive because it lacked a control group. And he noted, “One argument why this combination may not hit a home run comes from a French study published in 2005 by Olivier Chiotot, MD, and colleagues, who looked at temozolomide in combination with BCNU.

Although the study [*Annals of Oncology* 2005,16:1177–1184] saw interesting improvements in survival, there were no hints of such magnificent long-term survival.”

**We were stunned,** the study’s chief investigator, ULRICH HERRLINGER, MD, said of his team’s reaction to the findings that 50% of the whole cohort survived more than two years.

He and his colleagues concluded that the combination may add a survival benefit, but with greater risk of acute toxicity. The *JCO* article states that the improvement in survival “might be the best rate ever observed in a glioblastoma analysis,” and that: “it does not appear to be bias driven.”

Furthermore, the long-term survivors in the study were not particularly young: The median age was 57. The authors acknowledged that second resections and multiple salvage therapies might also have influenced overall survival to some extent in addition to the change in therapy.

**‘Old Fashioned’**

Dr. van den Bent urged caution in assessing the value of data from such a small study, which was also less conclusive because it lacked a control group. And he noted, “One argument why this combination may not hit a home run comes from a French study published in 2005 by Olivier Chiotot, MD, and colleagues, who looked at temozolomide in combination with BCNU.

Although the study [*Annals of Oncology* 2005,16:1177–1184] saw interesting improvements in survival, there were no hints of such magnificent long-term survival.”

---

By Peter Goodwin

---

**Glioblastoma: Lomustine/Temozolomide Combination Extends Survival by 50%**

BY PETER GOODWIN

**Small Study:**

**Glioblastoma: Lomustine/Temozolomide Combination Extends Survival by 50%**

BY PETER GOODWIN

---

The 1,200-patient RTOG 0525 study being conducted by Marl R. Gilbert, MD, and colleagues at M. D. Anderson Cancer Center is looking at standard-dose vs intensified temozolomide, with both regimens allocated to two treatment groups: MGMT methylated or non-methylated.

**MGMT Methylation**

Four out of eight patients receiving the intensified regimen were alive at 56 months, two of them without any recurrence, and the investigators noted that methylation of the O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter in tumor tissue was associated with a much longer median overall survival of 34.4 months compared with only 12.5 months in patients without such methylation.

Dr. Herrlinger noted that since MGMT is an enzyme that detoxifies the DNA changes brought about by temozolomide, when it is methylated the detoxification should be low, so temozolomide is expected to have a good effect in patients who have a methylated MGMT promoter. But, on the other hand, in patients with a non-methylated MGMT promoter there should be high MGMT expression in the tumor cell and high detoxification, reducing the anti-neoplastic benefit of temozolomide.

“And that’s what we saw in our group,” Dr. Herrlinger said. “This has been demonstrated previously for standard temozolomide therapy, and we were able to show this also happens in our temozolomide-plus-lomustine therapy”.

Side effects on the therapy included thrombocytopenia, leukopenia, and risk of infection. Two patients died. And the German team reported an increase from 16% to 57% in the incidence of World Health Organization Grade 4 hemotoxicity in the intensified group compared with patients receiving the standard doses.

**Off-Study**

But the gains demonstrated in this study have prompted the investigators to launch a Phase III study comparing the combination of lomustine plus temozolomide versus temozolomide alone; and Dr. Herrlinger suggested that young patients with newly diagnosed glioblastoma without any comorbid disease could be treated off-study with this combination:

“Clinicians have to keep in mind that this still remains experimental. But we in Bonn, at least, are giving this combination therapy to some of our patients.”

**No Control Group**

He and his colleagues concluded that the combination may add a survival benefit, but with greater risk of acute toxicity. The *JCO* article states that the improvement in survival “might be the best rate ever observed in a glioblastoma analysis,” and that: “it does not appear to be bias driven.”

Furthermore, the long-term survivors in the study were not particularly young: The median age was 57. The authors acknowledged that second resections and multiple salvage therapies might also have influenced overall survival to some extent in addition to the change in therapy.

**‘Old Fashioned’**

Dr. van den Bent urged caution in assessing the value of data from such a small study, which was also less conclusive because it lacked a control group. And he noted, “One argument why this combination may not hit a home run comes from a French study published in 2005 by Olivier Chiotot, MD, and colleagues, who looked at temozolomide in combination with BCNU.

Although the study [*Annals of Oncology* 2005,16:1177–1184] saw interesting improvements in survival, there were no hints of such magnificent long-term survival.”

---

**Small Study:**

**Glioblastoma: Lomustine/Temozolomide Combination Extends Survival by 50%**

BY PETER GOODWIN

---

“Clinicians have to keep in mind that this still remains experimental. But we in Bonn, at least, are giving this combination therapy to some of our patients.”

---

**The 1,200-patient RTOG 0525 study being conducted by Marl R. Gilbert, MD, and colleagues at M. D. Anderson Cancer Center is looking at standard-dose vs intensified temozolomide, with both regimens allocated to two treatment groups: MGMT methylated or non-methylated.**
Harry D. Bear, MD, PhD, Director of the Breast Health Center at Virginia Commonwealth University Massey Cancer Center, has received the NSABP’s Distinguished Investigator Lifetime Achievement Award. Over the past 20 years, Dr. Bear has led several international trials that have resulted in major changes in the treatment of breast cancer and increased the chances for breast conservation among women with the disease. He became a research investigator with NSABP in 1984 and has served on the Board of Directors since 1991.

George Prendergast, PhD, has been appointed Editor-in-Chief of Cancer Research as of January for a five-year term. He is President and CEO of Lankenau Institute for Medical Research in Wynnewood, PA, and has previously served as a senior editor and deputy editor for the journal. An author on several early scientific papers on the mechanisms of action for drugs that are now in clinical development, Dr. Prendergast’s primary research interests include the molecular and cellular biology of cancer, cancer immunology, preclinical models of cancer progression and therapy, and drug discovery and mechanisms.

The Keck School of Medicine of the University of Southern California has received a $5 million gift from the Ellison Medical Foundation to support the development of the Center for Applied Molecular Medicine. David B. Agus, MD, Professor of Medicine at the Keck School who joined the faculty there on April 1, will be principal investigator for the project, titled Molecular Technologies in Cancer. He will also direct the new USC multidisciplinary Westside Prostate Cancer Center.

John H. Glick, MD, Director of the Abramson Cancer Center at the University of Pennsylvania and Professor of Medicine at the University of Pennsylvania School of Medicine, was presented with the Medal of Inspiration by The Wellness Community of Philadelphia at its annual Evening in the Park celebration and awards ceremony. The medal, which is given to a corporation, foundation, or individual for exemplary efforts to help people with cancer and their loved ones improve the quality of their lives by providing better resources for them, was presented to Dr. Glick for 30 years of work in cancer care.