Oncology’s Stepped-Up Efforts to Cut Hospital Use

BY LOLA BUTCHER

Faced with increasing pressure to reduce hospital admissions and readmissions, oncologists across the country are looking extra carefully at whether and how long their patients are hospitalized. Payers and policymakers are more and more equating hospital admissions with failed outpatient care, and it is considered only a matter of time until oncologists are evaluated—and paid—in relation to their patients’ use of hospital beds.

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Ovarian Cancer: Good Results with MEK Inhibitor Selumetinib in Low-Grade Serous Carcinoma

BY ROBERT H. CARLSON

The first prospective trial undertaken specifically in patients with low-grade serous carcinoma of the ovary shows that the MEK1/2 inhibitor selumetinib is active, with responses higher than typically seen with current chemotherapy or hormonal therapies for this often chemoresistant disease.

The Phase II trial, published in the February issue of Lancet Oncology (2013;14:134-140), may point the way to more successful molecularly targeted strategies for this relatively rare tumor, even though there did not appear to be any correlation between the tumors’ biomarkers and the patients’ response as the researchers had expected.

In the open-label trial of women with recurrent low-grade serous ovarian or peritoneal carcinoma, eight of 52 patients (15%) had a complete or objective partial response—with one complete response—and 34 (65%) had no disease progression at two years.

“Relative to chemotherapy, where the response rates are three to four percent in the recurrent setting, and to hormonal therapy, at about nine percent, a 15 percent response rate is very promising,” said the study’s senior author, David M. Gershenson, MD, Professor and Chair of the Department of Gynecologic Oncology and Reproductive Medicine at the University of Texas MD Anderson Cancer Center and Chair of the Gynecologic Oncology Group’s Rare Tumor Committee.

Selumetinib (also known as AZD6244 and ARRY-142886) is a selective, orally available, non-ATP competitive small molecule inhibitor of MEK1/2. Patients in the study were given selumetinib at a dose of 50 mg twice daily orally until disease progression.

Biomarkers Did Not Correlate

At the time the study was planned the researchers noted a high frequency of BRAF and KRAS mutations in low-grade serous ovarian tumors, and hypothesized that MAPK inhibition would be a potentially active intervention. But among the 16 patients identified with tumors with BRAF or KRAS mutations, only two had responses.

“Our results suggest that selumetinib is an active agent, but not necessarily because of BRAF or KRAS mutational activation per se,” the authors concluded.

In an interview, Gershenson said that one reason for the lack of correlation could be biomarker instability. Among the 52 patients, specimens were available for only 40, mutational analysis was done in 34, and in 28 of those the tissue was from the primary therapy and not from the recurrent tumor. “The question arises, are these biomarkers stable over time or do they change, so that what you find in the primary tumor may not be what you find in the recurrent tumor,” he said.

He noted that an unpublished study conducted with a group in Vancouver suggests that biomarkers may indeed change over time. “We don’t really understand the circuitry in these signal transduction pathways nearly as well as we think we do. And as we do these targeted therapy trials, we are learning that just because you have a mutation, that does not translate into a response.”

The study’s first author, John H. Farley, MD, COL (Ret), Professor in the Division of Gynecologic Oncology at Creighton University School of Medicine St. Joseph’s Hospital and Medical Center in Phoenix, explained in an interview that the MAP kinase pathway is very intricate and that some tumors may be going around the RAS/RAF mutational pathway.

“It appears that the MAP kinase pathway in these tumors is activated in a different way, other than KRAS and BRAF mutations. If you look at response to therapy as an expression of phosphorylated ERK downstream, there does potentially appear to be a correlation to response.”

He and his coauthors called this finding “potentially provocative in view of the...continued on page 8

Although low-grade serous ovarian cancer is less common and less aggressive than the high-grade variety, it is very difficult to treat when frontline therapy fails.

—Ezra Cohen

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disease-specific, and progression-free survivals of 49, 74, and 48 percent, respectively. Moreover, two-thirds of patients had Swallowing Performance Status Scale (SPSS) scores of ≤5, indicating that a gastrostomy tube was not required to maintain nutrition.

There are multiple considerations, therefore, when treating a patient with larynx cancer. Initial steps include staging and ascertaining whether a curative, organ-preservation approach is appropriate. For many patients this will consist of concurrent chemoradiotherapy of cisplatin (100 mg/m²) and single-daily fractionated radiotherapy. For almost two decades we have used an FHX-based regimen in these patients with appreciable success including those with large volume disease.

Current efforts are focused on further stratifying patients based on molecular characteristics of the tumor that will allow greater patient selection for chemoradiotherapy and even guide which agents are likely to be most effective.
specific strategies can mobilize millions of stem cells’ (1/10/13 issue)

I was interested to read the article in the January 10 issue about specific strategies that can mobilize millions of stem cells. Strategies mentioned included (1) avoid radiation, multiple cycles of chemotherapy, and myelotoxic drugs, (2) collect early in treatment, (3) use higher doses of filgrastim or pegfilgrastim, (4) utilize chemomobilization plus colony-stimulating factor, and (5) use plerixafor to augment filgrastim.

The diseases noted were lymphoma and multiple myeloma. These are different diseases with different treatment strategies, and the opportunity to mobilize after induction will depend on the treatment used during induction. The definition of “early treatment” is therefore likely the term culture-initiating cells were assessed in cultures.\(^1\)\(^2\) The results of these studies showed that mobilization of CD34+ cells, colony-forming cells, and long-term culture-initiating cells was far better during the first than the fourth cycle of chemotherapy and G-CSF. Moreover these studies showed that the mobilizing capacity rapidly decreased and was far less after one treatment of just four cycles of therapy.

The concern of collection in the first cycle of chemotherapy is that tumor cells may also be mobilized. It has been shown that myeloma cells do not mobilize, but it has not been extensively examined early during treatment; in lymphoma it appears that circulating lymphoma cells are rapidly eliminated by anti-CD20 if anti-CD20 is part of the therapy. To circumvent the high drug costs of plerixafor, use of leukapheresis should be considered during the first or second cycle of therapy.

The question then arises when to start leukapheresis: we kept as optimal when the white blood cell count increased from nadir to 4 × 10^9/L and performed leukapheresis on that particular day; this strategy made it possible to collect more than 2 × 10^6 CD34+ cells/kg during one 12-liter leukapheresis in most patients. Moreover it appeared predictable that this would occur on day 11 or 12 of cycle one when G-CSF was started on day 2 of the cycle. Our data are consistent with the recommendations made in the study reported in the article.

With CHOP-R being the standard treatment for patients with diffuse large B-cell lymphoma, the addition of G-CSF makes it possible to collect during cycle one on day 11 or 12 when the white blood cell count increases to 4 × 10^9/L. Moreover it is likely that by day 11 and 12 of the first cycle that lymphoma cells

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Low Toxicity Profile

In the trial—an abstract of which was reported at last year’s American Association for Cancer Research Annual Meeting (OT, 5/10/12 issue)—there were no treatment-related deaths. Grade 4 toxicities were cardiac (one), pain (one), and pulmonary events (one). Grade 3 toxicities that occurred in more than one patient were gastrointestinal (13), dermatological (nine), metabolic (seven), fatigue (six), anemia (four), pain (four), constitutional (three), and cardiac events (two). The patients were heavily pretreated: 30 (58%) had received three or more previous chemotherapeutic regimens; and 82 (65%) had previous regimens that contained platinum.

A trial of another MEK inhibitor is being planned, Gershenson said, noting that he will lead a Phase II/III international trial of trametinib (GSK1120212), which has a longer half-life than selumetinib. The trial, which he said has been approved by the National Cancer Institute’s Gynecologic Cancer Steering Committee and will take place in the U.S. and U.K., will directly compare trametinib with the attending physicians’ choice of hormonal and/or cytotoxic therapy. The trial with 250 patients is expected to begin this summer.

The study will analyze both recurrent and primary tumor tissue and will also require mandatory biopsy prior to starting therapy, he said. “We think that will give us a better chance of correlating the outcome to the biomarkers.”

Debulking Not Addressed

An editorial accompanying the study (“Towards Individualised Treatment.” Lancet Oncology 2013;14:101-102), noted that a strength of the study was the mandatory reference pathology of recurrent disease to exclude patients with progression to high-grade disease who would have been likely to benefit from chemotherapy; and recurrent borderline ovarian tumors that have excellent prognosis with surgical salvage alone.

A possible drawback, though, was that the issue of debulking surgery was not addressed. Elaborating in an email exchange, Sven Mahner, MD, Chief Consultant in the Department of Gynecology at University Medical Center Hamburg-Eppendorf in Germany, said that since a low-grade ovarian carcinoma can often be repeatedly surgically removed, it would be interesting to first operate on these patients and then treat them with selumetinib.

In response, Farley said that the main outcome of the study was progression-free survival and that debulking surgery would not have affected that endpoint—“Our patients were heavily pretreated, some with five previous treatments, and the time for surgical treatment had passed.”

Mahner was also asked about the lack of correlation of biomarkers and outcomes. He said he agreed with Gershenson that degradation of specimens can be a problem—“However, this also holds true for the specimens that biomarkers have originally been established on. A clinically useful biomarker should therefore be somewhat independent from this process—like hormone-receptor status or HER2 expression in breast cancer, for example.”

Biomarker-driven studies will remain an important tool in future development of many substances, he said, “and the selumetinib study is a good example, that a good biological hypothesis and targeted therapy can be successful despite a non-indicative marker.”

Letters