[News * Analysis * Commentary * Controversy]

May 10, 2011 * Vol. 33 * No. 9

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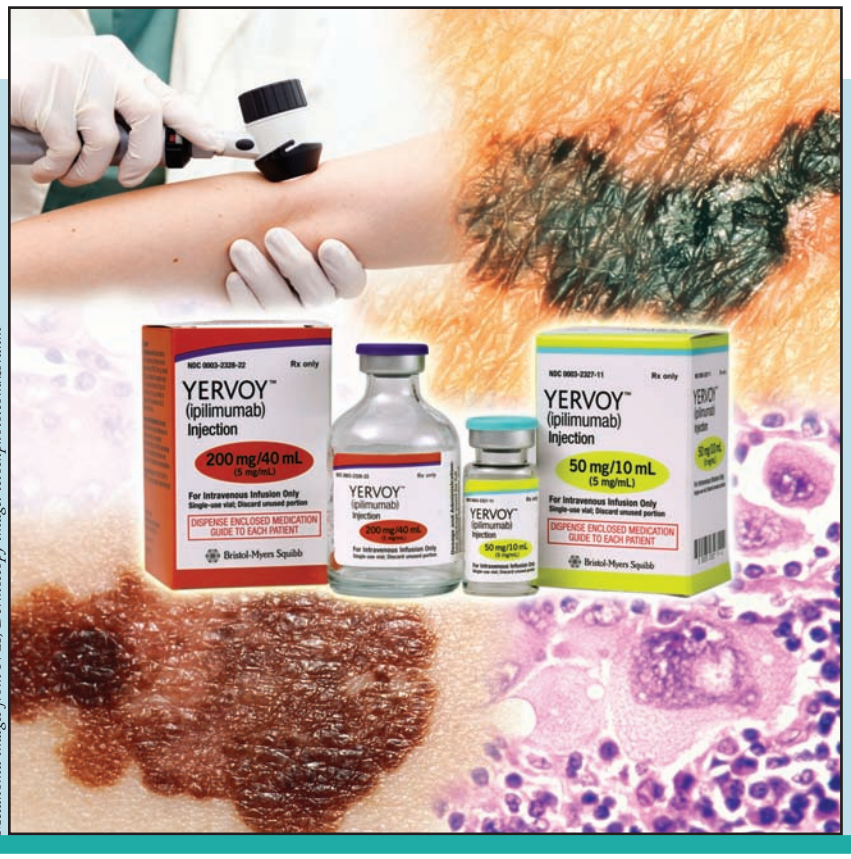

Melanoma images from NCI; Dermoscopy image: istockphoto.com/zoranm

Melanoma Care Notes from Ipilimumab Trialists

BY RABIYA S. TUMA, PHD

Ipilimumab is the first drug to prolong overall survival in patients with metastatic melanoma, and its recent FDA approval made headlines worldwide. Yet, ipilimumab (Yervoy) is not straightforward to use. A substantial proportion of patients who eventually respond initially develop tumor growth or new lesions, and side effects must be carefully managed to avoid serious problems. We asked physicians who participated in the clinical trials to share their thoughts on how best to use the drug.

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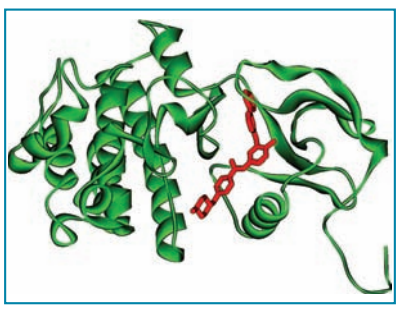

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Relieving Intractable Cancer Pain: Encouraging News from Gene Therapy Trial p.36

[ALSO]

PERIODICALS

Advanced Age No Barrier to Imatinib Response in Chronic Myeloid Leukemia

BY KURT SAMSON

iStockphoto.com/Yuri Arcurs

There is little difference in survival or cytogenetic response among younger or older patients with early Philadelphia-positive chronic myeloid leukemia (CML) receiving frontline treatment with imatinib, according to a five-year prospective study of patients enrolled in three clinical trials in Italy.

In an online March 30 advance publication of *Blood,* the journal of the American Society of Hematology, researchers at several Italian institutes compared data from clinical trials involving 559 patients with early chronic phase CML who were treated for a median of 60 months with imatinib, including 115 who were over age 65 when treatment began. The results showed that while more older patients died during the study period, as would be expected, there was little difference in major molecular or cytogenetic response among patients who began treatment before or after age 60.

GIANANTONIO ROSTI, MD: "The major findings of our work were that older patients over the age of 65 had identical response rates—hematologic, cytogenetic, and molecular—as younger patients, and that the mortality related to progression of CML was not different between older and younger patients."

The event-free survival rate among older patients was 55%, compared with 67% in their younger counterparts, failure-free survival was 78% vs 92%, progression-free survival was 62% vs 78%, and overall survival was 78% vs 89% in the younger group. But the differences, the researchers found, were all due to higher mortality among the older patients from other causes. No difference was observed when non-CML-related deaths were factored out.

"The major findings of our work were that older patients over the age of 65 had identical response rates—hematologic, cytogenetic, and molecular—as younger patients, and that the mortality related to progression of CML was not different between older and younger patients," said lead researcher Gianantonio Rosti, MD, Professor of Hematology and Oncology at St. Orsola-Malpighi Hospital, at the University of Bologna.

The median age of CML diagnosis is 60 years or older, while most CML patients involved in clinical trials average between 50 and 55, and there has been little data on outcomes in older patients with early-stage CML who

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start frontline imatinib after age 65. The two largest studies to date have involved fewer patients, with shorter outcomes, or later stage disease, but those studies too found little difference in survival or response between younger and older patients.

"We think, based also on other data in the literature, that a five-year follow-up is sufficient for evaluating response rates and risk of progression. It also represents an important follow-up for evaluation of long-term side effects, both in older and younger patients," Dr. Rosti said. "Of course collection of data regarding the long term safety will go on."

The main limitations of the study, he said, are that it is not possible to estimate the proportion of patients not allocated to imatinib during the enrollment period due to the presence of relevant co-morbidities that generally are more frequent in elderly patients, or due to age. Also, there were no data regarding low-grade toxicities.

"We think that imatinib therapy should be considered for all patients, regardless of age, but given the higher number of comorbidities, more attention in the management of toxicities, dosage, and concomitant drugs is warranted."

'Model' Study

OT Clinical Advisory Editor for Hematology/Oncology Mikkael Sekeres, MD, MS, Director of the Leukemia Program at the Cleveland Clinic Taussig Cancer Institute and Chair of the Hematology/Oncology Pharmacy & Therapeutics Committee, noted that the findings confirm what has been observed in solid tumor patients treated with other therapies.

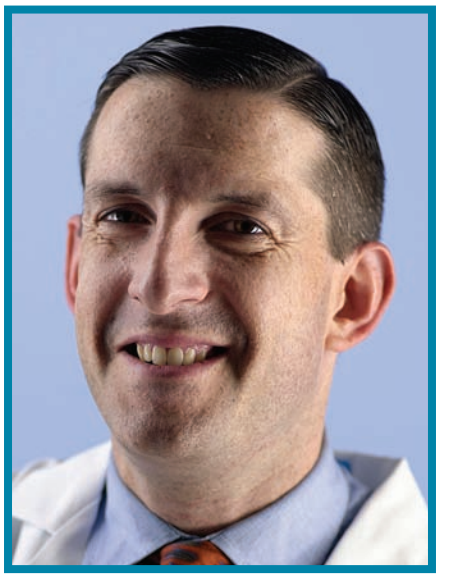
"Age, in and of itself, does not necessarily equal a poorer response or prognosis to treatment with newer disease modifying drugs. There are differences between patients, but it has become clearer that if you treat older CML patients as aggressively as younger patients, they fare just as well," he said, adding that the new study should serve as a model for other survival studies involving newer molecular-targeted cancer therapies in recognizing that in older patients, there are competing health risks not necessarily related to their cancer.

Nonetheless, getting large study populations for cancers like CML is difficult, as is acquiring accurate cause-of-death data, he explained.

"If a CML patient dies overnight while an internist is on duty and they have to fill out the death certificate, do they write down that the patient died of leukemia or of infection or bleeding? It's a judgment call, and usually leukemia is cited as the cause. Or say a patient is struck by a car and killed while they are crossing the street—Is the cause of death the accident or did they become confused because of an intracerebral hemorrhage due to their disease?"

Usually the cause of death is listed as the accident rather than the disease, he noted.

"Getting accurate cause-of-death data is always tricky, and that makes mortality studies even more challenging.



MIKKAEL SEKERES, MD, MS, said that the study should serve as a model for other survival studies involving newer molecular-targeted cancer therapies in recognizing that in older patients, there are competing health risks not necessarily related to their cancer.

"What this study does is underscore the importance of our need to revisit and modify existing prognostic systems for evaluating new molecular-based therapeutics to include better mortality data."

Earlier Data Confirmed

The findings are similar to those made in 2003 in a smaller study published in Cancer

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Advanced Lung Cancer: ASCO Issues 'Provisional Clinical Opinion' Recommending EGFR Mutation Testing Before Use of First-Line Targeted Drugs

The American Society of Clinical Oncology has issued a provisional clinical opinion (PCO) on the clinical use of epidermal growth factor receptor (EGFR) mutation testing to identify patients with advanced lung cancer who may benefit from tyrosine kinase inhibitors (TKIs) such as gefitinib (Iressa) and erlotinib (Tarceva).

The PCO, which is based on the results of five recent randomized clinical trials, recommends that patients with advanced non-small cell lung cancer (NSCLC) who are being considered for first-line therapy with an EGFR TKI should first have their tumor tested for EGFR mutations. Such testing is currently at both academic medical centers and some community medical centers.

A news release notes that an ASCO-convened panel examined evidence compiled through a review of the literature—in addition to suggestions by panel members—to develop the recommendation, which is published online in *JCO*.

"EGFR testing helps us move toward the goal of tailoring cancer treatments for each patient," said Panel Co-chair Vicki Keedy, MD, of Vanderbilt-Ingram Cancer Center. "We've learned over the years that NSCLC is really a collection of genetically distinct diseases. We want to treat patients with drugs that target the molecular drivers of their specific tumors, rather than using a one-size-fits-all approach. But how this approach affects overall outcome remains uncertain."

Clinical trials have shown that patients with EGFR mutations treated with first-line gefitinib and erlotinib benefit from the drugs in terms of response and progression-free survival, but not overall survival. Neither drug has FDA approval as first-line therapy for lung cancer.

The panel examined the use of EGFR mutation testing in first-line therapy for NSCLC in trials comparing an EGFR TKI with the standard chemotherapy of carboplatin and paclitaxel. ASCO information notes that the major impetus for the Provisional Clinical Opinion was IPASS, the Iressa Pan-Asian Study, a Phase III multicenter trial comparing gefitinib with standard carboplatin and paclitaxel as first-line treatment in patients in East Asia who had advanced NSCLC and were either non-smokers or light smokers.

ASCO asked the NCI's Physician Data Query (PDQ) Adult Cancer Editorial Board to assess the trial, which found that patients given gefitinib as initial therapy had longer progression-free survival than those receiving chemotherapy.

The IPASS trial found that among patients with negative tests for EGFR mutation, progression-free survival and response rates were greater in patients treated with chemotherapy, while patients with mutated EGFR had longer progression-free survival and higher response rates when treated with gefitinib.

ASCO notes that although the trial was conducted among Asian patients, the outcomes appear to be similar across populations. Four smaller studies examining the use of gefitinib (and in some cases, erlotinib) as first-line treatment reported similar results. None of the studies showed differences in overall survival between those who tested negative for EGFR mutations and those with mutations.

In its review, the panel acknowledged that erlotinib, which is approved in the United States as second-line therapy, is very similar to gefitinib, which has limited US approval for second-line therapy and is not readily available.

"Only a minority of patients with EGFR mutations respond to standard chemotherapy, and while there is some survival benefit, it's not as much as we'd like," said Panel Co-chair Giuseppe Giaccone, MD, PhD, Chief of the Medical Oncology Branch at the NCI. "We're finding that newer, molecularly targeted drugs like gefitinib and erlotinib are superior options for patients with EGFR mutations

"On the other hand, for patients who do not have the mutation, giving erlotinib upfront is not the right thing to do. It's not as efficacious for those patients, and we may be losing the opportunity to give chemotherapy, which clinical trials have demonstrated to be more effective."

Dr. Keedy stressed the importance of designing trials to determine whether first treating a patient who tested negative for an EGFR mutation with a TKI—which is very likely to be ineffective—delays chemotherapy and affects outcome.

Also still to be determined is whether outcome is affected for patients with an EGFR mutation who are given potentially ineffective chemotherapy and who don't immediately receive treatment with an EGFR TKI. The PCO pointed to several other research priorities, such as whether there are clinically significant differences between erlotinib and gefitinib among patients with EGFR mutations, since gefitinib is not FDA-approved in the United States.

Researchers would also like to know if outcome is affected for patients with an EGFR mutation who are given potentially ineffective chemotherapy, and don't immediately receive an EGFR TKI. The PCO pointed to several other research priorities, such as whether there are clinically significant differences between erlotinib and gefitinib among patients with EGFR mutations, since gefitinib is not FDA-approved in the US.

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by researchers at the University of Texas MD Anderson Cancer Center *(Cortes, Talpaz, O'Brien: Cancer 2003;98: 1105-1113)*.

In that study, 178 patients with newly diagnosed CML, including 49 patients 60 or older, were treated. The older patients had similar cytogenetic response rates and survival compared with younger patients at a median 16 months of follow-up. Age was not found to be an independent poor prognostic factor for survival or response to treatment.

Lead author Jorge E. Cortes, MD, Professor of Medicine and Chief of the CML Section in the Department of Leukemia, told *OT* that the new study's longer follow-up period is important, but that the findings come as "no surprise" due to the experience of oncologists treating older CML patients.

"The effectiveness of treatment is already pretty well-known, based a little bit on what is already in the published literature and a lot from perception in the treatment community," he said.

JORGE E. CORTES, MD: "The effectiveness of treatment is already pretty well-known, based a little bit on what is already in the published literature and a lot from perception in the treatment community….We once used imatinib only after interferon failure, but now we use it at diagnosis. There is no surprise here, but it is always nice to see that confirmation over a longer period has now been published."

Transplants and interferon used to be the frontline treatments, but not in older patients due to risks of complications and other health issues.

"There has been little published data available about the effectiveness of imatinib as frontline treatment in older patients with early CML, but this new study helps to confirm its effectiveness—it is a straightforward analysis," Dr. Cortes said.

"Data on imatinib in later-stage CML in older patients is much less relevant today. We once used imatinib only after interferon failure, but now we use it at diagnosis. There is no surprise here, but it is always nice to see that confirmation over a longer period has now been published."

"Getting accurate cause-of-death data is always tricky, and that makes mortality studies even more challenging."