

‘Making a difference in cancer care’

Cancer care – clinical and supportive – was front and center at the 2017 annual meeting of the American Society of Clinical Oncology in Chicago, where reported findings for a number of studies demonstrated improved survival outcomes for a range of tumors; enhanced patient quality of life; and the value for both providers and patients of drawing on patient-reported feedback.

Survival improves when patients with cancer self-report symptoms

Key clinical point Patients with metastatic cancer who self-reported symptoms experienced significant improvement in overall survival. **Major finding** Median overall survival with self-reporting of symptoms compared with usual care was 31.2 and 26 months, respectively. **Data source** A randomized controlled clinical trial of 766 patients. **Funding and disclosures** This study was supported by the National Institutes of Health and the Conquer Cancer Foundation of the American Society of Clinical Oncology. Dr Basch and Dr Burstein each reported having no disclosures.

Patients with metastatic cancer who self-reported symptoms during routine cancer treatment experienced a number of benefits, including a statistically significant improvement in overall survival, according to findings from a randomized, controlled clinical trial (see p. e184). The



DR BASCH

median overall survival in 441 patients receiving treatment for metastatic breast, lung, genitourinary, or gynecologic cancer who were randomized to the self-reporting intervention arm was more than 5 months longer (a nearly 20% increase) than in 325 patients receiving standard care (31.2 vs. 26 months), Ethan Basch, MD, of the Lineberger Comprehensive Cancer Center at the University of North Carolina, Chapel Hill, said at the meeting. “Another way to think of this is [in terms of] 5-year survival. At 5 years, 8% more patients were alive in the self-reporting group,” he said.

In addition, 31% of patients in the intervention arm had better quality of life/physical functioning, compared with those in the control arm, and 7% fewer patients in the intervention arm visited an emergency room during the study. The duration of potentially life-prolonging chemotherapy was increased by an average of 2 months in the intervention arm, he said (JAMA. 2017 Jun 4. doi: 10.1001/jama.2017.7156).

Symptoms such as nausea, pain, and fatigue are common among patients with metastatic cancer and can often go undetected by doctors and nurses until they become severe and physically debilitating, Dr Basch added, noting that patients are often hesitant to call the office between visits to report symptoms.

Dr Basch and his colleagues hypothesized that self-reporting of patient symptoms between visits or before a visit while the patient was in the clinic waiting area would prompt earlier intervention and improve symptom control and outcomes.

Study participants were patients at Memorial Sloan Kettering Cancer Center who had advanced solid genitourinary, gynecologic, breast, or lung tumors and who were receiving outpatient chemotherapy. Those assigned to the intervention group used tablet computers and an online web survey system to report on 12 symptoms commonly experienced during chemotherapy. The system triggers an alert to a nurse when a severe or worsening symptom is reported. Patients in the usual care group discussed symptoms during office visits and were encouraged to call the office between visits if they were concerned about symptoms.

Patients remained on the study until discontinuation of all cancer treatment, hospice, or death.

One possible explanation for the findings is that this self-reporting approach prompts clinicians to manage symptoms before they cause serious downstream complications, Dr Basch said.

The approach may also keep patients more physically functional, which is known from previous studies to have a strong association with better survival, and it may also improve management of chemotherapy side effects, enabling longer duration of beneficial cancer treatment. “In oncology, we often are limited in our ability to give life-prolonging treatment because people don’t tolerate it well,” Dr Basch explained.

“This approach should be considered for inclusion in standard symptoms management as a component of high-quality cancer care,” he concluded, noting that efforts are underway to test the next generation of systems to improve communication between

patients and care teams and to figure out how best to integrate these tools into oncology practice.

The system used in the this study was designed for research, but a number of companies have tools currently available for patient-reported outcomes, and others are being developed, Dr Basch said. A National Cancer Institute questionnaire, the PRO-CTCAE, is publicly available and can be loaded into patients' electronic health records for this purpose as well.



DR BURSTEIN

Harold J Burstein, MD, of Dana-Farber Cancer Institute, Boston, said the study findings validate the feeling among many clinicians that patient-focused, team-based care

can improve outcomes in a meaningful way for patients. If this were a drug ... it would be worth tens, if not hundreds of thousands, of dollars per year ... We don't have those same kinds of dollars to help implement these into our electronic health records or our systems. We need to find ways to support that and make it happen," he said.

— Sharon Worcester

TRK inhibitor shows 'striking' activity and durability across diverse cancers

Key clinical point Larotrectinib has good, durable efficacy when used to treat advanced cancers harboring TRK fusions.

Major finding The overall response rate was 76%, and 79% of responses were still ongoing at 12 months. **Data**

source An integrated analysis of phase 1 and 2 trials among 55 children and adults having 17 discrete types of advanced cancer with TRK fusions. **Funding and disclosures** Loxo Oncology funded the study. Dr Hyman disclosed that he has a consulting or advisory role with Atara Biotherapeutics, Chugai Pharma, and CytomX Therapeutics, and that he receives research funding from AstraZeneca and Puma Biotechnology.

Larotrectinib, an oral inhibitor of tropomyosin receptor kinase (TRK), has durable efficacy across diverse adult and pediatric cancers that harbor a genetic aberration known as TRK fusion, according to findings from an analysis of 3 trials reported at the meeting (see p. e184). Fusion of a TRK gene with an unrelated gene leads to uncontrolled signaling in the TRK pathway, potentially causing tumor growth and addiction to this input, David Hyman, MD, chief of early drug development at Memorial Sloan Kettering Cancer Center in New York, explained in a press briefing.

"One of the defining features of TRK fusions is that they are not just found in one cancer type, but in dozens of different cancer types, and not just in adults, but children as well, spanning the entire lifetime of the person," he noted. They are rare in common cancers and nearly universal in certain uncommon cancers; collectively, they are present in

possibly 5,000 cancers diagnosed each year in the United States.

Dr Hyman and his colleagues analyzed data from 55 patients having 17 discrete types of advanced cancer harboring TRK fusions who were treated with larotrectinib in phase 1 and 2 trials. Results showed an overall response rate of 76%, and the majority of responses were still ongoing at 12 months. "I believe these data support larotrectinib as a potential new standard of care for these patients," he said. "However, I want to emphasize that really recognizing this benefit in the community will require that we test patients more universally for the presence of TRK fusions or other tumor-agnostic biomarkers, such as microsatellite instability."



DR HYMAN

Study details

The investigators analyzed data from 3 trials in which patients with advanced TRK fusion-positive solid cancers received larotrectinib (LOXO-101): a phase 1 trial among 8 adult patients, a phase 1/2 trial among 12 pediatric patients (SCOUT), and a phase 2 "basket" trial among 35 adult and adolescent patients (NAVIGATE).

"These patients were identified by local testing," Dr Hyman noted. "We did not perform central screening to find the TRK fusions, and in fact, 50 different laboratories identified the 55 patients. So in a sense, this really represents the real-world identification of these patients."

In an integrated analysis, the overall rate of confirmed response as assessed by investigators was 76%, with complete response in 12% of patients and partial response in 64%. Two patients had such deep tumor regression that they experienced downstaging enabling them to undergo potentially curative surgery. Efficacy was consistent regardless of tumor type, which TRK gene was affected, and the fusion partner gene.

Median time to response was 1.8 months. "This is just a reflection of when the first scan was obtained. But in the clinic, patients reported dramatic improvement of their symptoms within days of starting therapy," Dr Hyman said.

With a median follow-up of 5.8 months, the median duration of response was not yet reached. In all, 79% of responses were still ongoing at 12 months. Median progression-free survival (PFS) was likewise not reached; the 12-month rate was 63%.

The leading treatment-emergent adverse events were fatigue (38%), dizziness (27%), nausea (26%), and anemia (26%). "This is an extremely well tolerated therapy with only 13% of patients requiring any form of dose modification and not a single patient discontinuing due to adverse events," he said.

It is not clear why some patients had apparent primary resistance to larotrectinib, but their TRK fusion test results may have been incorrect, Dr Hyman speculated. In all, 6 patients developed acquired resistance to larotrectinib; 5 of them were found to have an identical resistance mutation, and 2 went on to receive and have a response to LOXO-195, a next-generation TRK inhibitor that seems to retain activity in the presence of this mutation (Cancer Discov. 2017 June 3. doi: 10.1158/2159-8290.CD-17-0507).

TRK testing

Several next-generation sequencing-based tests already available clinically can pick up TRK fusions, Dr Hyman pointed out. “But it is important for the ordering physician to understand whether the tests they are ordering include fusion detection and, if it’s an option, to select it. Otherwise, they will not find TRK fusions. “The list price for these tests is in the low thousands of dollars,” he noted. In cancers in which sequential single-gene testing is already being done as standard of care, there is “minimal” incremental cost of instead using comprehensive testing that would detect TRK fusions.

Oncologists should be aware that obtaining test results can take weeks, Dr Hyman stressed. “This [testing] should be more broadly adopted and should be adopted at a point in the patient’s treatment [so that they] don’t become too sick, then don’t have an opportunity to be treated even when the test results come back positive.”

— Susan London

QoL preserved with ribociclib-letrozole for advanced breast cancer

Key clinical point Patients who took ribociclib plus letrozole had less pain and no drop in QoL compared with letrozole alone. **Major finding** QoL was sustained and pain scores decreased when ribociclib was added to letrozole for patients with advanced breast cancer. **Data source** Double-blind, placebo-controlled phase 3 trial of letrozole plus ribociclib compared with letrozole plus placebo in 668 patients with advanced hormone receptor-positive, HER2-negative breast cancer. **Disclosures** Dr Verma reported financial relationships with Novartis, which markets ribociclib, and other firms.

Patients with advanced breast cancer whose aromatase inhibitor therapy was supplemented with a cyclin-dependent kinase inhibitor had better PFS with no drop in quality of life (QoL). Health-related QoL for patients on the combination therapy was equivalent to that of patients on monotherapy in most aspects, but patients receiving both therapies had a sustained and clinically meaningful decrease in pain.

In addition, the time to definitive deterioration by 10% or more of the global health status/QoL scale score was similar between treatment arms (hazard ratio [HR], 0.944;

95% confidence interval, 0.720-1.237).

The MONALEESA-2 trial had previously shown that the CDK4/6 inhibitor ribociclib, when added to the aromatase inhibitor letrozole, significantly improved PFS for postmenopausal patients with hormone receptor-positive, HER2-negative advanced breast cancer, when compared with letrozole in combination with placebo.

Sunil Verma, MD, reported on health-related QoL and symptoms in the 2 arms of MONALEESA-2, showing change from baseline, time to a definitive 10% deterioration, and the mean scores for on-treatment time compared with end of treatment on the global health-status QoL subscale of the European Organization for Research and Treatment of Cancer’s (EORTC’s) 30-item core QoL questionnaire.

“During treatment, overall health-related quality of life was maintained from baseline and was similar in both arms,” said Dr Verma, the study’s first author. Changes during treatment were not statistically significant, and did not reach the predetermined threshold for a clinically meaningful difference. The effect of key symptoms such as fatigue, nausea, and vomiting on QoL was similar for patients receiving ribociclib or placebo, he said. Although symptom scores were slightly higher for patients in the active arm of the study, the results were not clinically significant.

Reporting validated, cancer-specific patient-reported outcomes from the trial, Dr Verma, professor and head of the department of oncology at the University of Calgary in Alberta, Canada, sought to “highlight the patient experience with a focus on health-related quality of life and symptoms,” he said during his presentation at the meeting. “A clinically meaningful – more than 5 points – improvement from baseline in pain score was maintained up to and including cycle 15 in the ribociclib plus letrozole arm.” The placebo arm had a mild, clinically insignificant improvement at most assessment points. For both treatment arms, pain scores increased a bit above baseline levels at the time of disease progression or end of therapy, he said.

Patients completed the EORTC 30-item core QoL questionnaire at their screening visit, and then every 8 weeks for the first 18 months. Then, they completed the questionnaires every 12 weeks until they experienced disease progression, died, were lost to follow-up or withdrew from the study, or stopped treatment.

Statistical analysis of the questionnaire results took into account the patients’ baseline scores, treatments received, and how they were stratified. Investigators assessed both statistical significance and the clinical meaningfulness of changes, defined as a change of 5-10 points.

In MONALEESA-2, 334 patients each were allocated to the ribociclib-letrozole arm and the placebo-letrozole arm. Patients in both arms, said Dr Verma, were very compliant with questionnaire completion. More than 90% of patients who were eligible completed questionnaire through cycle

19 of ribociclib or placebo. He explained that the overall numbers completing the questionnaire declined with time, as more patients had disease progression. Dr Verma said it is important to include those measures, because patients and their families care about “the quality of the time gained,” so patient-reported outcomes should be a part of risk-benefit assessments for new cancer therapies. “While delaying disease progression may help maintain patient quality of life, the addition of novel treatments to existing therapies can add toxicities, which may diminish quality of life,” he said.

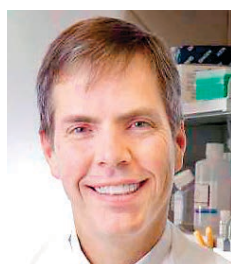
— Kari Oakes

Ibrutinib and beyond: optimizing therapy in relapsed CLL

Key clinical point Ibrutinib had durable efficacy in relapsed CLL, and combinations with other targeted agents or with CAR-T cells are promising. **Major finding** Long-term PFS was better with ibrutinib than with ofatumumab (HR, 0.133). The overall response rate with the triplet of ibrutinib, ublituximab, and umbralisib was 100%. In all, 89% of patients achieved no evidence of disease in marrow when anti-CD19 CAR-T cells were added to ibrutinib. **Data source** An update of a phase 3 randomized trial among 391 patients with previously treated CLL or SLL (RESONATE). A phase 1/1b trial including 19 patients with mainly relapsed or refractory CLL or SLL. A pilot trial among 10 patients with previously treated, mainly higher-risk, CLL or SLL. **Disclosures** See article text.

Ibrutinib monotherapy

In the phase 3 randomized RESONATE trial, investigators compared ibrutinib with ofatumumab, an anti-CD20 antibody, among 391 patients with CLL or small lymphocytic lymphoma (SLL), with crossover allowed. Initial results favored ibrutinib.



DR BYRD

Investigators led by John C. Byrd, MD, director of the division of hematology at the Ohio State University Comprehensive Cancer Center in Columbus, reported updated data in a poster session at the meeting, now with a median 44 months of follow-up in the ibrutinib arm.

Median PFS was not reached with ibrutinib, compared with 8.1 months with ofatumumab (HR, 0.133). The 3-year rate of PFS for ibrutinib and ofatumumab was 59% and 3%, respectively.

The pattern was generally similar across patients stratified by cytogenetics (deletion of 17p, deletion of 11q, or neither), IGHV and TP53 mutation status, and previous lines of therapy, reported Dr Byrd. The 3-year overall survival rate for ibrutinib was 74%. In analyses adjusted for crossover, patients given the inhibitor had a markedly lower risk of death than did peers given the antibody (HR, 0.37).

The overall response rate with ibrutinib was 91%. Although the rate of complete response increased with follow-up, it was still just 9%.

The most common grade 3 or worse adverse events were neutropenia (23%), pneumonia (17%), and anemia, thrombocytopenia, and hypertension (8% each). Major hemorrhage was reported in 2 patients (1%) in the ibrutinib group, and 3 (2%) in the ofatumumab group.

The investigators emphasized that these long-term results “show that extended treatment with ibrutinib is tolerable and continues to show sustained PFS in previously treated patients with CLL regardless of high-risk cytogenetics, adding that traditional poor prognostic factors for survival with chemoimmunotherapy, including del(17p) and del(11q), were not significant factors predictive of PFS outcomes with ibrutinib.

Funding and disclosures: Pharmaclics funded the trial. Dr Byrd disclosed that he receives research funding from Pharmaclics and other companies.

Ibrutinib plus ublituximab and umbralisib

Investigators led by Loretta J. Nastoupil, MD, tested a triplet consisting of ibrutinib with ublituximab (another anti-CD20 antibody) and umbralisib (TGR-1202), an oral PI3 kinase-delta inhibitor, in a phase 1/1b trial of 38 patients with generally heavily pretreated leukemias and lymphomas, including 20 with CLL or SLL. Notably, 8 patients with CLL (50%) had a 17p or 11q deletion.

The median time on study was 11.1 months, reported Dr Nastoupil, of the department of lymphoma/myeloma at the University of Texas MD Anderson Cancer Center, Houston. The overall response rate for the 19 evaluable patients with CLL or SLL was 100% (complete response in 32%, partial response in 68%). The main grade 3 or 4 adverse events in the entire trial population were neutropenia (18%) and pyrexia (8%). Only two patients discontinued treatment because of adverse events.

“An expansion cohort is ongoing at the highest dose, and we will clearly need more patients treated and longer follow-up to really know the efficacy,” commented invited discussant Jennifer R. Brown, MD, PhD, director of the Chronic Lymphocytic Leukemia Center at the Dana-Farber Cancer Institute in Boston.

Funding and disclosures: TG Therapeutics funded the trial. Dr Nastoupil has received honoraria and research funding from TG Therapeutics, and honoraria from Pharmaclics.

Ibrutinib plus CAR-T cells

Investigators in a pilot trial led by Saar Gill, MD, PhD, of the hospital of the University of Pennsylvania in Philadelphia, tested the combination of ibrutinib with chimeric antigen receptor-T cells (CAR-T cells) against CD19, on the basis of preclinical evidence of synergy. The trial participants were 10 patients with CLL or SLL who

had not achieved complete response with ibrutinib. All had a 17p deletion or a p53 mutation, or a complex karyotype, and some had a known ibrutinib resistance mutation.

At 3 months, 8 of 9 evaluable patients (89%) had no evidence of disease in bone marrow, reported Dr Gill. Seven patients (78%) achieved a complete or partial radiographic response in the spleen and lymph nodes. Overall, the treatment was well tolerated. One patient developed grade 4 tumor lysis syndrome, and two developed grade 3 cytokine release syndrome. But, none required anticytokine therapy.

Most patients remain on ibrutinib and are being monitored. In addition, the researchers plan to treat 25 more patients with the same combination.

Funding and disclosures: Novartis funded the trial. Dr Gill disclosed that he receives research funding from Novartis (institutional) and has patents for CAR-T cells for AML.

— Susan London

Pazopanib falls short as adjuvant therapy for high-risk RCC

Key clinical point Pazopanib is not efficacious for treating resected high-risk locally advanced RCC. **Major finding** Compared with placebo, pazopanib started at 600 mg daily did not significantly reduce the risk of DFS events (HR, 0.86; $P = .16$). **Data source** A phase 3 randomized controlled trial among 1,538 patients who had undergone nephrectomy for high-risk locally advanced RCC (PROTECT trial). **Disclosures** Novartis Oncology funded the trial. Dr Motzer disclosed that he is a consultant to Novartis and receives research funding from Novartis (institutional).

The antiangiogenic agent pazopanib is not efficacious when used as adjuvant therapy for resected renal cell carcinoma (RCC) with features that confer a high risk of recurrence, investigators in the PROTECT investigators reported at the meeting. “The trial did not meet its primary endpoint,” concluded lead investigator Robert J Motzer, MD, of Memorial Sloan-Kettering Cancer Center in New York. “Pazopanib is not recommended for adjuvant therapy following resection of locally advanced RCC.”

Adjuvant use of other agents in this class has yielded mixed results, Dr Motzer noted, citing the earlier ASSURE trial found that neither sunitinib nor sorafenib improved disease-free survival (DFS) or overall survival (Lancet 2016;387:2008-2016), and the S-TRAC trial that found that sunitinib improved DFS (N Engl J Med. 2016;375:2246-2254).

Pazopanib is an oral multitargeted tyrosine kinase inhibitor active against the vascular endothelial growth factor receptor (VEGFR). The PROTECT trial included 1,538 patients with resected pT2 (high grade), pT3, or greater nonmetastatic clear cell RCC, a highly vascular tumor typically reliant on aberrant signaling in the VEGF pathway.

The patients were assigned evenly to receive pazopanib or placebo for 1 year. The starting dose was lowered from 800 mg daily to 600 mg daily (with escalation permitted) after 403 patients had been treated.

In intention-to-treat analysis among patients started on the 600-mg dose and having a median follow-up of about 31 months, DFS was better with pazopanib but not significantly so (HR, 0.86; $P = .16$). In secondary analyses, pazopanib had a significant DFS benefit in patients started on the 800-mg dose (HR, 0.69; $P = .02$) and among the entire trial population started on either dose (HR, 0.80; $P = .01$).



DR. MOTZER

One possible explanation for the differing results seen with the 2 doses was the difference in follow-up, because the 800-mg group was treated earlier in the trial, said Dr Motzer. But with an additional year of blinded follow-up, the benefit in the 600-mg group diminished, but not in the 800-mg group.

Another possibility was the somewhat better performance of the placebo group used for comparison with the lower dose: the 3-year DFS rate with placebo was 64% for the 600-mg comparison but 56% for the 800-mg comparison. “One factor that could explain differences in the outcomes of the placebo groups includes unidentified patient demographic characteristics,” Dr Motzer added.

Overall survival was statistically indistinguishable between the pazopanib and placebo groups, regardless of dose. However, “the results are inconclusive as the data are not yet mature,” he said, with a definitive analysis planned for 2019.

Patients started on the 600-mg dose of pazopanib had a higher rate of grade 3 or 4 adverse events overall compared with those given placebo (60% vs 21%, respectively), driven in part by higher rates of hypertension and increased alanine aminotransferase levels. “Although the intent of modifying the protocol dose of pazopanib from 800 mg to 600 mg was to reduce the rate of discontinuation and improve the safety profile ... both cohorts had similar discontinuation rates and safety profiles,” Dr Motzer noted.

A QoL analysis for the 600-mg group using the 19-item Functional Assessment of Cancer Therapy Kidney Symptom Index showed values were consistently lower with the drug than with placebo during treatment, with a crossing of the threshold for a minimally important difference at week 8. Pharmacokinetic analyses from the trial, reported in a poster at the meeting, showed that in the group starting pazopanib at 600 mg, DFS was longer in patients who achieved higher drug trough concentrations at week 3 or 5.

— Susan London