The Utility of FDG-PET in the Treatment of Hodgkin Lymphoma

BY RICHARD SIMONEAUX

The last few decades have seen Hodgkin lymphoma (HL), which had been a frequently fatal malignancy, become a disease which is often curable using modern frontline and salvage therapies. Despite the successes noted in the treatment of HL, the therapies utilized have many toxicities associated with them. Consequently, researchers have sought a means to guide therapy and differentiate those patients for whom more vigorous chemotherapy is necessary from those who may only require limited treatment.

One imaging modality which has been employed in the treatment of patients with HL is FDG-PET (2-deoxy-2-(18F)fluoro-D-glucose positron emission tomography). In this technique, more metabolically active malignant... Continued on page 11

Breast Cancer at ESMO: Gaudy & Gaudi

BY GEORGE W. SLEDGE, JR., MD

The European Society of Medical Oncology’s 2019 Annual Meeting, held in Barcelona, had several interesting themes related to breast cancer. First and foremost, the CDK 4/6 inhibitors held sway. But there were also interesting stories related to novel immuno-oncology approaches to triple-negative breast cancer. While perhaps not immediately applicable, these were provocative and may show the way forward for this continuing unmet medical need. Finally, a further update on the TAILORx trial examined the fate of patients with a high Oncotype Dx recurrence score.

Let us begin with the CDK 4/6 inhibitors. Two large, randomized controlled trials presented overall survival data, and the news here is good. MONARCH 2 is a trial in ER-positive, HER2-negative endocrine therapy-resistant advanced breast cancer that randomly assigned patients in a 2:1 fashion to either abemaciclib plus fulvestrant or placebo plus fulvestrant. (As a conflict-of-interest statement, I was the principal investigator for this trial and had the pleasure of presenting the data in Barcelona.) MONARCH 2 now has fairly extensive follow-up (approaching a median of 4 years at data cut-off) and has a... Continued on page 10

ASH 2019: What to Know About This Year’s Conference

BY SARAH LACORTE

The 61st ASH Annual Meeting and Exposition will be held in Orlando, Fla., Dec. 7-10, 2019. Attendees will have access to thousands of scientific abstracts highlighting cutting-edge research in hematology. This conference is an opportunity to enhance your practice through educational programs while networking with leaders in the field. Check out highlights from the upcoming conferences to help you make the most of your time at ASH.

Program Details

Attendees will have a plethora of educational programs at their disposal:
- Scientific Spotlight Sessions
  - Monday, Dec. 9: Redox Biology in Thrombosis
  - Education Spotlight Sessions
  - Sunday, Dec. 8: Point-Counterpoint: Curative Therapies for SCD - Does it Make More Sense to Target the Root Cause Than All the Downstream Events
  - Monday, Dec. 9: Molecular Hematopathology Tumor Board
  - Monday, Dec. 9: Diving Into Rare Childhood Leukemias
  - Monday, Dec. 9: Is Chemoimmunotherapy for CLL on Life Support? (Point-Counterpoint)
  - Monday, Dec. 9: Street Drugs: Emerging Hematologic Complications of Illicit Drug Use
- Continuing Conversations With the Speakers
  - Saturday, Dec. 7: Genome Editing for Transplantation and Cellular Therapies... Continued on page 17
statistically significant (p = .0137) and clinically relevant improvement in overall survival, with a 9.4 month increase from 37.3 to 46.7 months. Pleasingly, benefit was seen in both patients with visceral metastasis and patients with primary endocrine therapy resistance, both previously tough groups to treat. Toxicity is similar to that reported at the initial progression-free survival presentation at the 2017 ASCO meetings, with the exception of an emerging signal for interstitial lung disease and deep venous thrombosis, both fortunately relatively rare events.

Immediately after the presentation of MONARCH 2, Dennis Slamon, MD, PhD, of UCLA (this year’s Lasker Award winner for his groundbreaking HER2 work) presented the results of the MONALEESA 3 trial. Similar to MONARCH 2, this trial randomly assigned patients to either ribociclib plus fulvestrant or placebo plus fulvestrant. The trial differed from MONARCH 2 in a number of ways: MONALEESA 3 was limited to postmenopausal patients (MONALEESA 7 having previously focused on premenopausal women), and patients could be receiving either first-line or early–relapse plus second-line therapy, unlike MONARCH 2’s requirement for endocrine therapy resistance.

Though the data are still emerging (follow-up on this trial is a median 39.4 months), a clear survival advantage was seen in MONALEESA 3. Median survival was 40 months in the control group and has not yet been reached in the combination arm, but a landmark analysis at 42 months shows a 58.2 percent overall survival in the combination arm versus a 45.9 percent rate in the control arm. Survival benefits were seen in both the first- and second-line settings.

So where are we now with the CDK 4/6 inhibitors? We now have overall survival data from several trials in addition to the two just presented. MONALEESA 7, the premenopausal frontline metastatic ribociclib trial, has demonstrated an overall survival advantage. PALOMA 3 has demonstrated a survival advantage in the endocrine therapy-sensitive population for palbociclib plus fulvestrant (though, disappointingly, not in the endocrine-therapy resistant population). Overall the trend from emerging data is clear: CDK 4/6 inhibitors improve both progression-free and overall survival, and by clinically meaningful amounts. I find it reasonable to consider these standard treatment options for patients receiving endocrine therapy for advanced breast cancer. I’m still not certain that any of the three CDK 4/6 inhibitors has a clear advantage over any of the others; trial outcome differences may reflect the differing populations enrolled rather than differences in drug efficacy.

That is not to say that we have answered all the questions we might ask regarding this class of drugs. We still await the overall survival results from several phase III trials, which will add to our knowledge regarding the relative benefits of these agents. We have just scratched the surface in terms of studies of mechanisms of resistance. We do know whether there will be important efficacy differences between these agents, though there are clearly differences with regard to toxicity. Currently attempts to compare these drugs from an efficacy standpoint rely on cross-study comparisons, and such comparisons are dangerous given the different enrollment criteria and patient populations treated on these trials. And we do not have any good sense, other than an anecdotal one, whether crossover from one CDK 4/6 inhibitor to another upon progression will provide benefit. This will depend, of course, on whether these agents have common resistance mechanisms. And the biggest question of all: will these agents, which have now proven their worth in advanced breast cancer, improve disease-free survival in the adjuvant setting, increasing the likelihood of cure?

We think of CDK 4/6 inhibitors primarily in terms of estrogen receptor–positive, HER2-negative breast cancer. But preclinical data suggests that some of the combination of HER2-targeted therapy with CDK 4/6 inhibition may prove synergistic in HER2-positive breast cancer. This has led to the use of these agents in clinical trials for advanced, drug-resistant HER2-positive breast cancer; one of these, monarchHER, was presented at the meeting by Sara Tolaney, MD, MPH, of Dana-Farber Cancer Institute.

The monarchHER trial was a randomized phase II study that enrolled hormone receptor–positive, HER2-positive patients who had received at least two prior HER2-directed therapies, one of which must have been T-DM1. A total of 237 patients were randomized to either abemaciclib plus trastuzumab plus fulvestrant (Arm A), abemaciclib plus trastuzumab (Arm B), or trastuzumab plus the investigator’s choice of chemotherapy. The trial’s primary endpoint was progression-free survival. There was a statistically significant improvement in PFS comparing Arm A and Arm C, with a delta of 2.6 months. Overall response rate was also improved comparing Arm A to Arm C (35.7% vs. 15.9%).

These results are not stunning. But are they the beginning of something new in the HER2 space? Expecting a great deal in third-line or greater advanced HER2-positive breast cancer may be asking too much for any drug. Might the combination have shown greater activity in an earlier line of therapy? Perhaps we’ll see.

**Triple-Negative Breast Cancer**

The other great area of interest for breast cancer at this year’s ESMO involved triple-negative breast cancer. The recent approval of atezolizumab in combination with nab-paclitaxel for PD-L1-positive frontline metastatic breast cancer, based on the Impassion130 trial, was one of the first steps forward in many years for this difficult-to-treat disease.

This year’s ESMO meeting saw another interesting take on immunotherapy for triple-negative breast cancer, this time in the neoadjuvant setting. Peter Schmid, MD, PhD, of the Barts Cancer Institute, presented the results of the KEYNOTE-522 trial, wherein patients with newly diagnosed TNBC with either T1CN+ or T2-4 Nx disease, regardless of PD-L1 status, were randomly assigned to receive either neoadjuvant carboplatin plus paclitaxel followed by anthracycline (doxorubicin or epirubicin) plus cyclophosphamide, with either concomitant checkpoint inhibition with pembrolizumab 200 mg q3w or a placebo. Patients then underwent surgery, and patients in the pembrolizumab arm continued therapy for another nine 3-week cycles.

The primary trial endpoint, pathologic complete response, favored the addition of pembrolizumab, with a pCR rate of 64.8 percent versus 51.2 percent (p = 0.00055). Benefit was seen whether or not a patient was PD-L1-positive. Interestingly, looking just at the control arm of the study, PD-L1-positive patients have a higher pCR rate to chemotherapy than to their PD-L1-negative colleagues (34.9% vs. 30.3%). This implies that (similar to studies of tumor infiltrating lymphocytes in the adjuvant TNBC setting) the immune system plays an important role in response to chemotherapy.

What do we do with this data? The FDA recognizes pathologic complete response as a valid surrogate for drug approval in breast cancer. Is the 13.6 percent difference in pCR rate seen in KEYNOTE-522 not just statistically significant but clinically important? Should pembrolizumab be considered the new standard of care in the neoadjuvant triple-negative breast cancer setting?

It is an important question. The use of pathologic complete response rates as a surrogate for clinical benefit has proven controversial. A basic question—namely “what increase in pCR rate is needed to give what improvement in distant disease-free survival?”—is unanswerable when one crosses over into a novel therapeutic realm. Checkpoint inhibitors are toxic, expensive drugs, so we might wish for further follow-up in KEYNOTE-522 (event-free survival is still immature) before declaring victory.

And what do we make of the unimportance of PD-L1 as a biomarker for neoadjuvant pembrolizumab? In the metastatic TNBC setting, biomarker-negative patients failed to benefit from atezolizumab. Is the neoadjuvant setting different from the adjuvant setting?
A Predictive Tool
Regarding the utility of FDG-PET as a means for predicting patient outcomes, Bair commented, “As early as 2005, studies began to demonstrate the substantial predictive utility of interim FDG-PET in HL. One of the first prospective studies to document the predictive utility of interim FDG-PET was the previously mentioned study by Galamini and colleagues in 2007, which reported on outcomes in patients primarily with advanced stage HL.

“They found 2-year PFS rates of 95 percent and 13 percent in patients with interim PET-negative and PET-positive disease, respectively, after 2 cycles of therapy. In fact, FDG-PET even demonstrated superiority over the conventional IPS in predicting progression-free survival.”

Challenges in FDG-PET Use
“The use of FDG-PET is not without its challenges,” Bair noted, “especially in the context of response-adapted treatment. Clinicians who regularly use FDG-PET in the evaluation of patients with HL know that FDG uptake due to inflammation, infection, or other process can commonly produce false-positive results, thereby complicating interpretation. In addition, HL is unique among other types of lymphoma because the malignant Hodgkin-Reed-Sternberg cells usually comprise only 1-2 percent of the tumor.”

Further highlighting the difficulties with this modality, Bair noted, “One recent systematic review by Adams and colleagues reported that, among lesions found to be FDG-avid on interim or end-of-treatment scans and subsequently biopsied, only about 50 percent were confirmed to have active malignancy (Eur J Haematol 2016;97(9):491-498). Conversely, a negative interim FDG-PET doesn’t perfectly predict cure—5-10 percent of patients with early-stage HL and 10-20 percent of patients with advanced stage disease and a negative interim PET scan will go on to relapse.

“Interpreting the use of additional biomarkers into response assessment and risk stratification will likely result in greater predictive accuracy, thereby overcoming or minimizing some of these limitations.”

Immunotherapies & FDG-PET
“HL is known to be a disease associated with immune dysregulation and immunotherapy has already been demonstrated to play an important role in the treatment of this disease,” Bair stated.

Two prominent immunotherapies for the treatment of classical HL (cHL) are the checkpoint inhibitors nivolumab and pembrolizumab. In May 2016, nivolumab was granted accelerated approval by the FDA for the treatment of patients with cHL who have relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin therapy. For pembrolizumab, the FDA granted accelerated approval in March 2017 for the treatment of adult and pediatric patients with refractory cHL, or those who experienced relapse after three or more previous lines of therapy.

“The incorporation of immune therapies such as PD-1 inhibitors into the treatment of HL introduces additional complexity into the interpretation of FDG-PET treatment response,” Bair commented. “These therapies are associated with well-known radiographic phenomena: delayed response and pseudo-progression.

“The Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC), which have recently been developed by Cheson and colleagues, provide some guidance in differentiating pseudo-progression from true progression (Blood 2016;128(21):2489-2496); however, additional prospective validation will be important,” he noted.

Future Directions
When queried about the future prospects of FDG-PET for guiding HL therapy, Bair replied, “Certainly for the foreseeable future, FDG-PET will remain an important tool in the assessment of treatment response and risk prediction in patients with HL. The anatomic, functional, and prognostic information provided by FDG-PET cannot be captured with any other currently available modality and for this reason, it will remain an essential tool in the near future.”

“As previously mentioned, FDG-PET is limited in terms of resolution (resulting in false-negative results), as well as specificity (resulting in false-positive results, for example, in the setting of benign inflammation or infection). Therefore, the most important advance in the coming years will be to combine the results of FDG-PET imaging with additional clinical data, such as circulating tumor DNA levels, to provide a more robust understanding of disease burden, treatment response, and prognosis in each individual patient.”

Regarding other potentially useful applications of FDG-PET, Bair stated, “Additional approaches to characterizing disease burden and response with this modality have been developed; one such method is total metabolic tumor volume. These methods might provide additional prognostic information for patients and clinicians, and some studies have suggested that total metabolic tumor volume might outperform more conventional staging systems (i.e., IPS) in predicting outcomes. However, further validation is required before this parameter can be incorporated into routine clinical practice.”

Richard Simoneaux is a contributing writer.

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or is atezo different than pembrolizumab? We still have a great deal to learn. Biomarkers have always been tricky, and PD-L1 is no different. Hope Rugo, MD, of UCSF revisited Impassion 130 through the lens of PD-L1, looking at three different immunohistochemical measures of PD-L1, analyzing their analytical concordance with each other and estimates of clinical activity.

To cut to the chase, concordance was not great (64% and 69%, respectively, vs. the SP-142 assay used in the trial). As a medical oncologist, I rarely think about what antibody is used to perform immunohistochemistry on the tissues we send to the lab. But assay accuracy clearly matters, and one wonders how much of the differences one sees in clinical trials (or in the real world of the clinic) is a function of variable or imperfect testing.

Revisiting TAILORx
Finally, Joseph Sparano, MD, at Albert Einstein College of Medicine, gave an update on the TAILORx trial. TAILORx is the gift that keeps on giving for those interested in genomic assays in patients with lymph node-negative, ER-positive breast cancer. The ESMO 2019 data focused on patients with a high Oncotype DX recurrence score (defined as a recurrence score of 26 or above). Patients entering TAILORx with a high recurrence went into a registry and were encouraged to receive chemotherapy, which most did, with a grab bag of chemotherapy regimens, followed by endocrine therapy. With 5-year median follow-up on 1,389 patients, freedom from distant recurrence was 93 percent, a better-than-expected result and an improvement on older 1980s-era NSABP results. This presentation, like the earlier abemaciclib paper, was simultaneously published in JAMA Oncology (2019; doi:10.1001/jamaoncol.2019.4794).

So that was the news from Barcelona, that lovely Catalan city on the western edge of the Mediterranean. Barcelona is architecturally famous for the work of Antoni Gaudi, and his Sagrada Familia Basilica, one beautifully weird piece of work, remains unfinished more than a century after the foundation stone was laid: the Catalans seem constitutionally incapable of finishing the work. It could be a metaphor for breast cancer research: a strange, often other-worldly, yet highly valuable task that never seems quite finished. But we may hope that both the basilica and breast cancer are getting closer to completion.”

Richard Simoneaux is a contributing writer.