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ONCOLOGY & HEMATOLOGY

MEETING REPORT

ASCO 2017

Summaries of new research from the world's largest oncology conference

At this year's annual meeting of the American Society of Clinical Oncology (ASCO 2017), investigators discussed the latest findings in cancer research. The editors of *NEJM Journal Watch Oncology and Hematology* were on hand to report on new advances in breast cancer, genitourinary cancer, lung cancer, gastrointestinal cancer, and malignant hematology. Abstracts can be viewed in the ASCO meeting abstracts library (http://abstracts.asco.org/199/CatView_199_S.html). **— *The Editors,* NEJM Journal Watch Oncology and Hematology**

Breast Cancer

Highlights of the latest treatments

Abemaciclib for HR-positive/HER2-Negative Metastatic Breast Cancer

The approach to treating patients with ER-positive metastatic breast cancer has changed in the last couple of years with the adoption of strategies partnering endocrine therapy with targeted therapy, such as an mTOR inhibitor or CDK4/6 inhibitors. The approved CDK4/6 inhibitors, palbociclib and ribociclib, extend progression free-survival (PFS) for patients when combined with endocrine therapy versus endocrine therapy alone. These two CDK4/6 inhibitors are generally well tolerated, with asymptomatic neutropenia being the most adverse event.

Now, in the MONARCH 2 study (abstract 1000), Sledge and colleagues have evaluated the efficacy and safety of a third CDK4/6 inhibitor, abemaciclib, in patients with HR-positive, HER2-negative metastatic breast cancer who had disease progression on first-line endocrine therapy and who had not received chemotherapy. Patients were randomized to receive fulvestrant with or without abemaciclib.

PFS was prolonged with abemaciclib plus fulvestrant versus fulvestrant alone (16.4 vs. 9.3 months; $P<0.0000001$). The combination was generally well tolerated, but gastrointestinal symptoms were more common with abemaciclib than what was observed with palbociclib and ribociclib in other trials. Abemaciclib is likely to be the third CDK inhibitor approved in the near future, posing the challenge of how to optimally use these drugs.

Neoadjuvant Pembrolizumab for HER2-Negative Breast Cancer

Checkpoint inhibitors have demonstrated an anti-tumor signal in breast cancer in recent trials, but they have not been approved for breast cancer treatment despite being approved to treat other diseases, such as melanoma and lung cancer. Part of the challenge may be that breast cancer has a "middling" mutational load or expression of neo-antigens, compared with other malignancies.

The I-SPY platform incorporates an adaptive design in the neoadjuvant setting to quickly drop compounds that would appear to have limited success in a larger trial and to proceed with more promising drugs. This approach was used by Nanda and colleagues (abstract 506) to evaluate the role of the immune checkpoint inhibitor pembrolizumab combined with weekly paclitaxel versus paclitaxel alone prior to doxorubicin and cyclophosphamide in the neoadjuvant setting for patients with HER2-negative disease.

The pathological complete response (pCR) rate was higher for patients receiving pembrolizumab than for patients receiving paclitaxel alone (controls) among those with HER2-negative disease (46% and 16%, respectively) as well as among those with HER2-negative/ER-negative disease (60% and 20%) and HER2-negative/ER-positive disease (34% and 13%).

These results signal the promise of checkpoint inhibitors in patients with breast cancer in both the metastatic and adjuvant setting. Numerous trials with a variety of agents in the metastatic

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disease setting and the adjuvant setting are ongoing. All that remains to complete the story are the data.

Adjuvant Pertuzumab plus Trastuzumab for HER2-Positive Early Disease The provisional approval of pertuzumab (along with trastuzumab and chemotherapy) by the FDA in the neoadjuvant setting for patients with HER2-positive disease was based on a high pCR rate that was observed in clinical trials. To provide a definitive randomized clinical trial in the adjuvant setting, von Minckwitz and colleagues conducted the long awaited APHINITY trial (abstract LBA500), in which patients with early stage breast cancer were randomized postoperatively to chemotherapy with trastuzumab for 1 year or chemotherapy with both trastuzumab and pertuzumab for 1 year.

With follow-up of <4 years, patients receiving dual HER2 targeting with trastuzumab and pertuzumab had a superior PFS compared with those receiving trastuzumab alone (difference, 1.7%; P=0.045). The benefit of pertuzumab was observed across subgroups, but was greatest in patients with node-positive disease (difference, 3.2%) and in those with ER-negative disease (difference, 2.3%).

The addition of pertuzumab to adjuvant chemotherapy and trastuzumab may offer the greatest benefit for those with high-risk disease, whereas those with lower risk disease could avoid the addition of pertuzumab to their adjuvant regimen.

Olaparib for Patients with HER2-Negative *BRCA*-Mutated Disease PARP (poly ADP-ribose polymerase) inhibitors have been in development for several years and offer the prospect of a significant anti-tumor effect, particularly in *BRCA*-mutated tumors. PARPs bind to areas of DNA damage and set up the "scaffolding" to recruit other DNA repair enzymes. In tumor cells that already have DNA repair limitations due to a *BRCA* mutation, affecting other mechanisms of DNA repair with a PARP inhibitor can lead to cell death. The oral PARP inhibitor olaparib was reported in a small study (*Lancet* 2010; 376:235) to have anti-tumor activity as a single agent in *BRCA*-mutated, metastatic breast cancer (objective response rate, 41%).

Now, in the OlympiAD trial (abstract LBA4), Robson and colleagues evaluated the use of olaparib versus standard chemotherapy in patients with HER2-negative (ER-positive or triple-negative) breast cancer and a known or suspected *BRCA* mutation. Patients were required to have received prior anthracyclines and taxane therapy and up to two lines of prior chemotherapy in the metastatic disease setting.

PFS (the primary endpoint) favored olaparib versus chemotherapy (7.0 vs. 4.2 months; P<0.009). PFS also seemed to be better in patients who had not received prior platinum therapy. The objective response rate also favored olaparib (69% vs. 31%), but survival was similar with either treatment. Adverse effects of any grade with olaparib were manageable, with nausea, anemia, vomiting, fatigue, and neutropenia being most common. Based on these data, olaparib stands a good chance to be approved as the first PARP inhibitor for treatment of *BRCA*-mutated disease. Many other PARP inhibitors are also being developed as breast cancer therapies.

— William J. Gradishar, MD

Genitourinary Cancer

Highlights of the latest treatments for urothelial, renal cell, germ cell, and prostate cancers

Pembrolizumab for Cisplatin-Ineligible Advanced Urothelial Cancer Until recently, therapeutic options for cisplatin-ineligible patients with advanced urothelial cancer were limited. Carboplatin-based chemotherapy has been considered a standard of care, and recently atezolizumab received FDA approval for this patient population.

O'Donnell and colleagues reported results from the KEYNOTE-052 trial (abstract 4502), which evaluated the efficacy and safety of first-line therapy with the PD-L1 inhibitor pembrolizumab for 370 advanced urothelial cancer patients (median age, 74). All patients were deemed cisplatin-ineligible on the basis of renal function, performance status, grade 2 or higher neuropathy or hearing loss, or significant congestive heart failure.

Patients received standard-dose pembrolizumab every 3 weeks for 24 months

or until disease progression or intolerable toxicity. The primary endpoint was objective response rate; secondary and exploratory endpoints included biomarker correlative studies.

At median follow-up of 9.5 months, the objective response rate was 29%, and the complete response rate was 7%. With longer follow-up, the response rate increased 5%. The median duration of response had not been reached.

This large phase II experience provides additional assurance regarding the activity and safety of checkpoint inhibitor therapy. With the level 1 evidence of a survival benefit demonstrated in the KEYNOTE-045 trial, the role of pembrolizumab is firmly established as a standard of care in advanced urothelial cancer.

No Role for Pazopanib After Nephrectomy for Locally Advanced Renal Cell Cancer The lack of a role for adjuvant tyrosine kinase inhibitor (TKI) therapy for locally advanced renal cancer seemed to have been settled by the large negative U.S. Intergroup ASSURE study (*NEJM JW Oncol Hematol* May 2016 *and Lancet* 2016; 387:2008), in which patients with locally advanced renal cancer received the drug or placebo for 1 year. Although initially designed and powered to treat patients at 800 mg/day, the study was amended after accrual of 403 patients to administer a starting dose of 600 mg/day, and an additional 1135 patients were accrued. The primary objective was amended to test the impact of 600 mg/day on disease-free survival (DFS). Secondary objectives included quality of life and DFS of the entire patient population and those treated with 800 mg/day.

The primary objective of DFS in the 600 mg/day group was not met, and incidence of grade 3 or 4 toxicity was significantly greater with pazopanib than with placebo (60% vs. 21%). The investigators concluded that there is no role for pazopanib in the adjuvant setting. These results along with those of the ASSURE study suggest no routine role for adjuvant TKIs in locally advanced renal cancer.

PET Assessment of Residual Seminoma The management of postchemotherapy masses in patients with seminoma has evolved following retrospective evidence of the utility of positron-emission tomography (PET) imaging in lesions >3 cm. Typically, patients with masses <3 cm would be managed expectantly with intermittent computed tomography (CT) assessment.

To provide additional insight into the utility of PET imaging in this setting, Cathomas and colleagues used a large germ cell registry to retrospectively study 91 patients with metastatic seminoma and residual PET-positive lesions after chemotherapy (abstract 4521).

At a median follow-up of 29 months, the median time from the last day of chemotherapy to PET imaging was 7 weeks. Post-PET management involved repeated imaging in 51% of patients, resection in 35%, biopsy in 10%, and radiotherapy in 4%. Histology of the resected specimen identified necrosis only in 25 cases (78%) and vital seminoma in 7 cases (22%). No biopsy revealed viable seminoma. This analysis demonstrated that PET-positive, post-chemotherapy residual lesions were false-positive in about 75% of patients.

The utility of PET imaging for assessment of residual seminoma appears low. Therefore, routine CT scanning with most patients managed expectantly should be the standard of care.

Combination Therapy for Metastatic Prostate Cancer Investigators for the STAMPEDE and LATITUDE studies showed that combining androgen-deprivation therapy (ADT) with abiraterone plus either prednisolone or prednisone significantly improved survival in men with metastatic disease and that this combination should be adopted as the standard of care (for complete summaries of these published studies, see *NEJM JW Oncol Hematol* Jul 2017).

In the STAMPEDE study (abstract LBA5003), James and colleagues compared ADT alone or with abiraterone and prednisolone in 1917 patients with newly diagnosed, locally advanced, or metastatic disease who were starting ADT. At a median follow-up of 40 months, 3-year overall survival was significantly improved with combination therapy versus ADT alone, as was treatment-failure–free survival.

In the LATITUDE study (abstract LBA3), Fizazi and colleagues randomized 1199 patients with newly diagnosed, metastatic, castration-sensitive prostate cancer to receive ADT plus placebo or abiraterone and prednisone. At a median follow-up of 30.4 months, median OS was significantly longer in the abiraterone group than in the placebo group.

— Robert Dreicer, MD, MS, FACP, FASCO

Lung Cancer

Highlights of new treatments for patients with non–small-cell lung cancer and malignant pleural mesothelioma

Osimertinib for EGFR T790M-Mutated NSCLC Osimertinib, an oral, irreversible, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) with central nervous system (CNS) penetrance, is currently FDA-approved for patients with *EGFR* T790M-mutated NSCLC. The prior AURA3 trial by Mok and colleagues (*NEJM JW Oncol Hematol* Feb 2017), of whom 30 received osimertinib and 16 received chemotherapy.

Compared with chemotherapy, osimertinib was associated with a higher CNS objective response rate (ORR; 70% vs. 31%; odds ratio, 5.13; P=0.015), longer median duration of response (8.9 vs. 5.7 months), and greater median best percentage change from baseline (–43% vs. –16%). The CNS median progression-free survival (PFS) was prolonged with osimertinib (11.7 vs. 5.6 months; P=0.004) and was seen in patients with baseline CNS metastases (8.5 vs. 4.2 months, hazard ratio, 0.32; P<0.001) and in those without baseline CNS metastases (10.8 vs. 5.6 months; HR, 0.40; P<0.001). In the 7 patients with baseline leptomeningeal metastases, 2 had a complete leptomeningeal response with osimertinib and 2 had partial response.

This study demonstrates that osimertinib has good CNS penetrance and superior CNS efficacy compared with chemotherapy in refractory *EGFR*-mutated NSCLC. The osimertinib CNS response was rapid (~6 weeks), was protective against cumulative CNS progression, and can be effective against leptomeningeal disease. It is anticipated that osimertinib will likely change the *EGFR*-mutation space once results of the front-line FLAURA trial are known, and it will likely become the preferred front-line regimen.

Dacomitinib vs. Gefitinib for Advanced *EGFR*-Mutated NSCLC Mok and colleagues conducted the ARCHER 1050 trial (abstract LBA9007) to compare gefitinib with dacomitinib, a second-generation irreversible EGFR TKI, in 452 treatment-naive NSCLC patients with *EGFR*-activating mutations. Patients were not allowed to have CNS metastases and were stratified by Asian ethnicity and type of *EGFR* mutation (exon 19 vs. exon 21 L858).

In the intent-to-treat population, dacomitinib versus gefitinib improved median PFS (14.7 vs. 9.2 months; HR, 0.59; $P<0.0001$). Whereas ORR was similar with dacomitinib or gefitinib (74.9% and 71.6%, respectively), the duration of response was significantly longer with dacomitinib (14.8 vs. 8.3 months; $P<0.0001$). Dacomitinib was associated with a higher rate of any grade diarrhea, paronychia, dermatitis acneiform, and stomatitis, whereas gefitinib was associated with a higher rate of any grade alanine aminotransferase increase. Dacomitinib was also associated with a higher rate of treatment-related serious adverse events (9.3% vs. 4.5%), higher discontinuation rate due to toxicity (9.7% vs. 6.7%), and more dose modifications (66.1% vs 8.0%).

Although this trial supports the use of dacomitinib in the first-line setting, it is anticipated that this landscape will soon change rapidly with use of osimertinib (see above summary). It therefore remains unclear whether dacomitinib will play a major role in the *EGFR*-mutation space.

Alectinib vs. Crizotinib for Advanced ALK-Positive NSCLC The prior standard of care for ALK-positive NSCLC was to administer crizotinib, a first-generation ALK inhibitor that does not have significant CNS penetrance. Alectinib, a next-generation ALK inhibitor with CNS penetrance, is already FDA approved for use in crizotinib-refractory ALK-positive NSCLC patients. Now, Shaw and colleagues have conducted the ALEX study (abstract LBA9008) to compare first-line alectinib versus crizotinib in 303 treatment-naive patients with ALK-positive disease. Between 38% and 42% of patients had baseline brain metastases.

Median PFS was superior with alectinib versus crizotinib (not reached vs. 11.1 months; HR, 0.47; $P<0.0001$), as were independent radiographic review median PFS (25.7 vs. 10.4 months; HR, 0.5; $P<0.0001$), and time to CNS progression (HR, 0.16; $P<0.0001$). ORR was similar with alectinib and crizotinib (83% and 76%, respectively), but alectinib was associated with a longer duration of response (not reached vs. 11.1 months; HR, 0.36). The PFS subgroup analysis favored alectinib in all groups analyzed and appeared to yield a neuroprotective benefit in patients with no preexisting brain metastases. Patients with baseline CNS disease who received alectinib achieved a higher CNS response (81% vs. 50%) and longer median CNS duration of response (17.3 vs. 5.5 months). Alectinib was associated with less grade ≥3 toxicity (41% vs. 50%), a lower rate of dose reductions (16% vs. 21%), and fewer dose interruptions (18% vs. 25%).

The ALEX trial has reshaped the ALK-positive NSCLC front-line setting to now include alectinib as the preferred therapy. These positive PFS data are consistent with the J-ALEX study (*Lancet* 2017; 390:29) of alectinib conducted in Japan, albeit at a lower dose. Alectinib is now the preferred front-line option, largely due to the high CNS penetrance and well-tolerated safety profile. It remains to be seen what the resistance mechanisms are to alectinib and whether other ALK inhibitors will be able to salvage alectinib-refractory patients. Of particular interest will be brigatinib and lorlatinib.

Adjuvant Gefitinib vs. Vinorelbine Plus Cisplatin for Stage II–IIIA *EGFR*-Mutated NSCLC In the ADJUVANT trial (abstract 8500), Wu and colleagues randomized 220 stage II–IIIA (N1-N2) resectable NSCLC patients with an activating *EGFR* mutation (del exon 19 or exon 21 L858) to gefitinib versus cisplatin plus vinorelbine for 4 cycles.

Disease-free survival (DFS) was significantly longer with gefitinib than with cisplatin plus vinorelbine (28.7 vs. 18 months; HR, 0.6; $P=0.005$). Gefitinib was associated with higher rates of any grade rash, liver function test elevation, and diarrhea but markedly less grade ≥3 toxicity (12.3% vs. 48.3%). No cases of interstitial lung disease were observed in either arm. The quality-of-life analysis favored the gefitinib arm.

This trial provides compelling prospective data that adjuvant EGFR TKIs may provide clinical benefit versus chemotherapy for patients with resectable stage II–III *EGFR*-mutated NSCLC. However, overall survival (OS) results will need to be analyzed. Also, the manner in which the patients were staged remains unknown, and the comparison arm used an older adjuvant chemotherapy regimen (cisplatin-vinorelbine), whereas in the U.S., it is common to give newer regimens such as cisplatin-pemetrexed to non-squamous NSCLC patients. Although these results were positive, adjuvant oral EGFR TKIs should replace chemotherapy only in the setting of clinical trials and should not yet be given as standard of care.

Nintedanib for Malignant Pleural Mesothelioma Since the MAPS trial (*NEJM JW Oncol Hematol* Mar 2016), Nowak and colleagues randomized 87 patients with epithelioid or biphasic MPM to cisplatin-pemetrexed with or without the oral VEGFR, PDGFR, FGFR TKI nintedanib.

The addition of nintedanib improved the ORR (57% vs. 44%; OR, 1.66) and median duration of response (6 vs. 4 months). Nintedanib also significantly improved median PFS (9.4 vs. 5.7 months; HR, 0.54; $P=0.010$) and demonstrated a trend for improvement in median OS (18.3 and 14.2 months, respectively), with OS benefit across most subgroups, except for patients with biphasic histology. Nintedanib had a higher rate of dose reductions (27.3% vs. 17.1%) but a lower rate of treatment discontinuation due to toxicity (6.8% vs. 17.1%).

This trial provides supportive evidence that anti-angiogenics with platinum-pemetrexed in MPM are effective. However, it remains unclear whether the oral TKIs (nintedanib, cediranib) will have better efficacy than the monoclonal antibody bevacizumab and whether there is a predictive biomarker that can identify patients who are likely to have the greatest benefit. The LUME-Meso trial has been expanded into a phase III registration trial. If the study is positive, it will change standard of care in the front-line setting for MPM. ***— Anne S. Tsao, MD***

Gastrointestinal Cancer

Key trials in colorectal, gastric, pancreatic, and hepatocellular cancer

Duration of Colon Cancer Therapy: 3 or 6 Months? A plenary session presentation of the IDEA trial by Shi and colleagues (abstract LBA1) released pooled international data from six phase III trials comparing the use of 3 versus 6 months of capecitabine plus oxaliplatin or FOLFOX chemotherapy for more than 10,000 patients with stage III colon cancer. Of these, 72% had N1 disease, 28% had N2 disease, 79% were T1-2 or 3, and 21% were T4. The primary endpoint, disease-free survival (DFS), was designed to show noninferiority for 3 versus 6 months of treatment, allowing a 12% relative risk increase with shorter therapy.

Completion of all treatment cycles was higher with 3 months of therapy (86%–90%) versus 6 months (65%–71%). Grade 2 neurologic toxicity was reduced from 32%–36% to 12%–14% with shorter therapy, and grade 3-4 neurotoxicity was reduced from 9%–16% to 3%. There was a 0.9% difference in 3-year DFS, which did not meet the criteria for noninferiority. However, low-risk T1-3 N1 disease achieved near equivalence with 3 months of therapy; DFS in low-risk patients differed by only 0.2%.

By regimen, FOLFOX failed to demonstrate noninferiority with 3 months of therapy in either high- or low-risk stage III disease, whereas 3 months of capecitabine plus oxaliplatin achieved noninferiority and a benefit clearly noninferior for low-risk T1-3 N1 disease. For T4 N2 disease, capecitabine and oxaliplatin noninferiority could not be proven.

Three other trials — the study by Andre and colleagues from France (abstract 3500), the TOSCA study by Sobrero and colleagues from Italy (abstract 3501), and the SCOT study by Iveson and colleagues from the U.K. (abstract 3502) — generally supported the results of the IDEA trial.

The Andre study failed to demonstrate noninferiority of 3 versus 6 months of FOLFOX therapy for either low- or high-risk stage III disease, with an 8% inferior disease-free survival for high-risk stage III disease and a 2% inferior disease-free survival for low-risk stage III disease. Data from the SCOT trial indicated noninferiority for 3 versus 6 months of capecitabine plus oxaliplatin in either low- or high-risk stage III disease. Collectively, data from the three trials support the use of 3 months of adjuvant chemotherapy for low-risk stage III disease with a potential preference for capecitabine and oxaliplatin. For high-risk stage III disease, 6 months of therapy remains the standard of care. Any decision to truncate adjuvant therapy needs to be reviewed with patients, given the overall small differences in outcomes in most of the data sets presented in this series.

Vitamin D of Modest Benefit in Metastatic Colon Cancer Ng and colleagues conducted a randomized phase II trial (SUNSHINE; abstract 3506) in which 139 treatment-naive patients with metastatic colon cancer received FOLFOX plus bevacizumab with or without high-dose vitamin D3. Vitamin D supplementation modestly improved progression-free survival (PFS) from 11.2 to 13.1 months, with an equivalent response rate of 55% and a suggestion of improvement in disease control from 84% to 96%.

Vemurafenib Improves Survival in Metastatic Colorectal Cancer In the SWOG S1405 trial (abstract 3505), Kopetz and colleagues evaluated the effect of adding the *BRAF* inhibitor vemurafenib to standard cetuximab plus irinotecan in 92 patients with *BRAF*-mutant metastatic colorectal cancer (CRC).

Vemurafenib significantly improved PFS from 2.0 to 4.3 months (HR, 0.48). A higher response rate (16% vs. 4%) and a higher rate of disease control (67% vs. 22%) were also achieved. Patients crossing over to vemurafenib treatment at progression achieved a 17% response and a PFS of 5.8 months. Overall survival (OS) improved with vemurafenib from 5.9 to 9.6 months.

Radiotherapy Ineffective for Liver Metastases from CRC A salient negative trial (FOXFIRE) by Sharma and colleagues (abstract 3507) assessed adding selective internal radiotherapy (SIRT) using yttrium-90 resin microspheres to first-line FOLFOX chemotherapy, with a permissible added use of bevacizumab, for patients with liver metastases from metastatic CRC and limited extra hepatic disease. The addition of SIRT failed to improve OS or PFS.

Prognostic Factors in Metastatic CRC Two studies updated results of the CALGB/SWOG 80405 trial (*NEJM JW Oncol Hematol* Aug 2014) of first-line chemotherapy with either bevacizumab or cetuximab in patients with exon 12 and 13 *KRAS* wild-type metastatic CRC.

In the first study, Venook and colleagues showed that a right-sided primary tumor was an independent prognostic and predictive factor for worse outcome (abstract 3503). The data also suggested a better survival benefit for bevacizumab versus cetuximab combined with chemotherapy in right-sided tumors.

In the second study, Innocenti and colleagues used DNA mutational analysis to confirm that the presence of a *BRAF* mutation has an adverse effect on OS (abstract 3504) and that OS was similar between MSI-high versus MSI-stable patients. The data also indicated that OS might be improved in patients with ≥8 versus <8 mutations (HR, 0.67; P=0.02).

Perioperative Chemotherapy for Gastric Cancer: A New Standard A practice-changing trial conducted by Al-Batran (FLOT4-AIO; abstract 4004) compared FLOT (docetaxel, oxaliplatin, and 5-FU) versus standard ECF (epirubicin, cisplatin, and 5-FU) in 716 patients with gastric or gastroesophageal (GE) junction cancer treated with surgery. Of these, 56% had GE junction cancers, 44% had distal gastric cancers, 70%–75% had T3 disease, and 78%–81% had node-positive disease. Most (90%) completed preoperative chemotherapy, and 94%–97% proceeded to surgery.

Patients treated with FLOT versus ECF had a higher rate of curative resection (84% vs. 77%; P=0.011). OS was improved with FLOT (50 vs. 35 months; P=0.012), with an improvement in projected 5-year overall survival from 36% to 45%. PFS was also improved from 18 to 30 months (P=0.004). These results establish FLOT as a potential new standard of care in the perioperative chemotherapy management of resectable gastric and GE cancer.

Pembrolizumab Active in Advanced Gastric Cancer The KEYNOTE-059 study by Bang and colleagues (abstract 4012) evaluated pembrolizumab plus 5-FU and cisplatin in 259 patients with chemotherapy-refractory gastric cancer. Of these, an equal number had gastric and

GE junction cancers, 57% tested positive for PD-L1 expression, and 52% received ≥2 prior chemotherapy regimens.

The response rate was 11.6%, and the disease control rate was 27%. A higher response was observed in PD-L1–positive versus negative patients (15.5% vs. 6.4%); more responses were seen in patients receiving third-line versus fourth-line treatment (15.4% vs. 6.4%). Most patients progressed early with a median PFS of 2 months, a median OS of 5.6 months, and a 12-month OS rate of 23.4%. In seven patients who tested MSI high, a 57% response rate was observed. These results substantiate a signal of activity for immune checkpoint inhibitors in advanced gastric cancer.

Capecitabine Bests Observation for Biliary Tract Cancer The practice-changing BILCAP study by Primrose and colleagues (abstract 4006) evaluated the use of adjuvant capecitabine for 6 months versus observation in 447 patients after biliary cancer resection. Half of patients had intrahepatic or hilar cholangiocarcinoma versus either gallbladder or common bile duct cholangiocarcinoma. A negative margin resection was present in 62%–63% of patients, and 46%–48% had node-positive disease.

OS was similar with treatment versus observation (51.1 and 36.4 months, respectively; HR, 0.81), but was significantly improved when the analysis was adjusted for prognostic factors (HR, 0.70; P=0.007). Relapse-free survival was improved from 17.6 to 24.6 months with adjuvant chemotherapy (HR, 0.76; P=0.039). No quality-of-life detriment was observed with adjuvant chemotherapy.

No Improvement with SIRT for Locally Advanced HCC In another key negative trial (SIRveNIB) Chow and colleagues compared yttrium microsphere SIRT versus standard sorafenib in 182 patients with locally advanced hepatocellular carcinoma (HCC; abstract 4002). OS was similar for SIRT versus sorafenib (8.8 and 10.0 months, respectively), as was time to tumor progression (6.1 and 5.3 months). Because 52 patients randomized to SIRT could not be treated, the study potentially favored the SIRT population due to enhanced patient selection, but SIRT still did not improve survival outcome.

Lenvatinib Effective for Unresectable HCC Cheng and colleagues (abstract 4001) compared the use of standard sorafenib versus lenvatinib, a newer-generation multitargeted TKI in nearly 1000 international patients with unresectable HCC. Hepatitis B was the most common cause of liver disease (48%–53%) followed by hepatitis C (19%–27%).

Noninferiority for OS for lenvatinib versus sorafenib was achieved (13.6 vs. 12.3 months; HR, 0.92). PFS was significantly improved with lenvatinib (7.4 vs. 3.7 months; HR, 0.66; P<0.00001). A higher response rate was also observed for lenvatinib (24.1% vs. 9.2%). Rates of treatment-related adverse events were similar between therapies, with more hypertension with lenvatinib (23% vs. 14%) and more hand-foot reaction with sorafenib (11% vs. 3%). ***— David H. Ilson, MD, PhD***

Malignant Hematology

Highlights of new treatments for myeloma, leukemia, and lymphoma

CAR-T-Cell Therapy for Relapsed or Refractory Myeloma Chimeric antigen receptor T-cell (CAR-T) immunotherapy is highly active in acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), and B-cell non-Hodgkin lymphoma (NHL). Fan and colleagues have now developed a CAR-T-cell therapy targeting the B-cell maturation antigen (BCMA) that is expressed on myeloma cells and have used it to treat patients with relapsed or refractory myeloma (abstract LBA3001).

Of 19 patients, 18 responded with complete or near-complete remission, including minimal residual disease–negative responses in some patients more than 6 months after treatment. A total of 14 patients developed the cytokine release syndrome commonly observed with CAR-T therapy, but only 2 cases were grade 3 or 4. No patient has developed disease progression, although follow-up was short. CAR-T-cell therapy targeting BCMA is a highly promising new treatment for patients with relapsed or refractory myeloma.

Long-Term Outcomes of Bendamustine plus Rituximab for NHL Flynn and colleagues reported long-term results of the BRIGHT trial (abstract 7500) of bendamustine plus rituximab (BR) versus R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in 447 previously untreated patients with indolent NHL or mantle-cell lymphoma. At a follow-up of 65 months, progression-free survival (PFS) was significantly improved with BR versus R-CVP or R-CHOP (65.5% vs. 55.8%; P=0.0025), and overall survival (OS) was similar (82% and 85%, respectively); 43%–45% of patients received maintenance R.

In the StiL NHL1 study (abstract 7501), Rummel and colleagues compared BR versus R-CHOP in indolent NHL and MCL and, at follow-up of 117 months, likewise found improved PFS benefit and similar OS with BR. They also identified a significant benefit for time to next treatment with BR.

Long-Term Follow-Up of Ibrutinib for CLL In the prior RESONATE trial, *N Engl J Med* 2014; 371:213), Byrd and colleagues compared the use of ibrutinib versus ofatumumab in CLL patients who progressed after one or more prior therapies and found that, at a median follow-up of 9.4 months, ibrutinib improved PFS, OS, and response rate. Now, these investigators report durable responses with ibrutinib at a median follow-up of 44 months (abstract 7510) even in patients with high-risk cytogenetics: del(17p) or del(11q).

The overall response rate with ibrutinib was 91%, and 3-year OS was 74%. Grade 3 or higher serious adverse events with ibrutinib included major hemorrhage in 6% of patients, atrial fibrillation in 6%, and hypertension in 8%. Overall, ibrutinib was discontinued in 27% owing to disease progression and in 12% owing to adverse events.

Stem-Cell Transplantation for Poor-Risk Follicular Lymphoma Patients with follicular lymphoma (FL) who experience early chemoimmunotherapy failure have poorer outcomes compared with those who achieve more durable responses. To investigate the potential role of hematopoietic stem-cell transplantation (SCT) for such patients, Godfrey and colleagues conducted a retrospective analysis of 440 FL patients who had disease progression within 2 years of induction treatment with rituximab plus chemotherapy and underwent SCT (abstract 7508). Of these patients, 240 received autologous SCT, 105 received matched sibling donor (MSD) allogeneic SCT, and

95 received matched unrelated donor (MUD) allogeneic SCT.

Five-year nonrelapse mortality was significantly lower following autologous SCT (5%) versus MSD allogeneic SCT (17%) or MUD allogeneic SCT (33%; $P<0.0001$). Five-year OS was significantly higher following autologous SCT (70%) or MSD allogeneic SCT (74%) versus MUD allogeneic SCT (49%; $P=0.004$). The authors note that prior data show a 5-year OS of 50% in early-progressing patients who do not undergo SCT, which suggests that a prospective analysis of SCT in early-progressing FL is warranted.

— *Michael E. Williams, MD, ScM*

SUMMARY & COMMENT

Antithrombotic Therapy for Essential Thrombocythemia

A systematic review fails to find evidence of efficacy.

Essential thrombocythemia (ET) is a clonal myeloproliferative neoplasm affecting platelet production, complicated by microvascular and large vessel thrombosis as well as bleeding due to platelet dysfunction and acquired von Willebrand syndrome.

To examine whether antithrombotic therapy is safe and effective for ET, investigators conducted a systematic review of 24 nonrandomized studies encompassing 6153 ET patients; no randomized, controlled trials were found.

A history of thrombosis was reported in up to 46% of patients and bleeding in up to 26%. Antiplatelet therapy had a median relative risk for thrombosis of 0.74 (range, 0.26–3.48); any bleeding, 1.95 (0.48–11.04); and major bleeding, 1.3 (0.48–5.17).

COMMENT

The failure of this review to uncover evidence for the safety and efficacy of antithrombotic therapy for ET is not surprising, both because of the absence of randomized trials and the heterogeneity of the disorder. Patients with *JAK2* mutations are at higher risk for thrombosis than those with *CALR* or *MPL* mutations, and bleeding due to acquired von Willebrand syndrome is more likely in those with high platelet counts. Currently, treatment is recommended for those aged >60, those with cardiovascular disease or thrombosis, or those with a platelet count $\geq 1500 \times 10^9$/L (*Blood* 2016; 128:2403). **— *David Green, MD, PhD***

Chu DK et al. Benefits and risks of antithrombotic therapy in essential thrombocythemia: A systematic review. **Ann Intern Med** *2017 Jun 27; [e-pub]. (http://dx.doi.org/10.7326/M17-0284)*

Direct Oral Anticoagulants for Heparin-Induced Thrombocytopenia

A systematic literature review finds DOACs safe and effective for HIT.

Antithrombotic therapy is required to manage heparin-induced thrombocytopenia (HIT), but currently approved agents such as argatroban must be given parenterally and closely monitored. Whether direct oral anticoagulants (DOACs) are sufficiently potent to control HIT-related thrombosis is uncertain.

To address this question, investigators at McMaster University in Canada examined their own experience and conducted a systematic review of the literature regarding the use of DOACs for initial treatment of acute HIT as well as after other primary therapies.

A total of 80 patients received a DOAC for treatment of probable HIT; 67% received rivaroxaban, 17% apixaban, and 16% dabigatran. Rivaroxaban was the primary therapy for 25 of 46 patients; only one of the 46 had progression of thrombosis, and none had major bleeding.

A total of 12 patients received apixaban and 11 received dabigatran, generally after another primary therapy. Of these 23 patients, only one had a thrombotic event and none had major bleeding.

COMMENT

This observational study suggests that DOACs are safe and effective for acute HIT. These results are similar to those previously reported for fondaparinux (*NEJM JW Oncol Hematol* Mar 2015 and *Blood* 2015; 125:924). Because observational studies such as those reported here might be biased by patient selection, randomized trials that compare DOACs with either argatroban or fondaparinux are urgently needed. For the present, clinicians might consider prescribing a DOAC for acute HIT and tailoring the dose and duration of treatment for each patient. **— *David Green, MD, PhD***

Warkentin TE et al. Direct oral anticoagulants for treatment of HIT: Update of Hamilton experience and literature review. **Blood** *2017 Jun 23; [e-pub]. (http://dx.doi.org/10.1182/blood-2017-04-778993)*

Clonal Hematopoiesis Is a Risk Factor for Atherosclerosis

Clonal hematopoiesis of indeterminate potential is associated with excess risk for coronary heart disease.

Atherosclerosis is a disorder characterized by the accumulation of macrophages in atheromatous plaques. Macrophages that have differentiated from clones of hematopoietic stem cells with mutations in *DNMT3A*, *Tet2*, and *ASXL1* produce increased amounts of inflammatory cytokines and might be atherogenic.

To test the hypothesis that clonal hematopoiesis of indeterminate potential (CHIP) is a risk factor for atherosclerosis, investigators analyzed data from prior case-control studies encompassing 4726 participants with coronary heart disease (CHD) and 3529 controls. Whole exome sequencing focused on 74 genes known to be recurrently mutated in myeloid cancers. In addition, gene-expression analysis was conducted on *Tet2* knockout macrophages transplanted into atherosclerosis-prone mice exposed to LDL cholesterol.

Results were as follows:

- CHIP carriers had greater risk for incident CHD than noncarriers (adjusted hazard ratio, 1.9; $P<0.001$) and a greater risk for early-onset myocardial infarction (odds ratio, 4.0; $P<0.001$).
- Mutations in *DNMT3A*, *Tet2*, *ASXL1*, and *JAK2* were associated with CHD.
- CHIP carriers had a median score for coronary-artery calcification 3.3 times higher than noncarriers; furthermore, carriers with a variant allele fraction ≥10% had a 12-fold higher risk for increased coronary-artery calcification ($P=0.002$).
- The risk for incident CHD was 2.2-fold higher in those with an allele fraction ≥10% ($P<0.001$).
- *Tet2* knockout mice exposed to LDL loading had larger atheromatous lesions, and *Tet2* knockout macrophages secreted more chemokines and cytokines than control mice.

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COMMENT

Aging is a common denominator for the development of atherosclerosis and clonal expansion of hematopoietic cells with mutant genes. This study convincingly shows that the risk for atherosclerosis is increased by loss of function mutations in specific genes that mediate inflammation.

— David Green, MD, PhD

Jaiswal S et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. **N Engl J Med** *2017 Jun 21; [e-pub]. (http://dx.doi.org/10.1056/NEJMoa1701719)*

Keaney JF Jr. CHIP-ping away at atherosclerosis. **N Engl J Med** *2017 Jun 21; [e-pub]. (http://dx.doi.org/10.1056/NEJMe1706173)*

Treating Hemophilia by Decreasing Antithrombin

Fitusiran, an RNA interference agent that targets antithrombin, lowered antithrombin levels and increased thrombin generation.

Control of bleeding in patients with hemophilia requires the regular intravenous infusion of clotting factor concentrates, which is painful and expensive. An alternative approach is to enhance hemostasis by decreasing the levels of natural anticoagulants such as antithrombin.

To examine the safety and effectiveness of fitusiran, an RNA interference agent that specifically targets antithrombin, investigators conducted a dose-escalation study in 25 patients, 18 with hemophilia A and 7 with hemophilia B. Excluded were patients with thrombophilic disorders, liver dysfunction, or inhibitors. Fitusiran was given subcutaneously either weekly or monthly, and follow-up was for up to 112 days.

The maximum reduction of antithrombin was 89% from baseline and was achieved with a dose of 1.8 mg/kg and accompanied by increases in median peak thrombin levels that reached the lower end of the normal range. Antithrombin recovery occurred at the rate of 10% to 15% per month. Adverse effects included an increase in alanine aminotransferase in 36% of participants, but values exceeding three times the normal range occurred in only one man who also had chest pain of unclear etiology resulting in treatment discontinuation.

COMMENT

This study demonstrates that plasma procoagulant activity can be enhanced by reducing levels of antithrombin, even in patients with severe hemophilia. The patients who might benefit most from this approach are those with inhibitors, but although they were excluded from this study, plans call for their inclusion in the future. It is also worrying that fitusiran raised liver enzymes, although the increases were modest and mostly in those with a history of hepatitis C infection. The study is continuing to determine whether there will be a net clinical benefit from therapy with fitusiran. ***— David Green, MD, PhD***

Pasi KJ et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. **N Engl J Med** *2017 Jul 10; [e-pub]. (http://dx.doi.org/10.1056/NEJMoa1616569)*