Three-drug combo slows progression of multiple myeloma

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Three-drug combo slows progression of multiple myeloma

NAOMI RODRIG

An interim analysis from the multinational phase III CASTOR trial, presented recently at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting, showed that adding daratumumab to the standard two-drug regimen of bortezomib and dexamethasone (Vd) markedly improved outcomes of patients with recurrent or refractory multiple myeloma (RRMM). [ASCO 2016, abstract LBA4]

“Daratumumab is a human CD38 selective monoclonal antibody with direct and indirect anti-myeloma activity that has been approved in the US and Europe for RRMM. It depletes CD38+ immunosuppressive regulatory cells and promotes expansion of cytotoxic and helper T cells,” said lead author Dr. Antonio Palumbo from the University of Torino, in Torino, Italy. “We’ve suspected for a long time that CD38 is the major treatment target for multiple myeloma, but these results are unprecedented in this cancer.”

CASTOR was a multicentre open-label trial that randomized RRMM patients who had received one or more prior lines of therapy to receive daratumumab plus bortezomib and dexamethasone (DVd; n=251) or Vd (n=247) for 8 cycles, followed by daratumumab maintenance in the DVd arm. Baseline demographics and disease characteristics were well balanced between study arms. The primary endpoint was progression-free survival (PFS), with secondary endpoints for response rates, overall survival (OS), time to response and duration of response.

“At a median follow-up of 7.4 months, daratumumab significantly improved PFS, with an unprecedented 61 percent reduction in the risk of progression [p<0.0001]. Median PFS was 7.2 months in the standard treatment arm and not yet reached in the experimental arm,” reported Palumbo. “The estimated 1-year PFS was doubled from 26.9 percent with the standard regimen to 60.7 percent with the addition of daratumumab.”

The PFS benefits of daratumumab were consistent in all patient subgroups regardless of age, disease stage, prior stem cell transplantation or type of prior therapy. “According to the subgroup analysis, patients who had had only one prior line of therapy benefited the most, suggesting that early intervention can maximize the benefit of DVd,” Palumbo emphasized.

Response rates were also significantly im-
proved with daratumumab, including overall response (83 vs 63 percent with Vd; p<0.0001), very good partial response (59 vs 29 percent; p<0.0001) and complete response (19 vs 9 percent; p=0.0012). Time to response was relatively shorter in the DVd arm than in the Vd arm, with about 80 percent of the patients on daratumumab achieving partial response at 1 month.

“Importantly, adding daratumumab does not substantially increase toxicity. The rates of common adverse events such as thrombocytopenia, anaemia, and neutropenia, were only slightly higher in the daratumumab arm,” remarked Palumbo. “Given the encouraging results, this three-drug regimen with daratumumab can potentially be considered a new standard of care for RRMM patients.”

A longer follow-up of CASTOR will help to determine the impact of adding daratumumab on patient OS. Ongoing trials are also evaluating daratumumab in combination with another standard therapy for RRMM and testing various daratumumab-based regimens in newly diagnosed multiple myeloma.

Afatinib outperforms gefitinib in Asian patients with EGFR-positive NSCLC

ELVIRA MANZANO

The pan-ERB inhibitor afatinib improves progression-free survival (PFS), time-to-treatment failure (TTF) and objective response rate (ORR) compared with gefitinib among Asian patients with EGFR-positive non-small cell lung cancer (NSCLC) included in the LUX-Lung 7 trial. [APLCC 2016, ABS068]

“Median PFS and TTF were significantly longer with afatinib [11 and 13.7 months] than with gefitinib [10.9 and 11.5 months],” said study investigator Professor Kenneth O’Byrne, consultant medical oncologist at the Princess Alexandra Hospital in Brisbane, Queensland, Australia, at the Asia Pacific Lung Cancer Conference (APLCC) 2016 held recently in Chiang Mai, Thailand. “Among Asian patients, PFS was prolonged by 24 percent. OS [overall survival] data are not mature yet.”

The secondary endpoint of ORR by independent review was also higher with afatinib (70 vs 56 percent for gefitinib). ORR in Asian patients was 70 percent with afatinib versus 57 percent for gefitinib.
“Results were consistent across all subgroups evaluated, including Asian patients,” O’Byrne reported. “The improvement in efficacy was observed in both del19 and L858R populations.” Among Asian patients with del19 mutation, ORR was 72 and 68 percent, in favour of afatinib. In those with L858R mutation, ORR was also higher with afatinib (68 vs 42 percent with gefitinib).

LUX-Lung 7 was an international, phase IIb, randomized, open-label trial investigating the efficacy and safety of afatinib vs gefitinib in untreated patients with advanced, EGFR-positive NSCLC. The trial was done at 64 centres in 13 countries. [Lancet Oncol 2016;pii:S1470-2045(16)30033-X]

Patients were randomized to receive afatinib 40 mg once daily (n=160) or gefitinib 250 mg once daily (n=159) until radiological disease progression or beyond, by investigator decision. Median follow-up was 27.3 months. The coprimary endpoints were PFS by independent review, TTF, and OS. Over half of the participants were Asians (59 percent with afatinib; 55 percent with gefitinib). Baseline characteristics such as ethnicity and type of EGFR mutation were similar between arms.

“Adverse events in both groups were consistent with previous experience using the drugs and were manageable, leading to equally low rates of treatment discontinuation [6 percent for both],” said O’Byrne.

The most common grade ≥3 adverse events reported were diarrhoea, rash and acne with afatinib, and liver enzyme elevations with gefitinib.

“LUX-Lung 7 confirms the benefit of irreversible ErbB blockade with afatinib over reversible EGFR inhibition with gefitinib in the treatment of EGFR-positive NSCLC,” he concluded.
Combination therapy proves effective in resected pancreatic cancer

JENNY NG

Results from one of the largest pancreatic cancer trials ever conducted may change the standard of care for patients with pancreatic cancer who have undergone surgery.

In the ESPAC-4 (European Study Group on Pancreatic Cancer-4) phase III randomized controlled trial, patients with resected pancreatic ductal adenocarcinoma achieved significant survival benefits with the addition of capecitabine to standard gemcitabine chemotherapy. Patients who received the combination regimen had an estimated 5-year survival rate of 28.8 percent vs 16.3 percent with gemcitabine alone. [ASCO 2016, abstract LBA4006]

The median overall survival was 28.0 months in the combination arm vs 25.5 months in the monotherapy arm (hazard ratio [HR], 0.82; p=0.032).

“The difference in median survival may seem modest, but the improvement in long-term survival is substantial for this cancer,” said Dr. John Neoptolemos of the University of Liverpool, UK, lead author of the trial. “We’ve gone from a 5-year survival rate of 8 percent with surgery alone to nearly 30 percent with adjuvant therapy.”

In the study, 732 patients with pancreatic cancer who had undergone surgery within 12 weeks were randomized to receive either six 4-week cycles of intravenous gemcitabine alone or gemcitabine with oral capecitabine. Patients had a median maximum tumour size of 30 mm, while 42 and 55 percent had a WHO performance status of 0 or 1, respectively. Sixty percent of patients had R1 resections, with 80 percent having node-positive disease and 40 percent having poorly-differentiated tumours.

The patient characteristics were representative of a real-world pancreatic cancer population, with a large proportion of patients having unfavourable prognostic factors. The presence of these factors, however, did not affect the survival benefit seen with the combination regimen.
Patients in the two study arms had similar rates and types of treatment-related serious adverse events (SAEs). In the combination therapy group, 154 SAEs were reported among 24 percent of patients compared with 151 SAEs among 26 percent in the monotherapy group. Rates of severe diarrhoea (14 vs 5 patients) and fatigue (16 vs 14 patients) were higher with combination therapy, but patients’ quality of life remained comparable between the two arms.

These findings establish the safety and efficacy of the gemcitabine/capecitabine combination regimen and suggest a potential change in the standard of care for resected pancreatic cancer patients. Currently, gemcitabine is the standard adjuvant treatment for patients with surgically resected pancreatic cancer based on positive results from the ESPAC-1 and ESPAC-3 trials.

Given the improvement in survival with no increased toxicity, the results of ESPAC-4 also suggest an opportunity to add additional treatments to the combination regimen to further improve outcomes.

“Unfortunately, most patients are not candidates for surgery when they are diagnosed with pancreatic cancer,” noted Neoptolemos. “These findings are significant because they show that patients who can undergo surgery have a fighting chance of surviving with the combination of two commonly used chemotherapies.”

Benefits seen with 10 years of AI therapy in HR-positive BC

JENNY NG

Evidence now demonstrates a benefit with 10 years of aromatase inhibitor (AI) therapy in post-menopausal women with hormone receptor (HR)-positive early-stage breast cancer (BC).

Results from the randomized phase III MA.17R trial showed that extending adjuvant letrozole 2.5 mg daily for 5 years after completing an initial 5 years of AI therapy significantly reduced the risk of recurrence by 34 percent (hazard ratio [HR], 0.66; p=0.01) in women with HR-positive BC. After 5 years of follow-up, the rate of disease-free survival (DFS) was improved from 91 percent in patients receiving placebo after 5 years of initial AI therapy to 95 percent in
Expanded molecular testing improves lung cancer survival

JACKEY SUEN

More biomarkers should be included in the standard molecular testing for lung adenocarcinoma to improve patients' prognosis and survival, results of the LCMC II (Lung Cancer Mutation Consortium II) study suggest.

“In addition to EGFR mutation and ALK rearrangement, we analysed the frequency and clinical impact of a broader set of genetic alter-
mutations in lung adenocarcinoma. These include point mutations in AKT1, BRAF, ERBB2, KRAS, MAP2K1, PIK3CA and NRAS, as well as MET amplification, RET and ROS1 rearrangements, and PTEN and MET expression,” explained lead author Dr. Dara Aisner of the University of Colorado, Colorado, US. “Additional mutation data such as TP53 and PTEN were provided as available.” [ASCO 2016, abstract 11510]

A total of 875 patients with confirmed stage IV lung adenocarcinoma were recruited in this study. The patients were either prescribed standard treatment based on molecular testing results, or recommended to participate in clinical trial of agents specific for certain alterations.

The most frequent driver alterations in the study were KRAS mutation (25 percent), sensitizing EGFR mutation (10 percent) and ALK rearrangement (4 percent). AKT1 mutation was not detected, while other alterations were present in 0.5 to 3 percent of the studied population. “The remaining 44 percent had no detectable mutations by genotyping,” reported Aisner. “However, initial results from immunohistochemical analysis revealed MET expression and PTEN loss in 59 percent and 15 percent of the patients, respectively. The data are currently pending central review.”

“Smokers who carried detectable driver mutations had significantly longer overall survival [OS] than those who did not [median, 2.7 vs 1.6 years; p=0.008]. Therefore, identification of driver mutations is important in lung adenocarcinoma patients who have a smoking history,” she stressed. “In addition, KRAS mutations tended to be associated with a worse prognosis in never smokers.”

“Doubleton mutations were reported in 4.1 percent of the patients, with the majority having co-occurring MET amplification/KRAS mutation, PIK3CA/KRAS mutations, MET amplification/EGFR mutation or PIK3CA/EGFR mutations,” noted Aisner.

“TP53 mutations might confer a worse prognosis in patients harbouring sensitizing EGFR mutations who were treated with targeted therapy [median OS, 2.9 years vs not reached in counterparts without TP53 mutations; p=0.02],” she added. “TP53 mutations are likely underreported, because the positivity rate was 48 percent by next-generation sequencing, but only 8 percent by non-next-generation sequencing in our study.”
Trastuzumab biosimilar shows comparable efficacy, safety

NAOMI RODRIG

A biosimilar trastuzumab antibody (Myl-1401O) has demonstrated comparable efficacy and safety to branded trastuzumab (Herceptin®) in women with HER2-positive metastatic breast cancer, potentially expanding patient access to affordable effective treatment. The data were presented at the ASCO 2016 meeting held recently in Chicago, Illinois, US. [ASCO 2016, abstract LBA503]

“Myl-1401O was proposed as a possible biosimilar based on previous physicochemical analyses, nonclinical, pharmacokinetic and pharmacodynamic studies. This trial was designed to evaluate its comparative efficacy and safety vs trastuzumab,” said lead study author Dr. Hope Rugo from the University of California San Francisco, California, US.

The randomized phase III trial, conducted at 95 sites across Asia, Europe, Africa and Latin America, enrolled 500 women with HER2-positive metastatic breast cancer to receive taxane chemotherapy with either trastuzumab or Myl-1401O as first-line treatment for a minimum of eight cycles, followed by trastuzumab alone until disease progression. The primary endpoint was overall response rate (ORR) by blinded central evaluation at week 24, and secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety.

“For the 458 patients evaluable for efficacy, the ORR at week 24 was 69.6 percent for Myl-1401O vs 64 percent for trastuzumab. The ORR ratio of 1.09 was within the predefined equivalence margin,” reported Rugo. “Median PFS was not yet reached, and safety was comparable. Serious adverse events, mostly related to neutropenia, occurred in 38 percent of patients in the Myl-1401O arm and 36 percent in the trastuzumab arm, with four fatal events in each arm. There was no change in cardiac function from baseline to week 24.”

The investigators concluded that given in combination with a taxane, the proposed trastuzumab biosimilar Myl-1401O could be a new first-line treatment option for HER2-positive metastatic breast cancer.

“Trastuzumab has markedly improved survival of women with HER2-positive disease but many women around the world can’t benefit from trastuzumab due to its high cost,” remarked Rugo. “We hope that the introduction of biosimilars will expand patient access to this effective drug, which has already benefited thousands of people around the globe.”
Normal endometrium prior to tamoxifen therapy tied to reduced uterine cancer risk

JAIRIA DELA CRUZ

Use of tamoxifen for the prevention or treatment of breast cancer is believed to have a negative impact on endometrial health in women, but it appears that women who have a normal endometrium prior to therapy initiation have a reduced risk of developing pre-malignant conditions, according to a study presented at the ASCO 2016 meeting.

Researchers followed 296 postmenopausal women with early-stage oestrogen receptor-positive (ER+) breast cancer (median age 59.5 years) who were randomized to tamoxifen or tamoxifen plus medroxyprogesterone acetate (MPA; 10 mg for 14 days every 3 months). All patients underwent ultrasound examinations at baseline, and at years 2 and 5 to check for endometrium thickness. Based on the literature, the tamoxifen control arm was projected to have an endometrial abnormality rate of 30 percent.

Of the patients, 169 (57 percent) were eligible for evaluation at year 2, 89 in the tamoxifen arm and 80 in the tamoxifen plus MPA arm. Endometrial thickening ≥5 mm occurred in 67 percent of women receiving tamoxifen compared to 60 percent of those taking tamoxifen plus MPA (p=0.40). These patients underwent endometrial biopsies.

Endometrial abnormality rate was lower than expected. There were four cases of proliferative endometrium and one of hyperplasia in the tamoxifen arm (rate 6 percent; 95 percent CI, 0.02 to 0.13) and one case of proliferative endometrium in the tamoxifen plus MPA arm (p=0.11). All abnormalities were benign.

The rate of benign endometrial abnormalities overall at year 2 was 3.6 percent (6 of 169; 1.3 to 7.6 percent), with only one (of 102) new benign proliferative event at year 5.

While tamoxifen offers significant survival benefit in the adjuvant treatment of ER-positive breast cancer, its proliferative effect on the endometrium may potentially induce abnormalities that can lead to uterine cancer.

The findings suggest that a normal endometrium prior to initiating tamoxifen therapy should reassure patients of a very low risk of future endometrial events, researchers said. However, validating the results in a larger cohort is required before any changes in practice could be made in asymptomatic postmenopausal women.
Mobile-based follow-up improves lung cancer outcomes

NAOMI RODRIG

A web-based mobile application for early detection of symptomatic relapse in patients with advanced lung cancer has demonstrated significant improvements in overall survival (OS), according to a French phase III trial. [ASCO 2016, abstract LBA9006]

The application, dubbed Moovcare™, involves a dynamic analysis of weekly patient-reported, self-scored symptoms, which automatically triggers a physician visit when certain predefined criteria of recurrence or complications are fulfilled. CT imaging is then quickly prescribed and appropriate care delivered.

After completing their front-line treatment, 121 stage III/IV lung cancer patients with no progression and a performance status of 0-2 were randomized to web-based follow-up or standard follow-up (CT assessment every 3-6 months or by physician discretion) in the trial. Maintenance chemotherapy or tyrosine kinase inhibitor (TKI) therapy were allowed. The median follow-up was 9 months.

“The median OS was 19 months for patients who used the mobile application vs 11.8 months in the standard-care arm [p=0.0014], with a hazard ratio for death of 0.33,” reported lead study investigator Dr. Fabrice Denis from the Institut Inter-regional de Cancérologie Jean Bernard in Le Mans, France. “The respective 1-year survival rates were 75 vs 49 percent, while relapse rates were similar in both arms, at 51 vs 49 percent.” The study was stopped at the preplanned interim analysis because of the favourable results in the experimental arm.

In addition, patients who used the mobile application had a better performance status, so that 74 percent were able to receive the full recommended treatment at disease recurrence. In contrast, only 33 percent of patients in the standard follow-up arm were well enough to receive the optimal treatment at relapse.

“Quality of life as measured by standard questionnaires was also improved using the web application compared with standard follow-up,” Denis noted. “Furthermore, the application could save resources since it reduced the annual average number of imaging
Temozolomide with RT improves OS in elderly glioblastoma patients

NAOMI RODRIG

Adding temozolomide chemotherapy to short-course radiation therapy (RT) in elderly patients with newly diagnosed glioblastoma significantly improves overall survival (OS) and progression-free survival (PFS), according to results from a global phase III trial. [ASCO 2016, abstract LBA2]

“This is the first study to test the combination of temozolomide plus RT in older individuals, who account for half of all patients with the disease,” noted lead investigator Dr. James Perry of the Sunnybrook Health Sciences Centre in Toronto, Canada. “In previous studies, a trend of decreasing benefit with the addition of temozolomide at increasing age was observed, and the question remained unanswered until now.”

A total of 562 patients aged ≥65 years (median, 73 years) with histologically confirmed newly diagnosed glioblastoma were randomized to receive short-course RT (40 Gy in 15 fractions over 3 weeks) or RT plus 3 weeks of concomitant temozolomide followed by monthly adjuvant temozolomide until disease progression or until completion of 12 cycles.

“RT plus temozolomide significantly improved OS compared with RT alone. The median survival was prolonged from 7.6 to 9.3 months, translating into a 33 percent reduction in the risk of death (p<0.0001),” Perry said. “Al-
though the difference may seem modest, adding temozolomide significantly increased the chances of surviving for 2 or 3 years. The 1- and 2-year survival rates were 37.8 and 10.4 percent with RT plus temozolomide vs 22.2 and 2.8 percent with RT alone.

PFS also improved from 3.9 months in the RT arm to 5.3 months in the combination therapy arm (p<0.0001; hazard ratio [HR], 0.50).

Perry added that quality-of-life (QoL) analyses showed no differences in the functional domains of the relevant questionnaires but the incidence of side effects such as nausea, vomiting and constipation was higher in the RT plus temozolomide arm. Upon disease progression, 39 percent of patients on RT plus temozolomide were able to receive systemic therapy, compared with 41 percent of patients on RT alone.

The study also confirmed that the benefit of temozolomide was greater among patients with O6-methylguanine-methyltransferase (MGMT) promoter methylation. In previous studies, MGMT methylation has been shown to predict a better response to chemotherapy and longer survival in patients with glioblastomas if temozolomide was added to RT. [N Engl J Med 2005;352:997-1003] “In 165 patients with MGMT methylation, the OS for patients receiving combination therapy vs RT alone was 13.5 vs 7.7 months, while the OS in MGMT unmethylated patients was 10.0 vs 7.9 months, respectively,” reported Perry.

“Although glioblastoma disproportionately affects older patients, there are no clear guidelines for treating these patients, and practices vary globally,” he remarked. “Our data provide the first evidence from a randomized clinical trial that temozolomide chemotherapy in combination with short-course RT significantly extends survival without detrimental effects to QoL.”

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**Left- and right-sided CRC differs in prognosis and treatment response**

**JACKEY SUEN**

A retrospective analysis of the phase III CALGB/SWOG 80405 trial revealed significant differences in survival and treatment response in patients with metastatic colorectal cancer (CRC) arising in the left vs right side of the colon.

First-line bevacizumab-based treatment was found to be more effective in patients with right-sided primary tumours, while first-line cetuximab-based treatment performed better in those with left-sided primary tumours. [ASCO 2016, abstract 3504]

“While previous studies suggested that tumour location may impact clinical outcomes
in CRC, the effect we observed in this analysis appeared to be far greater than what we expected,” said lead investigator Professor Alan Venook of the University of California, San Francisco, California, US.

The current analysis included 293 patients with KRAS wild-type right-sided primary tumours (caecum to hepatic flexure) and 732 patients with KRAS wild-type left-sided primary tumours (splenic flexure to rectum) from CALGB/SWOG 80405, a trial comparing the efficacy of bevacizumab- and cetuximab-based therapy as first-line treatment in metastatic CRC. [https://clinicaltrials.gov/ct2/show/NCT00265850]

Significantly longer median overall survival (OS) was observed in patients with left- vs right-sided primary tumours (33.3 vs 19.4 months; hazard ratio [HR], 1.55; p<0.0001).

Furthermore, patients with left-sided tumours who received bevacizumab-based treatment had longer OS than their counterparts with right-sided tumours (median, 31.4 vs 24.2 months; HR, 1.32; p=0.01).

“Surprisingly, a big difference in median OS of 19.3 months was observed in those with left- vs right-sided tumours who were randomized to receive cetuximab-based treatment [36.0 vs 16.7 months; HR, 1.87; p<0.0001],” pointed out Venook.

“Cetuximab was more effective than bevacizumab in improving OS in patients with left-sided tumours [HR, 0.82; p=0.01],” he reported. “In contrast, an OS trend favouring bevacizumab was noted in those with right-sided tumours [HR, 1.26; p=0.08].”

“The prognostic and predictive values of left vs right primary tumour location are not something magical. Possible explanations include differences in the distribution of mutations, transcriptional subtypes and hypermethylation,” he suggested. “Embryology may explain these differences – the midgut forms the right colon while the hindgut forms the left colon during embryonic development.”

Another interesting finding was noted in their exploratory analysis of patients with KRAS mutant tumours. “Although cetuximab is not indicated in KRAS mutant CRC, those with right-sided KRAS mutant tumours who received cetuximab had longer OS than their KRAS wild-type counterparts [median, 23.3 vs 16.7 months],” noted Venook. “If this is eventually confirmed by other studies, we know less about RAS than we think we do.”

“First-line cetuximab and bevacizumab have different treatment effects in subgroups defined by left vs right sidedness of primary tumours,” he concluded. “The study results will influence decisions on treatment sequences, but will not preclude my use of either agent, at least for now.”
Erdosteine protects lung cancer patients against cisplatin-induced nephrotoxicity, said researchers at the recent APLCC 2016 in Chiang Mai, Thailand.

This protective, randomized, double-blinded clinical trial recruited 60 lung cancer patients undergoing cisplatin-based doublet chemotherapy. Creatinine clearance (CrCr), serum/urine neutrophil gelatinase-associated lipocalin (NGAL), serum/urine Cystatin C, and urine kidney injury molecule 1 (KIM-1) measures were obtained to assess the effects of erdosteine in preventing nephrotoxicity. [APLCC 2016, abstract ABS030]

The intervention group (n=30) received 600 mg oral erdosteine twice daily, while the control group (n=30) received standard cisplatin treatment.

While no significant difference between the intervention and control group was observed at baseline, decreased expression of NGAL and urinary KIM-1 were seen in the intervention group. CrCr levels declined in the control group and serum/urine Cystatin C levels remained the same in both groups.

These results point toward the protective effect of erdosteine, said the researchers, indicating the need for further studies that investigate the effect of different erdosteine doses on lung cancer patients. This would enable identification of an optimal dose for lung cancer patients, they said.

Cisplatin is the most widely used chemotherapy drug for the treatment of lung cancer. However, the toxic effect of cisplatin on tissues, organs and the kidney limits the use of this drug. Cisplatin-induced neurotoxicity could be due to tubular cell death and inflammation, the researchers suggested, drawing on recent research findings.

Erdosteine is commonly used for the exacerbation of chronic obstructive bronchitis and treatment of various lung diseases. The anti-inflammatory property of erdosteine and its indirect action against errant receptor tyrosine kinase made this the drug of choice.
How to manage AEs associated with EGFR TKIs, ALK inhibitors among NSCLC patients

ELVIRA MANZANO

Compared with standard chemotherapy, EGFR tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) inhibitors are associated with improved efficacy in patients with EGFR-mutant and ALK-rearranged non-small cell lung cancer (NSCLC). However, these agents are not without adverse events (AEs), says a leading oncologist at the APLCC 2016.

“Both EGFR TKIs and ALK inhibitors are generally less toxic than chemotherapy,” said Professor Caicun Zhou, director of the Department of Oncology, Shanghai Pulmonary Hospital and chairman of the Oncology Department of Tongji University in Shanghai, China., “However, these TKIs are associated with a number of bothersome AEs that need to be managed carefully.”

Improper management of AEs could affect tolerability and efficacy of therapies as duration of targeted therapies with progression-free survival of about 1 year is longer than chemotherapy, he added.

Diarrhoea, for example, induced by EGFR TKIs, requires good patient evaluation, diet modification and standard dose loperamide, said Zhou. If diarrhoea is resolved within 12 hours, loperamide should be discontinued and the diet adjusted. For persistent diarrhoea (grade 1/2), loperamide should be increased to 4 mg and 2 mg every 2 hours thereafter. Severe diarrhoea (grade 3/4) that comes with fever, dehydration and blood in stool however requires hospital admission, octreotide administration, intravenous fluids, and antibiotics as needed. “Laboratory studies are also required as well as titration of octreotide dose upward as necessary,” added Zhou. [Curr Oncol 2011;18:126-138]

The risk factors for diarrhoea include female sex, low body surface area, comorbidities, renal failure, and elderly age. “If patient is to be started on afatinib, prophylaxis with antidiarrhoeal diet – no spicy and greasy foods – is rec-
ommended,” said Zhou. Milk is also avoided, so are cabbage, Brussel sprouts and broccoli as these are difficult to digest. [Future Oncol 2015;11:267-277]

The presence of paronychia in some patients requires temporary discontinuation of EGFR TKI for 2-4 weeks. Upon improvement to grade 1, EGFR TKI may be reintroduced, said Zhou. Dose is dependent on clinician discretion. “If toxicities do not worsen, we usually escalate the dose.”

If paronychia does not improve, EGFR TKI should be discontinued and clobetasol cream 2-3 times daily should be started as needed, he added.

Interstitial lung disease (ILD) or interstitial pneumonitis associated with EGFR TKIs may also present in NSCLC patients, requiring physicians’ careful review of patient history, risk factors, respiratory signs and symptoms, and chemotherapy or radiation. “If your patient develops ILD, it is crucial to discontinue the drug and initiate high-dose steroids, coupled with oxygen therapy or mechanical ventilation as supportive treatment,” said Zhou.

Third generation EGFR TKIs meanwhile showed striking efficacy against T790M mediated acquired resistance, with minimal efficacy against WT EGFR and low rate of skin rashes, he added.

“We have also good data to show that second generation ALK inhibitors can successfully overcome acquired resistance to crizotinib and are well-tolerated,” Zhou said.

“Overall, alectinib and ceritinib were both well-tolerated, with low proportions of patients needing dose reduction, interruption and withdrawal. The most common AEs reported with alectinib were constipation, fatigue and peripheral oedema and most were grade 1 to 2.” [N Engl J Med 2014;370:1189-1197; J Clin Oncol 2016;34:661-668; Lancet Oncol 2016; pii:S1470-2045(15)00614-2; Lancet Oncol 2016;17;234-242]

Radiotherapy may enhance tumour metastasis

PEARL TOH

Researchers have uncovered a mechanism that might explain the potential uptick in tumour cell migration following radiotherapy.

Radiation causes lung cancer cells to increase interleukin-6 (IL-6) cytokine expression,
which draws macrophages to the cells. However, IL-6 cytokines could promote tumour cell detachment while macrophage infiltration could enhance tumour cell migration to other parts of the body.

“These findings may be clinically significant since several reports suggested the potential risk of radiation in increasing tumour metastasis despite its beneficial effects on reducing primary tumours,” the researchers said during a presentation at the recent IASLC Asia Pacific Lung Cancer Conference (APLCC) 2016 held in Chiang Mai, Thailand. “This paradigm challenges the current radiation treatment in lung cancer therapeutics.”

Using in vitro cell culture models for non-small cell lung cancer (NSCLC), H157 and A549, the researchers found that more macrophages migrated to tumour cells exposed to 6 Gy radiation compared with non-irradiated cells (p<0.01). Furthermore, irradiated tumour cells had increased levels of IL-6 (p<0.01). [APLCC 2016, ABS075]

Tumour cells that had their levels of IL-6 reduced by small interfering RNA (siRNA) recruited less macrophages after radiation compared with tumour cells with normal IL-6 levels (p<0.01).

Additionally, when mouse models were implanted with IL-6 depleted tumour cells, fewer macrophages migrated to the site after radiation compared with tumours with normal IL-6 levels (p<0.001), confirming the role of IL-6 in radiation-induced macrophage migration.

Radiation also increased the levels of specific set of cytokines, the CC chemokine ligand (CCL) 2 and CCL5 chemokines, which were known to be induced by IL-6 itself, in the tumour cells (p<0.001).

Blocking the activity of either CCL2 (p<0.001) or CCL5 (p<0.01) with neutralizing antibodies significantly reduced the number of macrophages migrating to irradiated tumour cells. This was further reduced when both CCL2 and CCL5 were blocked simultaneously (p<0.001).

As the microenvironment of a tumour can influence tumour cell behaviour, the researchers grew the lung cancer cell lines with conditioned media (CM) that was used to grow macrophages.

CM contains all the secretory factors, including cytokines, also released in vivo by macrophages, which suggests that macrophage infiltration could enhance the metastatic potential of tumour cells.

Tumour cells grown in CM were more invasive compared with tumour cells cultured in control media (p<0.001).

Further analysis showed that tumour cells cultured in CM had increased expression of genes associated with cell detachment and metastasis, such as N-cadherin (p<0.01), matrix metallopeptidase 9 (MMP9)(p<0.001), and transforming growth factor beta 1 (TGF-β1) (p<0.05).

“In order to overcome this undesired effect, an elucidation of molecular mechanisms that govern radiation-induced macrophage infiltration would be revealing,” the researchers said, suggesting that targeting the CCL2/CCL5 pathway in combination with standard radiotherapy might help reduce macrophage infiltration.
Researchers have reported the clinical features and treatment outcome of pulmonary sarcomatoid carcinoma (PSC), which is a subgroup of non-small cell lung cancer (NSCLC) that has not been well-studied.

“Because of its rarity, there are insufficient data regarding clinical manifestation, treatment response, and prognosis of PSC,” said the researchers during the recent APLCC 2016.

PSC is a rare tumour comprising about 1 percent of all lung malignancies. PSC is loosely categorised into five subtypes: pleomorphic, spindle cell, giant cell, carcinosarcoma, and pulmonary blastoma. [Arch Pathol Lab Med 2010;134:49–54]

The retrospective study analysed 22 patients (mean age 66.8 years, 20 male, two female) who have been diagnosed with PSC from 2009 to 2015 in Korea. [APLCC 2016, abstract PA06]

Ninety percent of the PSC patients were current or former smokers. The most common presenting symptom in PSC patients was respiratory symptoms (46 percent) followed by abnormal chest radiography (27 percent) and cancer-related pain (18 percent).

Spindle cells carcinoma was the most common subtype (46.7 percent) among the 15 patients examined microscopically, followed by pleomorphic carcinoma (40 percent) and giant cell carcinoma (13.3 percent).

Out of the 12 PSC patients tested for epidermal growth factor receptor (EGFR) mutations, two were tested positive, with a mean overall survival (OS) of 13.1 months, which appeared to be a better prognosis compared with those who tested negative for EGFR mutation (mean OS 7.1 months).

Thirteen patients were given palliative chemotherapy for initial treatment, five received curative surgery, three were under best supportive care, and one was treated with radiotherapy.

Curative surgery had the greatest median OS – 16.9 months – followed by chemotherapy (median OS 8.7 months) and supportive care
(median OS 3 months).

Among those given chemotherapy, 10 patients were on platinum-based doublet combination chemotherapy, two were treated with a tyrosine kinase inhibitor (TKI), and another one was given docetaxel monotherapy.

Patients on TKI showed a higher median OS of 13.1 months compared with 8.3 months for patients on platinum-based doublet chemotherapy.

The median OS of all patients treated with chemotherapy in general was 8.7 months and their progression free survival was 49 days.

PSC patients had relatively fair outcome, with one patient who was positive for EGFR mutation showing promising survival data, according to the researchers.

“Their response to chemotherapy was less favourable than other NSCLC, but platinum doublet chemotherapy was considered for patients who have performance status (PS) 0 to 1,” they said.

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**Postprogression survival survival impacts overall survival in elderly lung cancer patients**

**ROSHINI CLAIRE ANTHONY**

Postprogression survival (PPS) has a bigger impact than progression-free survival (PFS) on overall survival (OS) of elderly patients with extensive disease small cell lung cancer (ED-SCLC) who were treated with first-line chemotherapy, according to a Japanese study.

There was a stronger correlation between PPS and OS in this group of patients (Spearman’s rank correlation coefficient \( r = 0.92; \) linear regression \( R^2 = 0.83; p < 0.05 \)) than between PFS and OS \( (r = 0.76; R^2 = 0.25; p < 0.05) \). The best response after second-line treatment and the number of regimens after progression beyond first-line therapy were independent prognostic factors for PPS \( (p < 0.05) \). [APLCC 2016, abstract ABS017]

“These results suggest that treatments administered after first-line chemotherapy affect the OS in elderly ED-SCLC patients,” said the study authors.

According to the authors, the effects of
first-line chemotherapy on OS could be confounded by subsequent therapies in patients with SCLC. Thus, to determine the association between PFS or PPS and OS, researchers studied 57 elderly patients with ED-SCLC who had been treated with first-line chemotherapy between July 1998 and December 2014. The patients were treated with carboplatin (area under the curve [AUC] 5 for 1 day) and etoposide (80 mg/m²/day on days 1, 2, and 3), with treatment for both paused for 21 days after each cycle. The cycle was repeated every 3 to 4 weeks up to 4 courses.

The American Cancer Society estimates that there will be about 224,390 new cases of lung cancer diagnosed and about 158,080 deaths from lung cancer in 2016 in the US alone. The elderly are the most affected group, as two out of three people diagnosed with lung cancer are aged ≥65 years. [American Cancer Society, http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics; accessed 17 May 2016]

In Singapore, lung cancer is the second most common cancer in men and the third most common in women. As in the US, most lung cancer cases are diagnosed in individuals aged ≥65 years. [Singapore Cancer Registry, Trends in Cancer Incidence in Singapore, 2010-2014, https://www.nrdo.gov.sg/publications/cancer; accessed 17 May 2016]

Carnitine levels may predict fatigue after platinum-containing chemotherapy

RADHA CHITALE

Urine carnitine levels may predict fatigue in thoracic cancer patients treated with platinum-containing chemotherapy, according to the results of a small study.

Fatigue is a common complaint after chemotherapy and it lowers quality of life and can affect therapeutic efficacy, but the pathogenesis of fatigue is unknown, said researchers from Toyama University Hospital in Toyama, Japan.

Carnitine is an amino acid derivative that plays a key role in cellular energy production. “A decreased level of plasma carnitine has been reported in the case of cancer patients who developed cachexia,” the researchers said.
“It has been reported that carnitine is excreted in the urine after the administration of platinum-type anticancer drugs.”

Their study included 7 male and 3 female patients, median age 66.5 years, with thoracic cancer treated with standard cisplatin-containing chemotherapy. Twenty-four-hour urine samples and blood samples were collected one day before chemotherapy (day 1) and again on day 2, 3, 4, and 8. The researchers measured free carnitine, total carnitine, and acylcarnitine concentrations and evaluated fatigue levels. [APLCC 2016, abstract PA15]

Total urinary carnitine levels peaked sharply at day 2, 24 hours after chemotherapy administration, reaching 632.9 µmol/L, a significant increase compared to day 1 when total urinary carnitine was 122.3 µmol/L (p=0.003). Carnitine levels fell immediately after day 2, reaching near-baseline levels and remaining low for the duration of follow-up.

Total plasma carnitine levels peaked 48 hours after chemotherapy at day 3, reaching 95.2 µmol/L, compared to day 1 (65.3 µmol/L, p=0.001). Unlike urinary carnitine, however, plasma carnitine levels did not peak as dramatically and declined gradually over the follow-up period.

“Fatigue levels were the most severe on day 4 and did not improve thereafter,” the researchers said, and they reported that emotional well-being, functional-well being, and social and family well-being did not improve.

“The study suggests an increase in the amount of carnitine excretion within urine is a possible predictive factor for the appearance of fatigue related to chemotherapy. Future studies will be planned to investigate the protective effects of carnitine administration for fatigue in patients with [cisplatin]-containing chemotherapy.”

NSCLC patients with uncommon EGFR mutations respond poorly to EGFR TKIs

RADHA CHITALE

Advanced non-small cell lung cancer (NSCLC) patients with uncommon mutations did not respond as well to first generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) as those with more common mutations, according to a small, retrospective Japanese study.

NSCLC patients with common EGFR mutations, such as exon 19 deletions or L858R mutations, respond well to standard EGFR TKI therapy but the efficacy for patients with less common mutations is unknown.
Using a patient database from the Kinki-chuo Chest Medical Center and Osaka Prefectural Medical Center for Respiratory and Allergic Diseases in Osaka, Japan, researchers selected 41 NSCLC patients with uncommon mutations who had been treated with the first-generation EGFR TKIs gefitinib or erlotinib as monotherapy between 2007 and 2014. Median patient age was 71 years. [APLCC 2016, abstract PA25]

The researchers identified the uncommon G719X, L861Q, and S768I EGFR mutations (in single and complex combinations) for inclusion in the experimental arm of the study.

Median progression-free survival (PFS), defined as the interval between first EGFR TKI initiation and the date when progressive disease or death was first documented, was 3.5 months among all patients with uncommon mutations. Median overall survival (OS), defined as from the date of first anti-tumour agent initiation until the date of death, or the last follow-up visit, was 6.3 months.

Among NSCLC patients with common EGFR mutations, PFS tends to be longer, about 10 months, than those without such mutations, though OS seems unaffected, making them good predictive biomarkers for EGFR TKI therapy. [N Engl J Med 2010;362:2380-2388; J Thorac Oncol 2009;4:22-29]

Treatment response varied among patients with uncommon mutations, with L861Q and G719A mutations responding better than those with G719B or G719C mutations. In fact, G719C-mutated patients responded notably worse compared to the rest of the patients with other uncommon mutations, the researchers said.

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**Lung cancer: A disease of women as it is of men**

**JAIRIA DELA CRUZ**

Neither a specific diagnostic approach nor “a gender-driven” therapy is currently available for women with lung cancer, according to an expert who discussed existing assumptions and evidence at the recent APLCC 2016. In line with this, Dr. Silvia Novello, associate professor at the Department of Oncology in the University of Turin, discussed changing...
epidemiology, the risk in never smokers, and molecular profile of lung cancer in the female population.

Epidemiology

Lung cancer is the leading cause of death among solid tumours in women, mirroring the situation that has been present in the US, as well as in other developed countries for many years, said Novello. However, disparities in lung cancer incidence exist among specific Asian American populations, with increased mortality rates in Filipino and Korean women but not in Chinese women.

Recent trends reflect an important increase in the incidence and mortality of lung cancer in women for many European countries including Hungary, Italy, France, Poland, Germany, and Spain, she said. In Italy, for example, incidence and mortality increased by 2.7 (2006 to 2014) and 1.6 percent (1999 to 2015), respectively, in female versus male population wherein there is a slight decrease in both incidence and mortality, she added. “In terms of histology, adenocarcinoma rates also grew considerably among women compared to men in the past 10 years (17 vs 1.8 percent per year, respectively).”

One study shows that patients aged <40 years accounted for 0.6 percent of incident NSCLC between 1978 and 2010, and were more likely to be women (51 percent). Female gender is described in several publications as a positive prognostic factor in this specific subgroup of lung cancer patients, she noted. [Front Oncol 2015;5:113]

Smoking habits

“Smoking habits are the primary cause of the increase in lung cancer even among women.” Novello strongly believes there is no gender difference in susceptibility to tobacco smoke.

She cited a recent large study that suggests similar relative risk for current smoking and the incidence of many smoking-related cancer between women and men in the US, with 121 for squamous carcinoma and 11.7 for adenocarcinoma in women and 114.6 and 15.6, respectively, in men. [Int J Epidemiol 2015;doi:10.1093/ije/dyv175]

While the findings likely reflect a convergence in smoking patterns among women and men in the US, this is not the case in many countries in Asia, where smoking prevalence is higher among males compared to females, she said.

Strong preventive action against smoking play a critical role in the reduction of lung cancer mortality rates. In the US, states that implement stringent policies to reduce the number of smokers have reported reductions in lung cancer-related deaths among adults aged 30 to 39 years. [Int J Environ Res Public Health 2016;13:362]

Novello noted some programmes for young people in terms of primary prevention in some Asian countries from the previous plenary session and identified several initiatives that have been pursued in Italy including lung cancer advocacy group for women and smoking prevention campaigns in schools.
Never-smoker population

“Women still represent the vast majority of patients with lung cancer among never smokers,” with a difference in terms of geographic distribution, she said.

Most of the lung cancer cases in never smokers occur in Asia and are of the adenocarcinoma type, she said. However, the exact causes of lung cancer in the never-smoker female population is unclear. [Nat Rev Cancer 2007;7:778-790]

Novello alluded to a large study including 634,000 women who were followed for 14 years that reported a lung cancer incidence of 0.2 percent in never smokers. Of the 34 risk factors examined, only three were identified as potentially significant such as taller height, asthma comorbidity, and non-Caucasian ethnicity. [Int J Cancer 2016;139:347-354]

Molecular profile of lung cancer

KRAS mutation appears to occur frequently in female versus male patients with lung cancer. Novello cited a French study describing the molecular profile of lung cancer in a cohort of patients with newly diagnosed NSCLC.

She pointed out the reported presence of the different types of KRAS mutations in the never smoker patient subset, saying that there is a correlation between KRAS mutation, the female gender, smoking history, and negative prognostic factor. [Clin Cancer Res 2008;14:5731-34]

EGFR mutations also commonly occur in women than in men and in never smokers than in former or current smokers, Novello said, mentioning a study investigating the distribution of EGFR in an Asian cohort. The last World Conference on Lung Cancer also raised another important point that gender difference in the incidence of EGFR may not be true when looking at rare mutations, she added. [APJCP 2016;17:965–971]

BRAF mutations in lung cancer are notably different compared to those in melanoma, she said. Evidence suggests a link between this type of mutation and poor prognosis in female patients with lung cancer. [J Clin Oncol 2011;29:3574-3579]

With HER2, mutations occur frequently in the never smoker and Asian populations, as well as in mucinous adenocarcinoma in women and younger women, she said. [Clin Cancer Res 2012;18:1947–1953]

One study that examined the enrichment of immune gene sets in women with NSCLC suggests that gender difference may emerge when tumour tissues are compared to normal tissues. [Oncotarget 2016;doi:10.18632/oncotarget.7943]

“This will probably have an impact on the clinical results [observed in immunotherapy studies] even if until now we do not have a strong evidence of this difference looking at the main results from the pembrolizumab or the nivolumab randomized trial,” Novello noted.
High smoking rates in Asia: What needs to be done

JAIRIA DELA CRUZ

Smoking rates are worryingly high in Asia, with the number of adult smokers reaching 121 million, half of whom live in Indonesia, according to an expert who addressed an audience of oncologists at the recent APLCC 2016. The Philippines has the second highest number of smokers with more than 17 million, followed by Vietnam with 15.3 million.

While the proportion of females are low, the bulk of the smoking population in the region not only include adult males but younger boys as well, said Professor Prakit Vathesatogkit, executive secretary of Action on Smoking and Health Foundation of Thailand.

This number translates to a significant health burden as smoking is the leading cause of deaths worldwide. Vathesatogkit noted that Asia has more than 400,000 thousand tobacco-related deaths annually, accounting for an estimated 107,000 of those associated with lung cancer. “Even the youngest oncologist will have no problem finding lung cancer patients in their practice,” he commented.

What is more troubling is that non-smoking adults and children pay a high price for being exposed to second-hand smoke, which increases the risk of lung cancer and respiratory diseases.

The percentage of children in the region exposed to second-hand smoke at home and in public places is very high, with Indonesia recording the highest at 68.8 and 78.1, respectively, followed by Vietnam at 58.5 and 71.2, as reflected by data between 2007 and 2013. “This is a bad sign for the number of lung cancer to come,” Vathesatogkit said.

The war against tobacco

The risks associated with tobacco consumption are well documented, and every country is clear on what it needs to do to prevent consumption among non-smokers and encourage cessation among smokers as part of a much bigger effort to curb related diseases and deaths.

Many governments have implemented the so-called “best buys,” or high-impact, cost-effective interventions to crack down on smoking, including raising taxes, publicizing health con-
sequences, and banning smoking and tobacco advertising, Vathesatogkit noted.

“We have the tool, we have the knowledge, and we have the expertise to control tobacco,” but despite these, smoking rates are still high in some countries, he said.

He pointed out that pressure from tobacco companies, political inertia, poor financial support, and weak intersectoral coordination are among the roadblocks that many face in controlling tobacco use.

**Physicians should actively join the fight**

Vathesatogkit called for active physician involvement to help stamp out tobacco habits and further the fight against the epidemic of tobacco-related diseases in Asia.

“Doctors are not doing enough to get people to quit smoking,” he said.

On another occasion, Vathesatogkit mentioned several ways in which health professionals can contribute. He said they can take on the role of educators to warn the public of the health risks associated with tobacco use and second-hand smoke exposure, of initiators to promote anti-smoking policies such as smoke-free workplaces, and of advocates to add their voices and weight to national and global tobacco control efforts like tax increase campaigns.

To provide a better understanding that more should be done, he cited a 2013 survey that reported the progress of 121 countries in developing tobacco dependence treatment systems in keeping with the guidelines and recommendations of the World Health Organization Framework Convention on Tobacco Control.

Only a small percentage of countries surveyed had mandatory recording of patient’s tobacco use status in medical notes (n=20), had national smoking cessation training standards (n=26), had a clearly identified budget for treatment (n=20), provided cessation support for health workers (n=55), and had quitline services (n=44). [Addiction 2013;108:1476-84]

Vathesatogkit emphasized that while the region has made some strides in the war against tobacco, winning requires the strong involvement of healthcare professionals.

“We all need to do more,” he concluded. 🌟
Reducing afatinib dose may lower treatment-related AEs in advanced EGFR-positive NSCLC

JAIRIA DELA CRUZ

Reducing the dose of afatinib may lower the incidence and severity of treatment-related adverse events (AEs) without compromising therapeutic efficacy in a subset of patients with EGFR-positive non-small cell lung cancer (NSCLC), according to a post-hoc analysis presented at the APLCC 2016.

The analysis was based on the LUX-Lung 3 (LL3) and LUX-Lung 6 (LL6) phase III trials including patients with EGFR-positive stage IIIIB/IV NSCLC who either received a reduced afatinib dose (<40 mg once daily) or remained on ≥40 mg dose once daily. The investigators looked at the impact of afatinib dose reduction on safety, pharmacokinetics, and efficacy.

The superiority of afatinib to chemotherapy under regimens of cisplatin plus pemetrexed in LL3 and cisplatin plus gemcitabine in LL6 have been reported previously, with progression-free survival (PFS) as the primary endpoint. Key adverse events associated with afatinib treatment were diarrhoea, rash/acne, stomatitis, and nail effects such as paronychia. [J Clin Oncol 2013;31:3327-34; Lancet Oncol 2014;15:213-22]

Afatinib dose adjustment schemes included treatment interruption for up to 14 days for patients with any grade ≥3 AEs until severity improved to grade 1 or baseline and reintroduction at a lower dose (10 mg decrements to a minimum of 20 mg) for patients with treatment-related grade 2 diarrhoea, prolonged vomiting, or grade ≥2 worsening of renal function. [APLCC 2016, abstract 134]

Dose reductions were necessary in 122 (53 percent) of 229 patients in LL3 and in 67 (28 percent) of 239 patients in LL6, with mostly occurring within the first 6 months of treatment (86
and 82 percent in LL3 and LL6, respectively), reported principal investigator Professor Yi-Long Wu, director of Guangdong Lung Cancer Institute in China.

Patients who dose-reduced were mostly female <50 kg, Asians, and older (≥65 years) in the LL3 cohort, he said. Median total treatment time was higher in the dose reduction group than in the unchanged dose group (371 vs 294 days in LL3; 428 vs 336.5 days in LL6).

Treatment-related AEs improved in terms of severity and incidence post-reduction period compared to pre-reduction period in the overall population. The percentage of patients who had grade ≥3 AEs (36 vs 49 percent), diarrhoea (5 vs 14 percent), rash/acne (15 vs 16 percent), stomatitis (5 vs 9 percent), or nail effect (0 vs 11 percent) was lower with post- vs pre-reduction period.

Plasma levels of afatinib measured on days 22 and 43 did not differ among patients who stayed on the 40 mg regimen. Plasma concentrations were higher at pre-reduction (day 22) than at post-reduction (day 43) among those who dose-reduced from 40 mg to 30 mg.

Moreover, afatinib plasma levels on day 43 were similar between patients who received the 40 mg dose and those who reduced to 30 mg, suggesting that lower afatinib dose may produce the same therapeutic response as higher dose in patients with EGFR-mutant NSCLC, Wu explained.

Efficacy outcomes were similar between patients in the dose reduction group (<40 mg) and the unchanged dose group (≥40 mg), with median PFS of 11.3 versus 11 months in LL3 and 12.3 vs 11 in LL6, respectively, he added. Median total treatment time was higher in patients who dose-reduced than in those who did not (371 vs 294 days in LL3; 428 vs 336.5 days in LL6).

“Post-hoc analyses from LL3 and LL6 suggest that tolerability-guided dose adjustment of afatinib is an effective measure to reduce treatment-related AEs without affecting therapeutic efficacy,” Wu said.

Asked whether he would recommend starting at a lower dose or at the approved 40 mg and only reducing dose as AEs occur, in female and underweight (<50 kg) patients with EGFR-positive NSCLC, Wu said there’s no need for an increased dose and that 30 mg may be good for select patients.

Afatinib is an irreversible ErbB family blocker, approved as a first-line treatment in EGFR-mutated lung cancer in several countries in Asia including Singapore, Malaysia, Hong Kong, Indonesia, Thailand, Philippines, Taiwan, and Korea.
Tyrosine kinase inhibitor prolongs postprogression survival in NSCLC patients

KAVITHA G. SHEKAR

Tyrosine kinase inhibitor (TKI) was found to prolong postprogression survival (PPS) in non-small cell lung cancer patients (NSCLC) patients, according to a research.

TKI continuation was significantly associated with longer PPS in patients with exon 19 deletion, compared to discontinuation (p=0.02). Of the 144 patients, 63 with a single lesion had a significantly longer PPS compared to those with 2 to 3 and ≥4 lesions (p=0.015). TKI continuation was also associated with a stable disease compared to the previous scan (p=0.017). [APLCC 2016, abstract ABS 081]

Multivariate analysis of age, gender, smoking history, change compared to prior scan, site progression extracranial lesions, brain metastasis, and chemotherapy showed longer PPS in NSCLC patients with exon 19 deletion, but not in those with L858R mutation (p=0.03).

Currently, the role of continuing first generation TKI in NSCLC patients after progression remains unknown, said the researchers. This study aimed to explore factors that may show benefit for TKI continuation, including longer PPS.

NSCLC patients with exon 19 deletions may benefit most from TKI continuation, said the researchers. However, larger prospective studies are required to strengthen these findings, they added.

Study participants included 144 NSCLC patients treated with epidermal growth factor receptor (EGFR) TKI from June 2009 to October 2014 in West China Hospital, Sichuan University. Patient records were retrospectively retrieved, and the number of progressive lesions upon first progression was recorded.
Platinum-based doublet chemotherapy may be the best treatment option for elderly patients with advanced non-small cell lung cancer (NSCLC) who are fit, whereas monotherapy using either gemcitabine, vinorelbine, or taxanes should be a valid option for those who are less fit, according to an expert.

To prove this point, Dr. Silvia Novello, assistant professor at the Department of Oncology, University of Turin in Turin, Italy reviewed findings from a well-known French trial that examined the effects of carboplatin plus paclitaxel treatment versus vinorelbine or gemcitabine monotherapy in a cohort of 451 patients aged 79 to 89 years with stage III to IV NSCLC. Primary endpoint was overall survival, and analysis was done by intention to treat.

Platinum-based doublet chemotherapy provided significant survival benefits compared with vinorelbine or gemcitabine monotherapy. Median overall survival was 10.3 months for doublet and 6.2 months for single-agent chemotherapy (p<0.0001), with 1-year survival rate of 44.5 and 25.4 percent, respectively. Toxicity was higher with doublet chemotherapy than with monotherapy. [Lancet 2011;378:1079-88]

The survival curves are impressive, Novello said. “There is a statistical significance, but there is also a difference in terms of toxicity profile.”

Greater toxicity may be an issue in immunotherapy when considering treatment options outside doublet chemotherapy regimens. Novello cited an unplanned analysis of data on fit elderly patients (aged ≥70 years) with advanced NSCLC from the Eastern Cooperative Oncology Group Trial 4599 who were randomized to paclitaxel plus carboplatin with bevacizumab (PCB) or PC only.

In the subset of elderly NSCLC patients, PCB versus PC did not result in improved survival and was further associated with a higher degree of toxicity, she said. Grade 3 to 5 toxicities occurred in 87 percent of elderly patients in the PCB arm compared to 61 percent in the PC arm, with treatment-related deaths of 7 and
“What is more important is that when comparing the toxicity between the elderly and younger population, there is a statistically significant difference in the PCB arm that is not true for the arm without bevacizumab,” she said.

In elderly patients with epidermal growth factor receptor (EGFR)-activating mutations, EGFR tyrosine kinase inhibitors (TKIs) are recommended as a first-line treatment, with gefitinib being the least toxic, said Novello.

Moreover, in those who failed previous chemotherapy, “there is a room to administer EGFR TKI as a second-line treatment because the efficacy is more or less the same compared to younger patients,” she added.

“[The approach to take when treating elderly patients with advanced NSCLC] is a choice, and we can make this choice by making the right screening in elderly patients.”

Novello said several factors must be taken into account in the management of lung cancer in this particular population. These include the absence of an agreement on the definition of “elderly,” existence of comorbid conditions, underrepresentation in clinical trials, limited social and financial resources, and adoption of biological rather than chronological age to guide medical decision.

However, she noted that it is difficult to ascertain the biological age as there are no specific biomarker or test to properly detect the maturity of the cells.

In addition, changes occurring with age should also be considered, such as increased body fat, decreased total body water, altered gastrointestinal system, and reduced renal, hepatic, and hematopoietic function, she said.

“This at the end means a different pharmacodynamics, especially with drugs requiring conversion to active metabolites, and increase in terms of toxicity not only related to chemotherapy,” Novello noted.

She proposed classifying elderly patients into three clinically meaningful categories, as follows: fit patients (functionally independent and without relevant comorbidity) who can receive full dose treatment; intermediate or vulnerable patients (dependent in one or more instrumental activities of daily living [IADLs] and/or have one or two significant comorbid conditions) who should receive special treatment precautions such as initial dose reduction and adequate home care; and frail patients (dependent on one or more ADLs, with three or more severe comorbidities, one or more geriatric syndromes, and aged >80 to 85 years) who are best suited for palliative and supportive care.

“We have to spend time, and the calculation in different publications is more or less 20 to 25 years to properly define elderly patients. In this way, we can probably better define the biological age, define which patients are good for clinical trials or for standard treatment or only for best supportive care,” she said.
A large study presented at EHA 2016 provides further evidence for the feasibility and safety of stopping tyrosine kinase inhibitor (TKI) therapy in patients with chronic myeloid leukaemia (CML) who have achieved a deep molecular response (MR).

Among 868 patients enrolled in the EURO-SKI study (European Stop TKI Study), rates of molecular relapse-free survival were 62 percent at 6 months, 56 percent at 12 months and 51 percent at 24 months. [EHA 2016, abstract S145]

“Importantly, patients who relapsed after TKI discontinuation were still sensitive to the TKI therapy, so there is no evidence of escape,” reported lead investigator Dr. Johan Richter of the Lund University, Sweden.

The EURO-SKI study included chronic-phase CML patients who had received TKI therapy for at least 3 years and achieved MR^4 for at least 1 year. The majority (94 percent) of patients received first-line TKI therapy with imatinib, while 4 percent received nilotinib and 2 percent received dasatinib.

“The median time from CML diagnosis to the first day of stopping TKI therapy was 92.7 months, and the median duration of MR^4 prior to TKI discontinuation was 56.3 months,” said Richter.

“After a median follow-up of 10 months, 348 patients had a molecular relapse, and five patients died in remission,” he reported. “Among patients who relapsed, 37 percent relapsed 6 months after TKI discontinuation, 43 percent relapsed at 12 months, and 50 percent relapsed at 36 months. Despite treatment interruption, the TKI therapy remained effective when re-introduced in the relapsed patients.”

While previous smaller studies had shown similar rates of durable remission in CML patients who discontinued TKI therapy following achievement of deep MR, the EURO-SKI study also shed light on the prognostic markers that
may increase the rate of durable deep MR after TKI discontinuation.

“The duration of TKI treatment and duration of MR were found to be significantly associated with molecular relapse-free survival at 6 months,” said Richter. “One additional year of imatinib treatment and 1 additional year in MR prior to TKI discontinuation increased the likelihood of staying in molecular remission at 6 months by 16 percent.”

The rate of molecular relapse-free survival at 6 months was 65.5 percent among patients treated with imatinib for at least 5.8 years, compared with 42.6 percent among those treated with imatinib for 5.8 years or less, he added.

“Patients’ BCR/ABL status should be assessed before attempting to discontinue TKI therapy,” he suggested. “In our study, 72 patients had BCR/ABL1 transcript levels above 1 percent after TKI discontinuation, while 11 patients lost complete cytogenetic response.”

Additional follow-up is planned in the 3-year study.

CHRISTINA LAU

Blinatumomab improves OS and remission rates in relapsed/refractory ALL

Blinatumomab, a bispecific T-cell engager (BiTE), nearly doubled overall survival (OS) and complete remission (CR) rate vs standard chemotherapy in patients with Philadelphia chromosome (Ph)-negative relapsed/refractory B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) in the phase III TOWER trial.

Median OS was 7.8 months in the blinatumomab arm vs 4 months in the standard of care (SOC) chemotherapy arm (hazard ratio, 0.71; p=0.011) in a prespecified interim analysis conducted after the occurrence of 248 deaths (75 percent) among 405 patients enrolled in the trial. [EHA 2016, abstract S149]

“Improvement in the primary endpoint of OS was consistent between subgroups based on age, prior salvage therapy, or prior allogeneic stem cell transplantation,” reported investiga-
tor Dr. Max Topp of the University Hospital of Wuerzburg, Germany.

CR was observed in 39 percent of patients receiving blinatumomab vs 19 percent of patients receiving SOC chemotherapy (p<0.001). The rate of combined CR or CR with partial or incomplete haematologic recovery was 46 vs 28 percent (p=0.001).

Adverse events, including neurologic events, occurred at similar rates between the two study arms. Adverse events associated with blinatumomab treatment were consistent with findings of previous studies.

“Based on these findings, the data monitoring committee recommended stopping the TOWER trial for efficacy before the planned final analysis,” said Topp.

In the trial, patients with Ph-negative relapsed/refractory BCP-ALL were randomized in a 2:1 ratio to receive blinatumomab (n=271) or SOC chemotherapy (n=134). Blinatumomab was administered in 6-week cycles with 4 weeks on (continuous infusion of 9 µg/day in week 1 of cycle 1, then 28 µg/day) and 2 weeks off therapy, with dexamethasone given pre-dose to prevent cytokine release syndrome. SOC chemotherapy consisted of investigator’s choice of one of four regimens: fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG) ± anthracycline, or regimens based on high-dose cytarabine arabinoside, high-dose methotrexate or clofarabine. Patients in remission after two induction cycles were eligible to continue therapy until relapse.

Blinatumomab is the first agent in the novel class of BiTE antibody constructs that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. The immunotherapy received accelerated approval by the US Food and Drug Administration (FDA) in December 2014 and conditional approval by the European Medical Association (EMA) in November 2015 for the treatment of Ph-negative relapsed/refractory BCP-ALL based on results of a single-arm phase II study. [Topp MS, et al, ASCO 2014, abstract 7005; Lancet Oncol 2015;16:57-66]

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Single-agent inotuzumab beats standard chemotherapy in ALL

JACKEY SUEN

The anti-CD22 antibody conjugate inotuzumab ozogamicin improves survival vs standard chemotherapy in patients with acute lymphoblastic leukaemia (ALL), the phase III INO-VATE ALL trial has shown.

Although the results did not meet the level of statistical significance set for the primary endpoint of overall survival (OS), restricted mean

In the trial, 326 patients with relapsed/refractory CD22-positive ALL were randomized to receive inotuzumab ozogamicin or standard chemotherapy with FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor), cytarabine plus mitoxantrone, or high-dose cytarabine.

“Progression-free survival was significantly longer in the inotuzumab ozogamicin group [median, 5.0 months vs 1.8 months for chemotherapy; hazard ratio (HR), 0.45; p<0.001],” reported Professor Hagop Kantarjian of the University of Texas MD Anderson Cancer Centre, Houston, Texas, US. “Median OS was 7.7 months with inotuzumab ozogamicin and 6.7 months with standard chemotherapy, failing to meet the prespecified statistical significance of p<0.0104 [HR, 0.77; p=0.0203].”

“However, the OS curves of the two arms separated only after about 14 months, favouring inotuzumab ozogamicin, which appeared to depart from the proportional-hazards assumption,” he added. “Therefore, we performed an exploratory post-hoc RSMT analysis, showing that RSMT was significantly longer in patients in the inotuzumab ozogamicin group [13.9 vs 9.9 months; p=0.0023].”

The 2-year survival rate was 23 percent with inotuzumab ozogamicin vs 10 percent with standard chemotherapy.

“Another primary endpoint of the trial was complete remission or complete remission with incomplete haematologic recovery [CR/CRi]. This was met based on an analysis of the first 218 patients randomized in the trial. The data was presented at the EHA 2015 Congress,” said Kantarjian. “CR/CRi was achieved in 80.7 percent of patients in the inotuzumab ozogamicin group vs 29.4 percent of those in the standard chemotherapy group.” [EHA 2015, abstract LB2073; *N Engl J Med* 2016, doi: 10.1056/NEJMoa1509277]

The most common grade ≥3 adverse events were cytopenias, which were significantly less common with inotuzumab ozogamicin.

“Eleven percent of patients receiving inotuzumab ozogamicin had veno-occlusive liver disease [VOD], but only 3 percent developed the disease during or shortly after treatment administration,” noted Kantarjian. “At our centre, the incidence of VOD is reduced to below 5 percent with preventive measures and by avoiding agents that damage the liver.”
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Lupus doubles women’s risk of pre-malignant cervical cells

RADHA CHITALE

Women with systemic lupus erythematosus (SLE) have twice the risk of pre-malignant cervical neoplasias that could become cervical cancer, compared to the general population, according to a Swedish study presented during the European League Against Rheumatism (EULAR) annual congress held recently in London, England.

“Previous evidence that SLE or its treatment might increase the risk of cervical neoplasia has been inconclusive,” said lead investigator Dr. Hjalmar Wadström from the Department of Medicine Solna at the Karolinska Institute in Stockholm, Sweden. “Our findings have confirmed that SLE is a risk factor for cervical malignancies, even after adjusting for important risk determinants such as previous cervical screening.”

The researchers established a cohort of 4,550 women with SLE through a Swedish national registry and compared them to matched controls (n=28,113). [EULAR 2016, abstract OP0189]

Within the SLE cohort, 1,783 were treated with antimalarial drugs, which are typical first-line therapy against lupus, and 1,981 were treated with more aggressive immunosuppressive drugs of the kind typically given to organ transplant patients.

The researchers recorded a total of 121 cervical dysplasia and cancer events comprising pre-malignant changes, in situ cancers, and invasive cancers, although the bulk of the events were pre-malignant changes; only five invasive cancers were recorded, which Dr. Johan Askling, a professor at the Karolinska Institute and a co-investigator on the trial, said matched the event occurrence of the normal population.

Compared to the general population, the rate of cervical dysplasia or invasive cancer was double among women with SLE (hazard ratio [HR], 2.12, 95 percent confidence interval [CI], 1.65-2.71). The rate was highest among women with SLE treated with immuno-suppressives (HR, 2.72, 95 percent CI, 2.01-3.67) and lowest among women with SLE treated with anti-malarials (HR, 1.52, 95 percent CI, 1.00-2.33).

The researchers adjusted for education, healthcare utilization, number of children, marital status, family history of cervical cancer, prior cervical screening during the 5 years before follow-up started, and start year.

Though the study showed women with SLE appear to be at increased risk of cervical
neoplasia and that immunosuppressive treatment was a marker of further increased risk of invasive cancer, Askling said it was unclear whether complications from SLE or complications from SLE treatment – both of which are known to be associated with immunological aberrations – drove the increased risk in immune suppressor-treated patients.

Clinicians should ensure women with SLE are screened for cervical cancer, Askling said, but no further additional measures need be taken at this stage.

**Testosterone therapy does not increase prostate cancer risk**

**KAVITHA G. SHEKAR**

Testosterone replacement therapy (TRT) does not increase prostate cancer risk, say Swedish researchers. The controversy of TRT and prostate cancer risk may be laid to rest with this latest research finding, presented at the American Urological Association’s 2016 Annual Meeting.

This case control study recruited 38,570 patients with prostate cancer (cases) and 192,838 age matched controls from the National Prostate Cancer Registry and Prescribed Drug Registry in Sweden between 2009 and 2012. TRT prescriptions were obtained by 284 cases and 1,378 controls. [AUA 2016, abstract 1145]

No significant association between TRT use and overall prostate cancer risk was observed (odds ratio [OR], 1.03, 95 percent confidence interval [CI], 0.90-1.17). TRT users also had lower risk for aggressive prostate cancer (OR, 0.50, 95 percent CI, 0.37-0.67). This lower risk was observed after 1 year of TRT use.

“Based on our findings, physicians should still be watching for prostate cancer risk factors, such as being over the age of 40, having African-American ancestry, or having a family history of the disease, in men taking TRT, but should not hesitate to prescribe it to appropriate patients for fear of increasing prostate cancer risk,” said lead study author Assistant Professor Stacy Loeb from New York University School of Medicine, New York, US.

“When used appropriately by men with age-related low testosterone who are otherwise healthy, TRT has been shown to improve sexual function and mood,” added Loeb.
“Overall, our study suggests that what is best for men’s health is to keep testosterone levels balanced and within a normal range,” said Loeb suggesting that symptomatic men with testosterone levels below 350 ng/dL should seek medical advice on TRT. She also noted that TRT use has increased drastically over the past years, which could be attributed to an increase in the ageing population.


In the US, 180,890 new cases of prostate cancer were diagnosed in 2016, with an estimated 26,120 deaths this year. [National Cancer Institute Surveillance, Epidemiology, and End Results Program. Available at: http://seer.cancer.gov/statfacts/html/prost.html. Accessed on 25 May 2016]

Genentech’s bladder cancer drug receives US FDA approval

RADHA CHITALE

The US Food and Drug Administration recently granted accelerated approval to the new anti-PD-L1 immunotherapy atezolizumab, which is sold as Tecentriq™ by Genentech Inc., for treating a type of bladder cancer that has seen no new therapies in about 30 years.

Accelerated approval, which is for medications for which there is an unmet need and demonstrable early clinical benefit, was based on the phase II open-label, multicentre, two-cohort IMvigor 210 trial to determine the safety and efficacy of atezolizumab in locally advanced or metastatic urothelial carcinoma patients regardless of PD-L1 expression who had progressed within 12 months of adjuvant or neoadjuvant platinum-based chemotherapy (the second cohort, n=310). [Lancet 2016; pii:S0140-6736(16)00561-4]

These patients (median age 66 years, 78 percent male) received 1,200 mg infusions of
atezolizumab every 3 weeks until unacceptable toxicity or radiographic or clinical progression, with median follow-up of 14.4 months.

Compared to a historical control overall tumour response rate of 10 percent, atezolizumab had an objective response rate (ORR) of 14.8 percent (p=0.0058). Patients with higher PD-L1 expression performed better than patients with lower PD-L1 expression (ORR, 26 percent vs 9.5 percent, respectively).

In all patients, complete response rate was 5.5 percent. Median duration of response was not reached in all patients or in the high PD-L1 expressing subgroup and was 12.7 months in the low PD-L1 expressing subgroup.

The most common grade 3-4 adverse reactions included urinary tract infection, nausea, and fatigue and there were no treatment-related deaths.

“This report is the first to show the association of The Cancer Genome Atlas subtypes with response to immune checkpoint inhibition and to show the importance of mutation load as a biomarker of response to this class of agents in advanced urothelial carcinoma,” the researchers said.

Results from the first cohort of the IMvigor 210 trial are not yet released and may clarify response durability. Roche, which owns Genentech and funded the IMvigor trials, has an ongoing phase III trial to compare atezolizumab with standard of care chemotherapy in metastatic urothelial cancer that progressed after initial treatment.
HBV vaccination in infants linked to reduced HCC in Taiwan

CHRISTINA LAU

A vaccination programme that immunizes infants against hepatitis B virus (HBV) has been linked to a reduced incidence of hepatocellular carcinoma (HCC) in Taiwan.

Researchers analysed data from two HCC registries in Taiwan that included 1,509 patients (age, 6-26 years) diagnosed with HCC between 1983 and 2011. Data on HBV immunization and prenatal maternal levels of HBV antigens in HCC patients born after 1984 were retrieved from the Taiwan Centre for Disease Control. [Gastroenterology 2016, doi: 10.1053/j.gastro.2016.05.048]

“Of the 1,509 HCC patients in the registries, 1,343 were born before and 166 were born after the launch of the HBV vaccination programme in Taiwan,” reported the researchers. “The incidence of HCC was 0.92 per 100,000 person-years in the unvaccinated birth cohort compared with 0.23 per 100,000 person-years in the vaccinated birth cohort.”

Compared with the unvaccinated cohort, the relative risk of HCC in the vaccinated cohort was 0.26 for patients aged 6-9 years, 0.34 for patients aged 10-14 years, 0.37 for patients aged 15-19 years, and 0.42 for patients aged 20-26 years. The risk reductions with HBV vaccination were statistically significant.

The lowest incidence of HCC (0.04 per 100,000 person-years) was reported in individuals who had received at least three doses of HBV vaccine and whose mothers were hepatitis B surface antigen (HBsAg)-negative. Furthermore, the relative risk of HCC was significantly lower in the 1984-1992 and 1992-2005 birth cohorts compared with the 1984-1986 cohort.

Taiwan began offering HBV vaccination to infants born to women who were seropositive for HBsAg and hepatitis B e antigen (HBeAg) in 1984. In 1986, the programme was expanded to cover all infants. The HBV vaccine used was originally a plasma-derived formulation, with four doses administered at <1 week, 1 month, 2 months and 12 months of age. In 1992, this was changed to a recombinant vaccine, with three doses given at <1 week, 1 month and 6 months of age. Neonates born to highly infectious women carrying HBsAg and HBeAg were given hepatitis B immunoglobulin ≤24 hours after birth.
Neoadjuvant endocrine therapy effective for oestrogen-receptor positive breast cancer

ROSHINI CLAIRE ANTHONY

Neoadjuvant endocrine therapy is a safe and effective option for women with localized oestrogen receptor-positive breast cancer, and due to its low toxicity, could be considered as combination therapy in the appropriate patient population, a systematic review and meta-analysis finds.

Neoadjuvant endocrine therapy as mono-therapy with aromatase inhibitors had similar clinical response rate (odds ratio [OR], 1.08, 95 percent confidence interval [CI], 0.50-2.35; p=0.85), radiological response rate (OR, 1.38, 95 percent CI, 0.92-2.07; p=0.12), and breast conservation surgery rate (OR, 0.65, 95 percent CI, 0.41-1.03; p=0.07) but lower toxicity when compared with combination chemotherapy. [JAMA Oncol 2016; doi:10.1001/jamaoncol.2016.1897]

The neoadjuvant endocrine therapy and aromatase inhibitor combination also appeared to be more beneficial than tamoxifen in terms of clinical response rate (OR, 1.69, 95 percent CI, 1.36-2.10; p<0.001), radiological response rate (OR, 1.49, 95 percent CI, 1.18-1.89; p<0.001), and breast conservation surgery rate (OR, 1.62, 95 percent CI, 1.24-2.12; p<0.001).

When combined with everolimus, celecoxib, zoledronic acid, gefitinib, dual endocrine therapy with aromatase inhibitors plus tamoxifen, or lapatinib, neoadjuvant endocrine therapy as dual therapy had a similar clinical response rate (OR, 0.91, 95 percent CI, 0.70-1.19; p=0.50) but a higher radiological response rate (OR, 1.49, 95 percent CI, 1.11-2.02; p=0.008) than monotherapy.

Dual combination therapy with growth factor pathway inhibitors also demonstrated a higher radiological response rate (OR, 1.59, 95 percent CI, 1.04-2.43; p=0.03) but not a clinical response rate (OR, 0.76, 95 percent CI, 0.54-1.07; p=0.11) compared with endocrine monotherapy.

“Although neoadjuvant chemotherapy is more widely used for fit patients than neoadjuvant endocrine therapy, both therapies have similar efficacy and low toxicity, and neoadjuvant endocrine therapy needs to be reconsidered as a potential option,” said the study authors.
According to the authors, the role of neoadjuvant endocrine therapy in oestrogen receptor-positive breast cancer, whether as monotherapy or combination therapy, is yet to be determined. They set out to identify the effect of neoadjuvant endocrine therapy on response rate and breast conservation surgery rate for oestrogen receptor-positive breast cancer by looking at 20 prospective, randomized clinical trials published between January 2001 and December 2014 (n=3,490) that had at least one neoadjuvant endocrine therapy arm.

“Given that the primary tumour remains intact during therapy, the neoadjuvant treatment approach allows for monitoring of treatment response and discontinuation of inactive therapy in the event of disease progression, thereby saving the patient exposure to potentially toxic therapy,” said the authors, who recommended that further study be done to identify the patient population for whom neoadjuvant endocrine therapy would be most effective.

“Neoadjuvant endocrine therapy also provides the opportunity to examine mechanisms of endocrine resistance, to optimize and compare endocrine therapies, and to investigate combination approaches with novel targeted therapies that may delay or prevent endocrine resistance,” the authors said.

Risk-based CT screening beats USPSTF recommendations for lung cancer death prevention

STEPHEN PADILLA

The use of a risk-based model for computed tomography (CT) screening for lung cancer prevented more lung cancer deaths than a model based on the US Preventive Services Task Force (USPSTF) recommendations, a study has shown.

To compare the modelled outcomes from risk-based CT lung-screening strategies with USPSTF recommendations, researchers analysed empirical risk models for lung cancer incidence and death in the absence of CT screening using data on ever-smokers from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO; 1193 to 2009) control
group. Covariates included age, education, sex, race, smoking intensity, duration, and quit-years; body mass index, family history of lung cancer, and self-reported emphysema. [JAMA 2016;315:2300-2311]

Researchers also conducted model validation in the chest radiography groups of the PLCO and the National Lung Screening Trial (NLST; 2002 to 2009), with additional validation of the death model in the National Health Interview Survey (NHIS; 1997 to 2001), a representative sample of the US. Models were applied to US ever-smokers aged 50 to 80 years (NHIS 2010 to 2012) to estimate outcomes of risk-based selection for CT lung screening, assuming screening for all ever-smokers yield the percent changes in lung cancer detection and death observed in the NLST.

The main outcome measures for model validity were calibration (number of model-predicted cases divided by number of observed cases [estimated/observed]) and discrimination (area under curve [AUC]). For modelled screening outcomes, the primary outcomes were estimated number of screen-avertable lung cancer deaths and estimated screening effectiveness (number needed to screen [NNS] to prevent 1 lung cancer death).

Lung cancer incidence and death risk models were well-calibrated in PLCO and NLST. The lung cancer death model calibrated and discriminated well for US ever-smokers aged 50 to 80 years (NHIS 1997 to 2001: estimated/observed = 0.94 [95 percent CI, 0.84 to 1.05]; AUC, 0.78 [0.76 to 0.80]).

Under USPSTF recommendations, the models estimated 9 million US ever-smokers would qualify for lung cancer screening and 46,488 (43,924 to 49,053) lung cancer deaths were estimated as screen-avertable over 5 years (estimated NNS, 194; 187 to 201).

In contrast, risk-based selection screening of the same number of ever-smokers (9 million) at highest 5-year lung cancer risk (≥1.9 percent) was estimated to avert 20 percent more deaths (55,717; 53,033 to 58,400) and was estimated to reduce the estimated NNS by 17 percent (NNS, 162; 157 to 166).
Mutations of the BRCA1 tumour suppressor gene are associated with a high risk of breast and ovarian cancer but the exact mechanism by which BRCA1 is involved in cancer pathogenesis has to date been unclear. Now, however, researchers have found that BRCA1 ubiquitin ligase activity plays a vital role in DNA repair. [Nature Structural & Molecular Biology 2016; doi:10.1038/nsmb.3236]

BRCA1 has been shown to facilitate the attachment of the protein ubiquitin to other proteins. Cells that lack this BRCA1 ubiquitin ligase activity are not able to perform DNA repair via homologous recombination and may subsequently be mutated, a process that can lead to cancer. Cellular experiments have shown that BRCA1 ubiquitin ligase activity is reliant on a partner protein, BARD1. By manipulating BARD1 and leaving the BRCA1 protein untouched, researchers were able to show that BRCA1 was required for ubiquitin attachment and that it played a key role in cellular response to, and repair of, DNA damage. They also found that BRCA1 has several other functions, all of which are independent of each other.

This finding has important clinical implications as physicians are worried that patients with low/no BRCA1 ubiquitin ligase activity may become resistant to targeted therapies such as olaparib. However, since BRCA1 has multiple functions, there are multiple targets that may be used to prevent tumour resistance.
Patients who receive opioid-free anaesthesia while undergoing breast cancer surgery require fewer postoperative painkilling medications, according to a recent study reported at the Euroanaesthesia 2016 meeting held in London, UK.

The researchers compared clinical characteristics and postoperative piritamide pain-killer consumption among 66 patients who received opiate (remifentanil, ketamine plus lidocaine; n=33) or non-opiate (clonidine, ketamine plus lidocaine; n=33) anaesthesia while undergoing mastectomy or lumpectomy in Brussels, Belgium. All patients were provided with a patient-controlled analgesia pump for controlling breakthrough pain during the first 24 hours postoperatively. Two patients were excluded from the final analysis due to incomplete data.

Patients who received opioid-free anaesthesia were found to have a significantly lower total mean piritamide usage during the first 24 hours postoperatively compared with patients in the opioid group (8.1 mg [range 2.0–14.5 mg] vs 13.1 mg [range 6.0–16.0 mg]). [Euroanaesthesia 2016, abstract 01AP14-10]

The researchers concluded that non-opiate anaesthesia during breast cancer surgery may reduce the need for postoperative painkillers and avoid opioid-associated side effects such as nausea and vomiting. However, they cautioned that further studies are required before non-opiate anaesthesia can be recommended for all breast cancer patients.
Mindfulness helps men with prostate cancer cope with active surveillance

One in four men with prostate cancer who choose active surveillance upon diagnosis will switch to definitive therapy because of difficulty coping with the associated fear and anxiety. However, mindfulness meditation, a form of contemplative awareness, can increase their resilience and reduce anxiety, say US-based researchers.

They conducted a pilot study in which 43 men on active surveillance were randomized to mindfulness training (n=24) or an attention control arm (n=19) for 8 weeks. Self-report measures of prostate cancer anxiety, uncertainty intolerance, global quality of life, mindfulness and post-traumatic growth (positive growth experienced as a result of a struggle) were determined at baseline, 8 weeks, 6 months and 12 months. [Psycho-Oncology 2016; doi: 10.1002/pon.4135]

Men who underwent mindfulness training reported significantly less prostate cancer anxiety and uncertainty tolerance following the intervention. Significant improvements in mindfulness, global mental health and post-traumatic growth were also noted. Although control group participants also reported an increase in mindfulness over time, longitudinal increases in posttraumatic growth were significantly larger among participants in the mindfulness group.

The researchers concluded that mindfulness training can help men cope with some of the stressors and uncertainties associated with active surveillance.
JULY

2016 Japanese Society of Medical Oncology Annual Meeting
28/7/2016 to 30/7/2016
Kobe, Japan
Tel: +81 78 303 1101
Fax: +81 78 303 3760
E-mail: jsmo2016@convention.co.jp
http://www2.convention.co.jp/jsmo2016/english/index.html

International Conference on Tumour Immunology and Immunotherapy
28/7/2016 to 30/7/2016
Melbourne, Australia
E-mail: tumourimmunology@conferenceseries.com
http://tumorimmunology.conferenceseries.com/

AUGUST

4th International Conference on Advances in Haematology and Oncology (ICAHO 2016)
13/8/2016 to 14/8/2016
Coeur d’Alene, ID, US
Tel: +1 888 843 8169
Fax: +1 650 618 1417
E-mail: hemeonc@binayfoundation.org
http://oncology.binayfoundation.org/

2nd International Conference on Prostate Cancer and Therapeutics
22/8/2016 to 23/8/2016
Philadelphia, PA, US
Tel: +1 888 843 8169
Fax: +1 650 618 1417
E-mail: prostatecancer@insightconferences.com
http://prostatecancer.cancersummit.org/

SEPTEMBER

International Liver Cancer Association 10th Annual Conference (ILCA 2016)
9/9/2016 to 11/9/2016
Vancouver, Canada
Tel: +32 2 789 2345
Fax: +32 2 743 1550
E-mail: infor@ilca-online.org
http://ilca2016.org/

2nd International Conference on New Concepts in B-Cell Malignancies
9/9/2016 to 11/9/2016
Estoril, Portugal
Tel: +33 01 57 27 68 33
Fax: +33 01 57 27 68 38
E-mail: nicolas.jaillard@univ-paris-diderot.fr

13th Asian Society for Neuro-Oncology (ASNO) Meeting / 9th Cooperative Trials Group for Neuro-Oncology (COGNO) Annual Scientific Meeting
11/9/2016 to 14/9/2016
Sydney, Australia
Tel: +61 2 9265 0700
Fax: +61 2 9267 5443
E-mail: asnocogno2016@arinex.com.au

36th Congress of the European Society of Surgical Oncology (ESSO36)
14/9/2016 to 16/9/2016
London, UK
Tel: +44 20 7903 3444
Fax: +44 20 7903 4807
E-mail: info@eso.org
http://www.ecco.org/EU/events/ESSO36

12th World Cancer Conference
26/9/2016 to 28/9/2016
London, UK
Tel: +1 888 843 8169
Fax: +1 650 618 1417
E-mail: worldcancer@insightconferences.com
http://cancer.global-summit.com/europe/

NOVEMBER

ESMO Symposium on Immuno-Oncology 2016
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Tel: +41 91 973 19 62
Fax: +41 91 973 19 18
E-mail: symposia@esmo.org
http://www.esmo.org/Conferences/Immuno-Oncology-2016

8th European Multidisciplinary Meeting on Urological Cancers
24/11/2016 to 27/11/2016
Milan, Italy
Tel: +33 01 57 27 68 33
Fax: +33 01 57 27 68 38
E-mail: nicolas.jaillard@univ-paris-diderot.fr
http://www.esmo.org/conference/3rd-international-conference-on-multiple-myeloma/

ESMO 2016 Congress
7/10/2016 to 11/10/2016
Copenhagen, Denmark
E-mail: registration@esmo.org
http://www.esmo.org/Conferences/ESMO-2016-Congress

13th Asia-Pacific Oncologists Annual Meeting
17/10/2016 to 19/10/2016
Kuala Lumpur, Malaysia
Tel: +61 2 9265 0700
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E-mail: asnocogno2016@arinex.com.au

13th Asia-Pacific Oncologists Annual Meeting
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Fax: +61 2 9267 5443
E-mail: asnocogno2016@arinex.com.au

48th Annual Congress of the International Society of Paediatric Oncology
19/10/2016 to 22/10/2016
Dublin, Ireland
http://www.siop2016.kenes.com/