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Enzalutamide prolongs survival in prostate cancer

Wey-Feng Ong

Overall survival (OS) was significantly prolonged by nearly 5 months in castration-resistant prostate cancer (CRPC) patients who were treated with enzalutamide (formerly MDV 3100), an oral androgen-receptor-signalling inhibitor, according to a recent study reported in the New England Journal of Medicine. [DOI: 10.1056/NEJMoa1207506]

AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV 3100) was an international, multicenter, phase III trial that enrolled 1,199 CRPC patients whose disease progressed after chemotherapy. Patients were randomized 2:1 to enzalutamide 160 mg/day or placebo. After a planned interim analysis, AFFIRM was stopped when 520 deaths were recorded. In enzalutamide-treated patients, median OS – the primary endpoint – was 18.4 months vs 13.6 months for those in the placebo arm. Enzalutamide use was associated with a 37 percent relative risk reduction of mortality vs placebo (hazard ratio [HR], 0.63; p<0.001). “On the basis of these results, the Independent Data and Safety Monitoring Committee recommended that the study be halted and unblinded, with eligible patients in the placebo group offered treatment with enzalutamide,” the authors wrote.

Subgroup analyses showed that the OS benefit associated with enzalutamide use was consistent across the entire patient cohort, regardless of age, baseline pain intensity, treatment location and disease progression type on study entry. A further multivariate analysis adjusting for stratification factors and baseline prognostic factors confirmed the validity of the survival benefit conferred by enzalutamide (HR, 0.58; p<0.001).

Secondary outcomes measured in the study also demonstrated the superiority of enzalutamide over placebo. Patients receiving enzalutamide had a prostate-specific antigen (PSA) response rate of 54 percent vs 2 percent for placebo. Soft tissue response rate, evaluated by Response Evaluation Criteria in Solid Tumors (RECIST), was 29 percent for enzalutamide vs 4 percent for placebo. Similarly, Functional Assessment of Cancer Therapy-Prostate (FACT-P) showed a greater quality-of-life improvement with enzalutamide (43 vs 18 percent with placebo).

In addition, time to PSA progression (8.3 vs 3.0 months in favor of enzalutamide; HR, 0.25), radiographic progression-free survival (8.3 vs 2.9 months; HR, 0.40) and time to first skeletal-related event (16.7 vs 13.3 months; HR, 0.69) were significantly longer in enzalutamide-treated patients.

One confounding factor which may have affected the study results was the subsequent use of other active treatments – abiraterone acetate and cabazitaxel – following study discontinuation. However, a higher proportion of patients in the placebo arm received these active agents than those in the enzalutamide arm.

Although patients who received enzalutamide were observed longer – twice that of placebo – similar rates of adverse events...
were noted in both study arms. The median time to first serious adverse event (SAE, grade ≥3) was 12.6 months and 4.2 months in the enzalutamide and placebo arms, respectively. In addition, patients receiving enzalutamide had a lower incidence of SAEs than those receiving placebo (45.3 vs 53.1 percent).

The study results also confirmed that androgen-receptor signaling is a valid therapeutic target for the entire spectrum of prostate cancer, and provided evidence supporting the hypothesis that androgen-receptor overexpression confers resistance to conventional anti-androgen agents, leading to a shorter period of tumor latency, the authors noted.
T-DM1 demonstrates OS benefit in metastatic breast cancer

Christina Lau

Trastuzumab emtansine (T-DM1) significantly extends overall survival (OS) of patients with HER2-positive metastatic breast cancer, according to updated results of the phase III EMILIA trial.


The EMILIA trial (n=991) has now met both co-primary efficacy endpoints of significant improvements in OS and progression-free survival (PFS).

Based on the updated OS results, patients in the lapatinib/capecitabine arm of the trial will be offered the option to switch to T-DM1. In addition, Genentech plans to initiate an Expanded Access Program (EAP) in the US so that certain patients with HER2-positive metastatic breast cancer can have access to T-DM1 while the company seeks regulatory approval.

T-DM1 is an antibody-drug conjugate comprised of the antibody trastuzumab and the chemotherapy DM1, attached together using a stable linker. The therapy is designed to target and inhibit HER2 signaling and deliver the chemotherapy DM1 directly inside HER2-positive cancer cells.

Previously presented results of EMILIA showed that in patients with HER2-positive locally advanced or metastatic breast cancer who had been treated with trastuzumab and a taxane-based chemotherapy, T-DM1 significantly improved PFS vs the lapatinib/capecitabine combination (9.6 vs 6.4 months; HR, 0.65; p<0.0001). Interim OS analysis demonstrated a trend towards improvement with T-DM1, but the difference vs lapatinib/capecitabine was not statistically significant at that time. [Blackwell KL, et al. ASCO 2012; abstract LBA1]

In the trial, grade ≥3 adverse events were less common with T-DM1 than with lapatinib/capecitabine (40.8 vs 57 percent). The most common grade ≥3 adverse events associated with T-DM1 were thrombocytopenia (12.9 vs 0.2 percent), increased levels of aspartate aminotransferase (AST) (4.3 vs 0.8 percent) and alanine aminotransferase (ALT) (2.9 vs 1.4 percent), and anemia (2.7 vs 1.6 percent). In most patients, AST and ALT levels were normalized by the time of the next T-DM1 dose.

“We are extremely pleased to announce that patients treated with T-DM1 survived...
significantly longer than those who received a standard option for this aggressive advanced breast cancer,” said Dr. Hal Barron, Chief Medical Officer and Head, Global Product Development of Genentech. “We believe that antibody-drug conjugates have the potential to change the future treatment of cancer, and we look forward to working with regulatory authorities in the hope of bringing another potential treatment option to people with HER2-positive metastatic breast cancer.”

Genentech has already submitted a Biologics License Application for T-DM1 to the US FDA, and Roche will be submitting a Marketing Authorization Application to the European Medicines Agency shortly.

While the companies will initially seek approval of T-DM1 as a treatment for patients with metastatic breast cancer who have previously been treated with multiple lines of therapy, the ongoing phase III MARIANNE trial is expected to provide support for the regulatory filing of T-DM1 as a first-line treatment for HER2-positive metastatic disease. In addition, the companies are evaluating the benefits of T-DM1 in combination with pertuzumab in patients with HER2-positive locally advanced or metastatic disease. Roche has also announced recently that three more T-DM1 trials are planned to investigate the drug for neoadjuvant use, adjuvant use, and for treatment of recurrence following surgery in patients with early disease.

According to industry analysts, Roche and Genentech hope that T-DM1 will eventually infiltrate the treatment algorithm of early-stage HER2-positive breast cancer, as most patients are diagnosed with localized disease. T-DM1 is also expected to replace trastuzumab in the majority of breast cancer patient settings in which trastuzumab is currently used.

Given the potential uses, the high prevalence of breast cancer and the fact that T-DM1 will be priced at a premium to trastuzumab, analysts foresee blockbuster potential for T-DM1, especially since trastuzumab will be facing generic competition following patent expiry in 2015.

In addition to T-DM1, there are approximately 25 antibody-drug conjugates in Roche and Genentech’s pipeline.
Bendamustine-based regimen benefits lymphoma patients

Yen Yen Yip

Bendamustine, a drug developed during the 1960s, is expected to change clinical practice for doctors treating indolent and mantle-cell lymphomas.

Originally developed and used to treat different types of non-Hodgkin’s lymphomas in the former East Germany, the drug had not been available elsewhere until 1990. “After reunification, doctors in western Germany were a bit skeptical to adopt this compound, as one can imagine,” said Dr. Matthias Rummel, Professor of Medicine at the University Hospital Giessen, Germany.

But the latest findings from the Study Group for Indolent Lymphoma (STiL) trial will likely reverse any skepticism that still remains.

The results demonstrated that a regimen of bendamustine combined with rituximab (BR) was not only more effective, but also less toxic than the standard chemotherapy.

The STiL trial was the first study to randomize 514 patients with previously untreated indolent non-Hodgkin’s lymphomas to six cycles of BR or standard R-CHOP chemotherapy.

For years, R-CHOP, which includes rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone, has been the preferred therapy for non-Hodgkin’s lymphomas such as mantle cell and follicular lymphomas, among others.

The BR regimen more than doubled progression-free survival (PFS) compared with R-CHOP. At a median follow-up of 45 months, the BR regimen was associated with a significantly longer median PFS of 69.5 months vs 31.2 months for R-CHOP (p=0.00001).

Of note, patients on R-CHOP experienced significantly higher rates of grade 3 and 4 hematotoxicity compared with BR, with more leukocytopenia (38.2 vs 12.1 percent) and neutropenia (46.5 vs 10.7 percent), thus requiring more use of granulocyte colony-stimulating factor (20 vs 4 percent; all p<0.0001).

“BR shows by far a lower toxicity,” said Rummel, who was the lead author of the STiL study. “Alopecia is a very prominent difference: nearly all patients had hair loss after R-CHOP, but not a single patient experienced hair loss with BR,” he added.

BR was also associated with fewer cases of infection and neuropathy than R-CHOP. While a higher incidence of skin reactions such as erythema and allergies occurred in the BR group, these events were generally much better tolerated.

“Bendamustine-based therapy allowed patients to have a better quality of life while undergoing treatment,” noted Rummel. “These long-term findings should be strong enough to change clinical practice ... BR should be considered as a preferred first-line treatment for patients with these disease entities.”

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HPV vs cytology screening for cervical cancer

Human papillomavirus (HPV) testing for cervical cancer screening is more sensitive but less specific than cytological screening. Cost-effectiveness analyses have varied between countries.

A microsimulation model (MISCAN) was used to compare the cost-effectiveness of more than 1,500 screening policies in five European scenarios. [BMJ 2012;344:17 (e670)]

The model showed that HPV testing was usually preferable. Primary cytological screening might be preferred when the cost of cytology was low, and when HPV was highly prevalent and HPV testing costly.

Dutasteride for localized prostate cancer?

Localized prostate cancer is relatively benign and many men may receive unnecessary treatment. A new study suggests that dutasteride treatment might benefit men with low-risk prostate cancer. [Lancet 2012; 379:1103-1111]

The trial, at 65 centers in the US and Canada, included 289 men aged 48 to 82 with low-volume, Gleason score 5-6 prostate cancer, who had chosen active surveillance rather than more aggressive treatment. Patients were randomized to dutasteride 0.5 mg daily. At 3 years, the rate of prostate cancer progression was 38 percent (dutasteride) vs 48 percent (placebo), a significant difference.

A commentator, however, points to previous evidence that dutasteride might have no effect on prostate cancer mortality. He believes that neither treatment nor diagnosis should be attempted for low-risk disease. [Lancet 2012;379:1078-1080]
Genetic variation in different parts of renal cancers

Genetic analyses of tumor samples may aid prognosis and treatment. Personalized-medicine strategies often depend on a single tumor biopsy sample but intratumor heterogeneity may make such sampling invalid. Now a study in London, UK has shown the extent of intratumor heterogeneity. [N Engl J Med 2012;366:883-892]

Exome sequencing, chromosome aberration analysis and ploidy profiling were performed on multiple spatially separated samples from the primary tumors and metastatic sites of four patients with advanced renal carcinomas. There was intratumor heterogeneity with 63 to 69 percent of somatic mutations not being present at all sample sites of the same tumor. This heterogeneity was found for an mTOR kinase mutation and for multiple tumor suppressor genes. Different regions of the same tumor could have gene expression signatures indicating good or bad prognosis. Allelic composition and ploidy profiling analysis also revealed extensive intratumor heterogeneity. Two of the four tumors showed ploidy heterogeneity and 26 of 30 samples from the four tumors showed divergent allelic imbalance profiles.

Since genetic analyses from multiple sites in a single tumor may give different results, management decisions based on a single sample may not be reliable, the authors suggested.
Changing paradigms in ovarian cancer management

Although paclitaxel plus platinum-based chemotherapy has remained the mainstay of ovarian cancer (OC) treatment over the past 20 years, 5-year survival has progressively increased from 15 to about 30 percent. Recently, the introduction of new treatment modalities has further increased 5-year survival to 40-50 percent. “Although most patients are presenting with late-stage metastatic disease, the increase in 5-year survival indicates that we are getting better at treating relapsed disease,” noted Professor Stan Kaye, Head of Drug Development Unit, Royal Marsden Hospital, London, UK.

Trials involving the addition of a third cytotoxic agent – such as gemcitabine and topotecan – to existing standard therapy provided no additional clinical benefits. [J Clin Oncol 2009;27: 1419-1425]

Intraperitoneal cisplatin plus IV paclitaxel chemotherapy showed significant progression-free survival (PFS) and overall survival (OS) improvements vs IV cisplatin plus paclitaxel. “However, benefits were only demonstrated in a single study, and the therapy was highly intolerable – with only 42 percent of patients in the intraperitoneal arm completing the six prescribed cycles,” Kaye emphasized. Patients’ quality-of-life was also significantly worse at 3-6 weeks following intraperitoneal therapy, but the adverse effects were transient. [New Engl J Med 2004;354:34-43]

“A promising new development in treating OC using conventional chemotherapy is the use of weekly paclitaxel,” remarked Kaye. [Nature Rev Clin Oncol 2010;7:575-582] “Compared with the conventional 3-weekly schedule, once-weekly paclitaxel demonstrated remarkable improvements in PFS and 5-year survival in first-line OC treatment. When given once a week at a lower dose, paclitaxel is very well tolerated.” [Lancet 2009;374:1331-1338, J Clin Oncol 30;2012(suppl); abstract 5003] Once-weekly paclitaxel is active in 20-50 percent of patients with relapsed disease, including those with platinum-resistant tumors. It has also demonstrated antiangiogenic effects, as confirmed by randomized trials in metastatic breast cancer patients. [Mol Cancer Ther 2004;3:1301-1310]

The introduction of the antiangiogenic
agent bevacizumab, which targets the vascular endothelial growth factor (VEGF), into OC treatment regimens has led to remarkable improvements in clinical outcomes.

While VEGF is essential for healthy ovaries, it is overexpressed in ovarian tumors, and is associated with carcinomatosis, ascites and poorer survival. [J Clin Oncol 2007;25:5150-5152, Int J Gynecol Cancer 2010;20:248-254]

"Since VEGF plays a key role in the biology of OC, it comes as no surprise that the most advanced anti-VEGF therapeutic agent – bevacizumab – shows more clinical activity as a single agent in ovarian cancer than in any other cancer, apart from renal cancer,” Kaye said.


The current consensus on first-line OC treatment is to use bevacizumab for patients who are most likely to benefit – ie, those with residual or stage IV disease. In patients with good prognosis, bevacizumab should be reserved for disease relapse. Bevacizumab can also be used in second-line gemcitabine plus carboplatin chemotherapy, as well as in naïve patients with platinum-resistant disease.

“Currently, there are six oral antiangiogenic agents under clinical evaluation in randomized trials; they may provide additional options when they become available,” said Kaye. “Another method of targeting angiogenesis is to use angiopoietin antagonists.”

When clinical results for these new agents become available, further investigation into sequential and/or combination approaches will be required to further optimize OC treatment outcomes. “Also, it would be important to understand why patients become resistant to these therapies,” he stressed.

Although there are several biomarkers predictive of outcomes of bevacizumab-based treatment, none has yet impacted patient selection. “Hence, further development and use of predictive biomarkers in improving patient selection will be the key to providing individualized therapy for OC patients and improving outcomes,” Kaye concluded.
Targeted therapy in mCRC: ASCO 2012 key takeaways

Several studies presented at the 2012 American Society of Clinical Oncology (ASCO) provided clinical evidence regarding important, but yet unanswered, questions pertaining to targeted therapy in metastatic colorectal cancer (mCRC).

“These issues include the benefit of continuing bevacizumab therapy beyond disease progression, the role of maintenance therapy, and the efficacy of novel anti-angiogenic agents such as aflibercept and regorafenib after first disease progression,” said Dr Brigette Ma, Associate Professor of Clinical Oncology at the Prince of Wales Hospital, who reviewed the data.

What does bevacizumab offer beyond progression?

In the Treatment across Multiple Lines (TML) randomized study, the clinical benefit of bevacizumab usage beyond first disease progression was prospectively evaluated in 820 patients with disease progression within 3 months of discontinuing first-line bevacizumab plus chemotherapy. All patients received second-line crossover chemotherapy, with or without bevacizumab.

Bevacizumab-containing therapy increased median overall survival (OS) vs chemotherapy alone by 1.4 months (11.2 vs 9.8 months; HR=0.81; p=0.0062) and progression-free survival (PFS) by 1.6 months (5.7 vs 4.1 months; HR=0.68; p<0.0001). Bevacizumab-related adverse events were not increased when it was continued beyond progression. No new safety signals were identified in this study and the adverse event profiles were consistent with previous reports. [J Clin Oncol 2012;30(suppl): abstract CRA3503]

“Although the TML study confirmed clinical benefits for mCRC patients in second-line therapy, the benefits are modest. As such, clinicians should avoid a ‘one-size-fits-all’ approach and provide their patients with biomarker-guided second-line therapy when considering bevacizumab beyond first disease progression,” suggested Ma.
Does maintenance therapy prolong PFS?

Bevacizumab plus erlotinib was shown in the DREAM\(^1\) trial to prolong PFS vs bevacizumab alone in the maintenance setting. Patients receiving maintenance therapy with bevacizumab plus erlotinib achieved a median PFS of 5.8 months vs 4.6 months in the bevacizumab-only arm (HR=0.73; \(p=0.005\)). Median PFS from study inclusion was 10.2 and 9.2 months, respectively. The main differences in toxicity between the two treatment arms were erlotinib-related, with 9 percent (vs 1 percent) of patients experiencing grade 3-4 diarrhea and 19 percent (vs 0 percent) of patients experiencing grade 3-4 skin rash. [\textit{J Clin Oncol} 2012;30(suppl): abstract LBA3500]

“While planned complete treatment discontinuation was shown to be deleterious in OPTIMOX\(^2\) in terms of shorter duration of disease control and PFS, bevacizumab-alone as maintenance treatment may not be the best choice for the control arm,” remarked Ma. [\textit{J Clin Oncol} 2009;27:5727-5733] “There are still unanswered questions regarding the role of erlotinib in mCRC as well as the influence of KRAS mutation status on erlotinib treatment,” she added.

Efficacy of aflibercept as a second-line antiangiogenic agent

Aflibercept – a novel fusion protein with antiangiogenic activity – was investigated as an add-on to FOLFIRI chemotherapy in VELOUR\(^3\), which enrolled patients with disease progression following first-line oxaliplatin-based chemotherapy.

The median PFS for patients in the aflibercept-containing arm was 6.9 months (vs 4.67 months on FOLFIRI alone; \(p<0.001\)), and median OS was 13.5 months (vs 12.1 months; \(p<0.001\)). Aflibercept-related adverse events led to increased treatment discontinuations due to asthenia/fatigue, infections, diarrhea, hypertension and venous thromboembolic events. [\textit{J Clin Oncol} 2012;30(suppl): abstract 3602] “A further subanalysis investigating the prior usage of bevacizumab in this patient cohort revealed no significant differences in PFS, OS or response rate,” noted Ma. [\textit{J Clin Oncol} 2012;30(suppl): abstract 3505]

Is regorafenib better than best supportive care?

Regorafenib is an oral, multitarget tyrosine kinase inhibitor which acts predominantly on VEGF receptors. In the CORRECT\(^4\) study, regorafenib plus best supportive care (BSC) was evaluated against BSC alone in mCRC patients who had progressed after all approved standard therapies. All patients in this cohort received prior bevacizumab therapy, and had three prior lines of treatment, on average.

Patients receiving regorafenib achieved a median OS of 6.4 months (vs 5.0 months on BSC alone; HR=0.77; \(p=0.0052\)) and PFS of 1.9 months (vs 1.7 months; HR=0.49; \(p<0.000001\)). “These modest improvements in OS and PFS were mainly driven by disease stabilization, as indicated by 42.8 percent (vs 14.5 percent) of patients achieving stable disease in the regorafenib-containing arm. Partial response was minimal in both treatment arms,” noted Ma.

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1. DREAM = Double Inhibition Reintroduction Erlotinib Avastin in Metastatic Colorectal Cancer
2. OPTIMOX2 = Optimized 5-fluorouracil-Oxaliplatin strategy
3. VELOUR = Aflibercept Versus Placebo in Combination with Irinotecan and 5-FU [FOLFIRI] in the Treatment of Patients with Metastatic Colorectal Cancer after Failure of an Oxaliplatin Based Regimen
4. CORRECT = Colorectal cancer treated with regorafenib or placebo after failure of standard therapy
Shorter chemo preferable in Hodgkin’s lymphoma

Six cycles of the multi-agent escalated chemotherapy regimen BEACOPP, followed by positron emission tomography (PET)-guided radiotherapy is less toxic and more effective in advanced stage Hodgkin’s lymphoma, according to researchers from the German Hodgkin Study Group (GHSG).

"Hodgkin’s is a highly curable malignancy in adults. There is ongoing controversy on how to best treat these patients, as many die from late side effects and that is a problem which can happen years after treatment. When we design our treatments now, we have to try to envision what is going to happen to our patients in 10, 20 or 30 years, which is not an easy task,” said GHSG Chairman Professor Andreas Engert, of the University Hospital of Cologne, Germany. [Haematologica 2012;97:531]

According to Engert, intensified chemotherapy with eight cycles of escalated BEACOPP has demonstrated significantly better tumor control and overall survival. However, it is associated with more toxicity than the ABVD chemotherapy regimen and other variants. [Blood 114(22):3705]

“We did this particular study, HD 15, to attempt to reduce toxicity of both chemotherapy and radiotherapy while maintaining efficacy,” he said.

The HD 15 trial compared the GHSG standard of care (eight cycles of BEACOPP escalated) with two reduced-intensity chemotherapy variants (six cycles of BEACOPP escalated and eight cycles of BEACOPP 14). Among the 2,182 patients enrolled, treatment with six cycles of escalated BEACOPP was not only better tolerated than eight cycles, but also resulted in improved tumor control (89.3 vs 84.4 percent) and overall survival (94.5 vs 91.9 percent). This was partly attributed to lower mortality due to treatment-related events (0.8 vs 2.1 percent) and secondary malignancies (0.7 vs 1.8 percent). [Abstract O1108]

“Whether or not patients need radiotherapy after chemotherapy has always been a lingering question. We only performed PET scans on patients who had residual disease after chemotherapy; only patients with active disease on PET received additional radiotherapy,” said Engert. Only 11 percent of patients received radiotherapy treatment after PET evaluation.

“This is a very practical and pragmatic approach to identify patients who are likely in need of more treatment because they are still metabolically active after chemotherapy, and this situation can be salvaged by radiotherapy,” he suggested.
Blinatumomab extends survival in ALL patients

The monoclonal antibody blinatumomab may achieve a high rate of complete remission and prolong overall survival in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL), a phase II trial has shown.

“We used a new type of third-generation antibody to engage the T-cells to hook up and kill off leukemic cells. The trick is to select a target that is expressed on leukemic cells or their healthy counterparts. We chose CD-19 firstly because it is a well expressed target on precursor B-cell ALL cells in comparison to CD-20, which is expressed in about 20 to 40 percent of cases. Secondly, CD-19 is not modulated during disease progression, so it is a stably expressed protein,” said Professor Max Topp of the University of Wuerzburg, Germany. [Hematologica 2012;97:540]

Relapsed/refractory B-precursor ALL in adults has a dismal prognosis where typically only 35-40 percent of patients reach a hematological complete remission (CR), with a median overall survival of approximately 4.5 months, he noted.

The 2-year study evaluated the efficacy, safety and tolerability of the bispecific T-cell engager (BiTE) antibody, blinatumomab, in adult patients with ALL who had relapsed following treatment with standard front-line chemotherapy or allogeneic stem cell transplant. [Abstract O1122]

A cohort of 36 patients received the antibody for 28 days followed by 2 weeks off therapy over a 6-week treatment cycle, for up to five cycles. Blinatumomab was delivered by continuous IV infusion at varied dose levels. The primary endpoint of the study was the rate of complete remission (CR) and complete remission with partial hematologic recovery (CRh*) within two cycles.

Twenty six of the 36 patients (72 percent) treated with blinatumobab across all the tested doses and schedules achieved a CR/CRh*. All but two patients with CR/CRh* also achieved a molecular response, ie, there was no evidence of leukemic cells by polymerase chain reaction (PCR). The median duration of response among the 26 responders was 8.9 months.

Topp added that adverse events including pyrexia, headache, tremor and fatigue were most frequently seen at the onset of treatment in cycle one. Fully reversible central nervous system (CNS) adverse events were observed in six patients, who were able to resume treatment after a rest period.

“We have established a well-tolerated blinatumomab dose schedule at 5 µg/m²/day for the first week, followed by 15 µg/m²/day for the following weeks. A high rate of hematologic and molecular remission in response to blinatumomab treatment in relapsed or refractory ALL was observed,” he reported. “These data support the initiation of a global phase II study in this setting.”
Panobinostat combo safe in relapsed multiple myeloma

The use of the pan-deacetylase inhibitor (pan-DACi) panobinostat in combination with bortezomib and dexamethasone for treatment of multiple myeloma (MM) showed a comparable safety profile to previously published clinical experience with bortezomib and dexamethasone, suggest data from PANORAMA 1.

Outcomes of MM patients have seen significant improvement over the years, largely due to the availability of two novel classes of drugs: immunomodulatory drugs (IMiDs; thalidomide and lenalidomide) and proteasome inhibitors (bortezomib). However, there is an unmet need for patients refractory to these agents and those with relapsed MM.

Panobinostat has demonstrated synergy with bortezomib in preclinical MM studies, which has been attributed to dual inhibition of the aggresome and proteasome pathways.

A phase Ib study of panobinostat and bortezomib demonstrated complete responses in 64.5 percent of patients with relapsed or relapsed/refractory MM. [EHA 2011; abstract 0314] A recent phase II study confirmed this activity in bortezomib-refractory MM patients.

Preliminary results from Panorama 2, a single-arm, open-label, phase II study in bortezomib-refractory patients conducted in the US met the predefined threshold, allowing continuation of study enrollment. [EHA 2011; abstract 0900].

PANORAMA 1, a global double-blind phase III study of panobinostat + bortezomib + dexamethasone vs placebo + bortezomib + dexamethasone, aims to evaluate the impact of panobinostat on progression-free survival in patients with relapsed MM. [Abstract P0291]

Professor Jesus San Miguel, Head of Hematology Department, University Hospital of Salamanca, Spain and colleagues enrolled 762 patients with relapsed or relapsed/refractory MM (1-3 prior lines of therapy) in the trial. The study comprised two treatment phases. Treatment phase I consisted of eight 3-week cycles of panobinostat (20 mg, oral) or placebo administered thrice weekly and bortezomib (1.3 mg/m² intravenous), administered twice weekly for 2 of 3 weeks. Dexamethasone (20 mg, oral) was administered on days of or after bortezomib. Patients who achieved clinical benefit moved on to treatment phase II, which consisted of four 6-week cycles with similar administration of panobinostat and dexamethasone and a modified once-weekly bortezomib schedule. Patients were followed up until disease progression.

Preliminary blinded data from a planned safety analysis of the first 563 randomized patients (525 panobinostat-treated patients) showed that 47.9 percent of patients were still undergoing treatment. Approximately half of the patients had received 2-3 prior lines of therapy while 57.3 percent had received prior stem cell treatment. Common adverse events included thrombocytopenia (47.6 percent), diarrhea (14.5 percent), and anemia (13.0 percent). No new or unexpected adverse events were observed.

The data monitoring committee thus recommended continuing the study as planned. Updated efficacy and safety data are expected next year.
Pemetrexed effective in NSCLC regardless of ALK status

Wey-Feng Ong


In a retrospective multicenter review conducted by the Massachusetts General Hospital, 121 patients with advanced, ALK-positive NSCLC were identified and compared with 266 patients with advanced, ALK-negative, epidermal growth factor receptor wild-type (EGFR WT) NSCLC. Of the ALK-negative patients, 79 had KRAS mutations while 187 had KRAS WT tumors. Progression-free survival (PFS) of these patients was stratified based on different pemetrexed regimens.

The data demonstrated no significant difference in median PFS when the patients were analyzed based on their ALK mutation, indicating comparable efficacy of pemetrexed irrespective of ALK mutation status.

Subgroup analyses of ALK-positive patients based on received treatment found that those receiving platinum-containing pemetrexed regimens had significantly longer median PFS than patients receiving nonplatinum-containing pemetrexed regimens or pemetrexed monotherapy (7.3 vs 5.5 months).

Notably, median PFS was significantly shorter when ALK-negative patients were treated with platinum-containing pemetrexed regimens in the first-line setting: ALK-negative patients with KRAS mutant tumors had a median PFS of 4.2 months while those with KRAS WT tumors had a median PFS of 5.4 months.

“However, among patients with a never- or light-smoking history (0-10 pack-year smoking history) treated with first-line platinum-containing pemetrexed regimens, there was no difference in PFS between ALK-positive and ALK-negative patients,” the study authors wrote.

Previous reports suggested that thymidylate synthase (TS) level is inversely correlated to pemetrexed sensitivity. Based on the TS transcript levels in 12 ALK-positive patients, low TS level – defined as TS < median TS level in unselected patients with resected lung carcinoma – was not associated with longer PFS. However, two patients with high TS level had the shortest PFS (21 and 54 days). [Cancer 2006;107:1589-1596; Oncologist 2009; 14:253-263; Clin Cancer Res 2008;14:1059-1064]

Although pemetrexed-based therapy has been demonstrated to prolong PFS in unselected NSCLC patients, those who are never or light-smokers may obtain additional benefit when treated with platinum-containing, pemetrexed-based regimens in the first-line setting, regardless of their ALK mutation status, the authors suggested.
Blood test could guide renal cancer therapy

Naomi Rodrig

Serum lactate dehydrogenase (LDH) is a prognostic and predictive biomarker of survival among renal cell carcinoma (RCC) patients treated with temsirolimus, according to a recent report, suggesting that a simple blood test could guide therapy for this tumor type. [J Clin Oncol, e-pub ahead of print, August 13, 2012]

LDH is involved in anaerobic glycolysis and regulated by the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (mTOR)-containing complex 1 (PI3K/Akt/TORC1) pathway as well as tumor hypoxia/necrosis. LDH is released upon cell death or injury, and elevated serum levels of the enzyme have been used to identify cancer, tissue damage and other disorders.

Previous studies indicated that elevated LDH levels are a risk factor for aggressive malignancy, signaling tumor progression. More recent research has suggested that high LDH may also indicate the activation of key genetic alterations that lead to tumor proliferation.

Based on these results, researchers from Duke University School of Medicine, Durham, USA analyzed data from a previous phase III trial. The 2007 trial demonstrated that temsirolimus significantly prolonged overall survival (OS) vs interferon alfa, the then standard of care, which had eventually lead to its approval for the treatment of metastatic RCC in patients with poor prognosis. [N Engl J Med 2007;356:2271-2281]

In the latest analysis, pretreatment and post-treatment LDH levels were evaluated in 404 poor-risk RCC patients who were treated with either temsirolimus or interferon alfa. The proportional hazards model was used to test for the prognostic and predictive association of LDH in predicting OS.

Mean baseline serum normalized LDH was 1.23 times the upper limit of normal (ULN). The multivariate hazard ratio for death was 2.81 for patients with LDH>ULN vs those with LDH≤ULN.

The data showed that patients with high baseline LDH levels survived significantly longer on temsirolimus than on interferon alfa. Among 140 patients with LDH>ULN, the median OS was 6.9 vs 4.2 months, respectively (p<0.002). The 6-month survival rate was 53.7 percent on temsirolimus compared with 39.5 percent on interferon alfa.

Among 264 patients with normal LDH, OS was not significantly improved with temsirolimus as compared with interferon alfa therapy (median, 11.7 vs 10.4 months; p=0.514)

“This is an exciting finding,” said lead study investigator Dr. Andrew Armstrong. “Being able to direct these patients to a treatment we know will help them would be a major advancement in their care. At the same time, patients who would not benefit from the treatment would be spared from a drug regimen with potential side effects that could diminish their quality of life.”

“Further investigation of the predictive role of LDH as a measure of benefit with PI3K/TORC1 pathway inhibition in other RCC risk groups and other tumor types is warranted,” the authors suggested.
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Capecitabine in metastatic breast cancer

Dr. Angus Kwong-Chuen Leung  
Associate Consultant  
Department of Clinical Oncology  
Queen Elizabeth Hospital  
Hong Kong

Presentation and clinical history

A 45-year-old premenopausal Chinese woman presented to our clinic in 1996 with 2-month history of left breast mass. She underwent a left modified radical mastectomy in March 1996. Pathology revealed a 3 cm Bloom & Richardson Grade 3 invasive ductal carcinoma. All 18 resected lymph nodes were negative. The resection margin was clear. Estrogen receptor (ER) was positive and progesterone receptor (PR) negative. Lymphovascular invasion (LVI) was negative. Human epidermal growth factor receptor 2 (HER2) status was not tested at the time. She received 5 years of adjuvant hormonal therapy with tamoxifen; treatment was completed in 2001.

The patient developed local chest wall recurrence in May 2005. A wide local excision confirmed an invasive ductal carcinoma, ER positive, PR negative. HER-2 score was 2, with equivocal results on fluorescent in situ hybridization (FISH) analysis (Ratio of average HER2/chromosome 17 centromere [CEP17] signals = 1.86). She was given adjuvant loco-regional radiotherapy (LR-RT), chemotherapy with FAC (5 fluorouracil [5FU], adriamycin and cyclophosphamide) for six cycles, followed by hormonal therapy with letrozole, which was started in March 2006.

The patient developed lung and bone metastases in November 2008. CT of thorax showed multiple lung nodules measuring up to 1.4 cm with enlarged hilar lymph node. In addition, there was a right chest wall nodule of 1.5 cm. Fine needle aspiration cytology (FNAC) of right chest wall nodule showed carcinoma cells consistent with ductal carcinoma (ER, strongly positive; PR, negative; c-erbB2, weakly positive; FISH analysis for HER2 amplification positive, ratio of average HER2/CEP17 signals = 2.61). She was given palliative chemotherapy and targeted therapy with paclitaxel, carboplatin (AUC 5) and trastuzumab for six cycles, followed by maintenance trastuzumab, for six cycles.

Disease progression was noted in September 2009. X-ray of cervical spine showed collapsed C7 and T1. Palliative RT from C5 to T1 was given and completed in September 2009. Re-staging CT in October 2009 showed new mediastinal and right hilar lymphadenopathy; interval increase in size and number of bilateral lung metastases; new mildly enlarged lymph nodes around gastro-esophageal junction; new subcutaneous right upper chest wall nodule around clavicle level; left lower cervical and left supraclavicular fossa metastatic lymphadenopathy; interval increase in number of lytic bony lesions in the sternum, and cervical and thoracic spine, compatible with bony metastasis. Bone scan in February 2010 showed multiple bone secondary metastases, with deterioration noted as compared with prior bone scan in December 2008.

The patient was put on palliative capecitabine (1,600 mg/m² for 2 weeks in each 3-weekly cycle, dose reduction to 80 percent in view of extensive bone metastases), and lapatinib (1,250 mg daily) in October 2009. Re-assessment CT in January 2010 showed good partial response. The previously noted cervical and left supra-clavicular...
lymph nodes, mediastinal lymph nodes, right chest wall nodule and lung nodules showed interval decrease in size and number.

Subsequent CT in April 2010 revealed shrinkage of right middle lobe nodule, now measuring 4 mm in section. The subcutaneous right upper chest wall nodule around clavicle level had resolved.

The regimen was well tolerated with no significant treatment delay. There was only grade 1 hand-foot skin reaction. Subsequent CT scans in August 2010, November 2010, and February 2011 revealed static disease. A total of 13 cycles of capecitabine and lapatinib were given from October 2009 to August 2010, when treatment was stopped upon patient’s request. Maintenance lapatinib was continued until March 2011.

A further disease progression was noted in April 2011 in right chest wall nodules. FNAC of right chest wall mass showed carcinoma cells, ER (Allred score, 7), PR negative, c-erbB2 score 2 FISH positive (Ratio of average HER2 / CEP17 signals = 2.56). PET-CT in April 2011 showed multiple metastases to lung, pleura, mediastinal lymph nodes, bilateral internal mammary lymph nodes, right chest wall and bone.

After a thorough discussion, the patient opted for an oral regimen and restarted treatment with capecitabine and lapatinib in May 2011. Palliative RT to L1 and L4 was done. PET-CT in August 2011 showed partial resolution of tumor lesions in bone, lungs, right chest wall and mediastinal lymph nodes. A total of eight cycles were given; treatment was stopped in October 2011 as the patient opted for a drug holiday.

**Discussion**

There is a consensus that histology examination is recommended for each relapse, as tumor characteristics may alter with time after treatment. With the emergence of new treatment options, examination of tumor biology is recommended to guide subsequent systemic therapy, so as to improve the efficacy of the treatment, patient’s survival and quality of life. Close collaboration between various specialties, including surgeons, pathologists, radiologists and oncologists, is crucial to patient-centered care.

Anthracyclines are established as a component of adjuvant and first-line treatment for metastatic breast cancer (mBC). In patients with tumor progression beyond anthracyclines, taxanes are often the next preferred treatment in the metastatic setting. However, the use of anthracyclines and taxanes earlier in the course of the disease, including in the adjuvant setting, has increased the likelihood of patients presenting with mBC that had recurred after treatment with these agents. Therefore, new therapeutic strategies are needed for these patients.

Capecitabine was developed as an oral fluoropyrimidine that mimics the action of infusional 5FU and, at the same time, offers greater tumor selectivity. The final metabolic step involves the conversion of 5’-deoxy-5-fluorouridine to 5FU by thymidine phosphorlase (TP). Since 5FU is significantly more active in malignant tissue than in adjacent healthy tissue, the conversion to 5FU confers increasing specificity for malignant cells.

Oral administration of chemotherapy is an attractive option for cancer patients as home treatment has been associated with improved quality of life. Single-agent capecitabine has demonstrated an overall response rate (ORR) of 20-30 percent and stable disease in 40-51 percent of patients.\(^1\) The median duration of response is up to 8.1 months.\(^1\) ORR may be further improved up to 42 percent by adding other chemotherapeutic agents (eg, docetaxel) or molecular tar-
geted therapies such as herceptin or lapatinib.\textsuperscript{3,4}

Pooled data of 875 patients with mBC treated with capecitabine showed that common side effects included hand-foot syndrome (52 percent), diarrhea (48 percent), and nausea (42 percent). The majority of treatment-related adverse events were classified as Grade 1-2. Myelosuppression and blood chemistry abnormalities were rare. As an oral agent, capecitabine offers an important advantage over other available agents and its use is associated with increased patient convenience and acceptance.

References:
Capecitabine in the treatment of metastatic gastric cancer

Dr. Conrad Lee
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Presentation and history

A 52-year-old man with good past health presented in September 2007 with epigastric pain. He underwent esophago-gastroduodenoscopy and was diagnosed with malignant ulcer. Distal radical gastrectomy was performed in a private hospital in October 2007. Pathology report confirmed PT2N2 moderately differentiated adenocarcinoma of the stomach. Preoperative CT scan revealed no distant metastasis.

The patient was subsequently referred to our center for adjuvant therapy. In view of his good general condition and node-positive disease, standard chemoradiation therapy (CRT) was started as per the NT0016 regimen, with 5-fluorouracil (5-FU) and folinic acid as the chemotherapeutic agents. During treatment, the patient had vomiting, diarrhea and mucositis.

CRT was completed in April 2008, after which the patient was followed up regularly. His carcinoembryonic antigen (CEA) level was 1.3 ng/mL in November 2008 and 1.1 ng/mL in July 2009.

In 2010, CEA rose from 1.8 ng/mL in March to 4.5 ng/mL in July and 9.8 ng/mL in October.

Investigations

CT scan, performed in October 2010, showed no recurrence in the abdomen and pelvis. However, PET-CT scan revealed bilateral lung masses measuring 5.2 cm in the left upper lobe and 4 cm in the right lower lobe, compatible with lung metastasis. The lung masses were HER2 negative.

Treatment

The EOX (epirubicin, oxaliplatin, capecitabine) regimen was started on 11 January 2011 after thorough discussion of treatment options with the patient. The starting dose of capecitabine was reduced by 25 percent as the patient had moderate renal impairment (creatinine clearance by the Cockcroft-Gault Equation, 55.7 mL/min).

EOX therapy was generally well tolerated with mild side effects. The patient experienced grade 1 nausea and vomiting, grade 1 parasthesia, and grade 1 hand-foot syndrome. Mucositis and diarrhea were not reported although the patient experienced these side effects during adjuvant 5-FU therapy.

Treatment was interrupted briefly (≤1 week) after cycles 1 and 5 as the patient developed neutropenia (lowest absolute neutrophil count [ANC], 1 x 109/L). Dosages of epirubicin and oxaliplatin were reduced by 20 percent in cycle 4, and the patient had a delayed recovery.

The patient responded well to EOX therapy, with serial chest X-ray showing continued decrease in size of the lung masses. At completion of treatment (16 May 2011, 6 cycles), the lesion in his left upper lobe and right lower lobe measured 3.4 cm and 2.4 cm, respectively. (Figures A and B)

The reduction in size of lung metastases was accompanied by a continued decrease in CEA
level. At the start of treatment, the patient’s CEA level was 20 ng/mL. This fell to 8.2 ng/mL in February 2011, 5.6 ng/mL in March 2011, 3.1 ng/mL in April 2011, and 2.6 in June 2011.

Follow-up chest X-ray in August 2011 revealed further reduction in size of the lung masses (left upper lobe, 2.8 cm; right lower lobe, 2.1 cm), as well as a further decrease in CEA level (1.6 ng/mL). (Figure C) Thereafter, the patient had remained well and was followed up regularly with chest X-ray.

In December 2011, however, there was a slight increase in size of the lesion in the patient’s left upper lobe. This increased further to 6.4 cm in February 2012, while the lesion in his right lower lobe remained static (about 2 cm). His CEA level increased from 5.6 ng/mL in December 2011 to 8.4 in February 2012.

The patient was subsequently referred to another hospital for participation in a clinical trial on second-line treatment of gastric cancer.

**Discussion**

EOX chemotherapy is a standard treatment for patients with advanced esophagogastric cancer. Its comparable efficacy vs 5-FU-containing triplets was demonstrated in the phase III REAL-2 (Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2) trial of 1,002 patients with previously untreated disease.¹

Patients in REAL-2 were randomized in a two-by-two design to receive epirubicin/cisplatin/5-FU (ECF), epirubicin/cisplatin/capecitabine (ECX), epirubicin/oxaliplatin/5-FU (EOF), or epirubicin/oxaliplatin/capecitabine (EOX). The trial met its primary endpoint, with the capecitabine-containing triplets being non-inferior to the 5-FU-containing triplets in terms of overall survival (OS) (HR, 0.86). Median OS in the ECF, ECX, EOF and EOX arms was 9.9, 9.9, 9.3 and 11.2 months, respectively.¹

In the trial, progression-free survival (PFS) in the EOX arm (7 months) was similar to that in other arms (ECF, 6.2 months; ECX, 6.7 months; EOF, 6.5 months). Toxicity of capecitabine and 5-FU was similar.¹

Consistent with these findings, our patient responded well to EOX therapy and had a reasonably long disease control. Notably, the size of lung metastases and CEA levels continued to decrease even after completion of treatment. Evidence of progression did not emerge until 7 months after EOX completion.

In patients with renal impairment treated with capecitabine, it is important to follow recommendations on dose adjustment according to creatinine clearance. In our patient, this reduced toxicity while maintaining the efficacy of treatment. The only side effect attributable to capecitabine was grade 1 hand-foot syndrome.

In conclusion, this case demonstrates the excellent efficacy and good tolerability of capecitabine-based regimens in patients with previously untreated, advanced gastric cancer. Capecitabine can be well tolerated despite prior toxicity with 5-FU treatment.

**Reference:**

Prolonged disease control with multidisciplinary treatment in advanced HCC

Dr. Foon-Yiu Cheung
Clinical Oncologist

Presentation and treatment

A 67-year-old man with hepatocellular carcinoma (HCC) presented with raised alpha-fetoprotein (AFP) during follow-up for hepatitis B cirrhosis in 2006. CT scan in 2006 revealed two hepatic nodules (1.4 and 1.6 cm) compatible with HCC.

Transarterial chemoembolization (TACE) for six cycles was given from January to October 2007. Angiography with TACE in October 2007 revealed inactive tumors in S8, S6 and the caudate lobe of the liver. Maintenance TACE was given in February and August 2008.

Follow-up CT scan in August 2008 revealed an interval increase in size of the three lesions, all of which showed satellite nodules.

Laparoscopic subsegmentectomy of S6 tumor on 12 November 2008 revealed HCC. However, postoperative AFP levels increased from 138 µg/L in October 2008 to 938 µg/L in February 2009. CT scan in April 2009 revealed inactive tumors in S8, S6 and the caudate lobe of the liver. Maintenance TACE was given in February and August 2008.

CT scan in February 2010 showed three foci of lipiodol uptake in S8 (3.1 cm), S1 (1.7 cm) and S3 (0.6 cm) of the liver, with no significant interval change. A 1 cm mass was seen at the right lung base, but the nature was indeterminate. However, chest X-ray in February 2010 revealed multiple bilateral lung nodules, measuring up to 1.5 cm at the right upper zone and up to 2.3 cm at the left upper zone.

The patient was put on sorafenib on 15 March 2010. The medication was well tolerated, and the patient had grade 1 hand-foot syndrome and grade 1-2 diarrhea. There were no hematological side effects. CT scan in April 2010 showed response to treatment. Subsequent CT scan in June 2010 revealed complete remission of lung metastasis, but the liver lesions remained static. CT scans in July, September and November 2010 also showed static liver lesions.

In May 2011, the patient was found to have multiple new liver lesions in S5, S6 and S7 on CT scan; the lung lesions remained in complete remission. Sorafenib was stopped. The patient refused second-line therapy in clinical trial despite a performance status of 1. He was on symptomatic care and passed away in November 2011.

Discussion

Liver cancer ranked fourth in terms of cancer incidence in Hong Kong and third in...
terms of mortality in 2009. The majority of local HCC cases are due to hepatitis B cirrhosis.

This case illustrates the importance of a multidisciplinary approach for local disease control in HCC, with sequential use of TACE and local excision. Multidisciplinary clinics for HCC are established in almost all large public hospitals in Hong Kong.

Sorafenib is an orally active multikinase inhibitor that inhibits tumor growth as well as angiogenesis. It is the only approved systemic therapy for HCC since 2007. The approval was based on results of the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial and the Asia-Pacific randomized trial. Both studies showed the same magnitude of mortality risk reduction compared with placebo (about 30 percent), although the absolute reduction was different.

In HCC patients treated with sorafenib, tumor number and size are prognostic factors for overall survival. This case illustrates that despite the presence of multiple secondary lesions in the lung, disease control can still be achieved for a relatively long duration if sorafenib is initiated early before the appearance of symptoms.

In this patient, sorafenib provided clinical benefit with stable disease for about 1 year before progression.

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Study supports BC chemotherapy during pregnancy

Naomi Rodrig

A recent observational study showed that chemotherapy for breast cancer (BC) during pregnancy was not associated with increased risk to mother or infant, suggesting it is feasible to treat pregnant women in the second and third trimesters. [Lancet Oncology, e-pub ahead of print August 16, 2012]

Investigators from seven European countries recruited 447 patients with a primary diagnosis of BC during pregnancy, 413 of whom had early disease. At the time of diagnosis, median patient age was 33 years, and median gestational age was 24 weeks. In total, 197 women received chemotherapy during pregnancy, while 171 were treated after delivery. Among patients treated during pregnancy, 90 percent received an anthracycline, 8 percent received cyclophosphamide plus methotrexate and flurouracil, and 7 percent received a taxane.

No significant differences in the women’s clinical outcomes were recorded between the two groups. Median disease-free survival for those starting chemotherapy during pregnancy was 70.6 months vs 94.4 months for those who started treatment after delivery (unadjusted hazard ratio, 1.13). The estimated 3-year overall survival (OS) rates were 84.9 and 87.4 percent, and the estimated 5-year OS rates were 77 and 82.4 percent, respectively.

Birthweight was affected by chemotherapy exposure after adjustment for gestational age, but not by the number of chemotherapy cycles. The lower birthweight among infants with in-utero exposure was considered “not clinically significant”.

No statistical difference was observed in the proportion of major birth defects between the two groups.

Although adverse events were more common in infants who were exposed to chemotherapy in-utero compared with those who were not (15 vs 4 percent), the difference was attributed to higher incidence of preterm labor among the exposed women. Indeed, side
effects, malformations or newborn complications were more common in infants born before the 37th week of gestation than in those born during or after the 37th week (16 vs 5 percent). “Most complications were reported in babies who were delivered prematurely, regardless of exposure to chemotherapy,” the authors wrote. “Since none of the infants was exposed to chemotherapy in the first trimester, the differences were most likely related to premature delivery.”

The study does not explain, however, why patients who received chemotherapy during pregnancy had a higher rate of preterm deliveries. The authors hypothesize that the cytotoxic drugs themselves or the physical and psychological stress related to BC may have played a role.

“Despite these findings, the optimum use of cytotoxic drugs in pregnant patients remains undefined, particularly regarding drug selection, dosing and dose intensity,” commented authors of an accompanying editorial. “Further clinicopharmacological studies are needed to determine whether the increased fetal risks shown could be minimized with optimized drug selection and dosing.” [DOI: 10.1016/S1470-2045(12)70331-5]

According to the editorialists, the concomitant incidence of BC and pregnancy is rising in high-income countries because of increases in maternal age at the time of first pregnancy. Hence, more data on the role of chemotherapy in this setting may help to balance embryo and fetal wellbeing with maternal prognosis.

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**Targeted drug shows efficacy in advanced, differentiated thyroid CA**

**Christina Lau**

Vandetanib, a multi-targeted tyrosine kinase inhibitor (TKI) against rearranged during transfection (RET), epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) signaling, has demonstrated efficacy in a phase II trial of patients with radioiodine-refractory locally advanced or metastatic differentiated thyroid carcinoma, according to a new study published in *Lancet Oncology*. [e-pub 13 Aug 2012; doi:10.1016/S1470-2045(12)70335-2]

The investigators randomized 145 patients at 16 European centers to receive vandetanib 300 mg per day (n=72) or matched placebo (n=73). The patients had papillary, follicular, or poorly differentiated disease.

As of data cut-off, 78 percent of patients had progressed (72 percent in the vandetanib group and 84 percent in the placebo group), and 28 percent had died (26 percent in the
vandetanib group and 29 percent in the placebo group). The primary endpoint of progression-free survival (PFS) was significantly longer for patients receiving vandetanib than placebo (11.1 vs 5.9 months; HR, 0.63; p=0.008).

According to the authors, “vandetanib is the first targeted drug to show evidence of efficacy in a randomized phase II trial in patients with locally advanced or metastatic differentiated thyroid carcinoma”. Although most cases of differentiated thyroid cancer are cured by surgery followed sometimes by radioactive iodine, there is currently no effective standard treatment for patients with radioiodine-refractory, advanced differentiated thyroid carcinoma.

However, they pointed out that further investigation of TKIs in this setting is warranted.

In the trial, the most common grade ≥3 adverse events were QTc prolongation (14 percent in the vandetanib group vs none in the placebo group), diarrhea (10 percent vs none), asthenia (7 percent vs 4 percent), and fatigue (5 percent vs none). Two patients in the vandetanib group vs one in the placebo group died from treatment-related serious adverse events (hemorrhage from skin metastases and pneumonia in the vandetanib group, and pneumonia in the placebo group).

Vandetanib was approved by the US FDA in April 2011 for treatment of metastatic medullary thyroid cancer in adult patients who are ineligible for surgery. According to its developer AstraZeneca, vandetanib is the only medicine to receive FDA approval specifically for use in patients with advanced medullary thyroid cancer.

The approval was based on results of the phase III ZETA study of 331 patients with unresectable locally advanced or metastatic medullary thyroid cancer, which showed significantly improved PFS in the vandetanib group vs placebo (≥22.6 vs 16.4 months; HR, 0.35; p<0.0001). [CAPRELSA package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2011]

In addition to ongoing trials on medullary thyroid cancer, vandetanib is being tested in lung, kidney and prostate cancers, glioma, glioblastoma, urinary tract cancer, and pancreatic carcinoma. [National Cancer Institute: http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=6393082]

Oral agent shows activity in refractory GIST

Christina Lau


Following phase I results demonstrating its tolerability, BIIB021 now shows an objective response rate of 22 percent based on PET in an open-label phase II study of 23 patients whose GIST progressed after first- and second-line therapy with imatinib and sunitinib.

HSP90 is a molecular chaperone for receptor tyrosine kinases KIT and platelet-derived...
growth factor receptor α (PDGFRα); their activating mutations are believed to be key drivers in the development and progression of GIST. According to the authors, treatment with HSP90 inhibitors can degrade any form of activated KIT or PDGFRα irrespective of their specific mutations, and may have anti-neoplastic utility following the emergence of tumor resistance to imatinib and sunitinib – for which therapeutic options are currently limited.

In the study, BIIB021 was initially given to 12 patients at a dose schedule of 600 mg twice weekly (ie, the maximum tolerated dose determined in phase I). As pathway inhibition did not appear sustained between twice-weekly doses, the next 11 patients received 400 mg thrice weekly.

The study met its primary endpoint of metabolic partial response (mPR), defined as >25 percent reduction in standardized uptake value (SUV\textsubscript{max}) from baseline to the first day of the second 28-day treatment cycle on FDG-PET, averaged over a maximum of five target lesions.

In total, five partial responses were seen (three on the twice-weekly schedule, two on the thrice-weekly schedule, including in patients with KIT exon 9 and 11 mutations). Nine patients had a smaller decline in SUV\textsubscript{max} below the threshold for mPR. Based on Response Evaluation Criteria in Solid Tumors (RECIST), the best response was stable disease (n=10, on both dose schedules). The duration of response ranged from 25 to 138 days.

Adverse events were mild to moderate, with the majority of patients discontinuing treatment due to progression rather than toxicity. Grade 3 dizziness and syncope, reported in phase I, was not seen in this trial.

According to the authors, the tolerability and lack of hepatotoxicity of BIIB021 offers a potential safety advantage over ansamycin derivatives such as IPI-504. “HSP90 inhibition represents a promising new strategy for targeted therapy of GIST. Notably, this approach does not rely on the presence of particular mutations to predict sensitivity to a given tyrosine kinase inhibitor, but rather may target oncogene-driven tumors more broadly,” they wrote. “Preclinical data have already suggested that HSP90 inhibition may be active in GIST that are inherently imatinib-resistant.”

“Further evaluation of BIIB021 in GIST is warranted,” they added.
Although tobacco and alcohol intake are widely considered as negative determinants of health, their association with cancer risk is complex and far from understood, as demonstrated in several new studies on cancer in women.

In one study, Oxford University researchers who analyzed data from the UK Million Women Study found that tobacco smoking was associated with increased risk of certain hematological malignancies, while moderate alcohol drinking appeared to have a protective effect against some lymphoid malignancies. \[Br J Cancer 2012;107:879-887\]

Approximately 1.3 million middle-aged UK women were recruited during 1996-2001 and followed up for death and cancer registration until 2009 (mean follow-up, 10.3 years). Potential risk factors were assessed by questionnaire.

During follow-up, 9,162 incident cases of hematological malignancy were recorded, including 7,047 lymphoid and 2,072 myeloid cancers.

Among predominantly moderate alcohol drinkers, higher intake was associated with lower risk of lymphoid malignancies, in particular large B-cell lymphoma (relative risk \[RR\], 0.85 per 10 g alcohol daily), follicular lymphoma (RR, 0.86) and plasma cell neoplasms (RR, 0.86).

In contrast, when compared with never smoking, higher cigarette consumption was associated with increased risk of Hodgkin’s lymphoma (RR, 1.45 per 10 cigarettes daily), mature T-cell malignancies (RR, 1.38) and myeloproliferative / myelodysplastic disease (RR, 1.42).

“These findings confirm and extend existing evidence for associations of subtypes of hematological malignancy with two common exposures in women,” the authors wrote.

The deleterious effects of smoking were also demonstrated in an analysis of 51 epidemiological studies looking at different subtypes of ovarian cancer. Individual participant data of 28,114 women with ovarian cancer and 94,942 women without ovarian cancer were analyzed centrally to assess ad-
justed RR of various ovarian cancers in smokers compared with never smokers. [Lancet Oncology 2012;13:946-956]

The data showed that overall ovarian cancer risk was only slightly increased in current vs never smokers (RR, 1.06). However, smoking-related risks varied substantially between tumor subtypes. Of nearly 18,000 epithelial ovarian cancers with specified histology, 13 were mucinous, 13 percent endometrioid, 5 percent clear cell and 52 percent serous.

For mucinous cancers, the incidence was increased in current smokers (RR, 1.79, p<0.0001). Interestingly, the increased risk was mainly seen in borderline malignant tumors rather than in fully malignant tumors (RR, 2.25 vs 1.49, respectively).

Both endometrioid and clear-cell ovarian cancer risks were reduced in current vs never smokers (RR, 0.81 and 0.8). No significant association was found for serous cancers (RR, 0.99).

The authors noted that the associations did not vary significantly by 13 sociodemographic and personal characteristics of the subjects, including their body-mass index, parity, and use of alcohol, contraceptives and menopausal hormone therapy.

“The substantial variation in smoking-related risks by tumor subtype is important for understanding ovarian carcinogenesis,” they suggested.

Lung cancer in never smokers: A different disease?

Naomi Rodrig

A comprehensive review that focused on lung cancer in never smokers (LCINS), suggests that – while smoking and tobacco exposure are recognized risk factors for lung cancer – alternative genetic pathways lead to LCINS development, making it in effect a distinct medical entity. [Eur J Cancer 20012;48:1299-1311]

According to WHO data, an estimated 25 percent of lung cancers worldwide occur in never smokers (people who have smoked less than 100 cigarettes in their lifetime). It is more common in women than men and in certain geographical regions (Asia > North America > Europe). Histologically, LCINS predominantly consists of adenocarcinoma type.

“The mere existence of LCINS suggests that risk factors other than smoking must be present,” the authors wrote. Epidemiological studies have identified several factors associated with lung cancer risk, but these are not found exclusively in never smokers. For example, women who used menopausal hormone therapy had a 1.76 higher risk of developing lung cancer than non-users, regardless of smoking status. [Maturitas 2010;65:198-204] Another study demonstrated that exposure to cooking oil fumes among Chinese never-smoking women was associated with an odds ratio of 2.12 for lung cancer occurrence. [Sci Total Environ 2006;366:500-513]

“The large proportion of women with LCINS suggests a hormonal element that may interact with other identified factors such as hereditary risks, a history of respiratory infections or disease, exposure to air pollution,
cooking and heating fumes, or exposure to ionizing radiation,” the review authors suggest.

However, important environmental risk factors such as exposure to environmental tobacco smoke (particularly in women) and exposure to workplace carcinogens (particularly in men), are absent in more than a third of LCINS cases, suggesting that a different etiology is involved in this cancer type.

According to the review, the study of genomic polymorphisms found constitutive DNA variations across subjects based on their smoking status, particularly in genes coding for enzymes that participate in the metabolism of certain carcinogens, genes coding for DNA repair enzymes, or those associated with tobacco addiction or inflammatory processes.

For instance, the type of molecular mutation in p53 or KRAS varies with smoking status. EGFR mutations are more frequent in never smokers, as are EML4-ALK fusions. “The mutually exclusive nature of certain mutations is a strong argument in favor of separate genetic paths to cancer for ever smokers and never smokers,” they wrote.

Importantly, mutation status impacts treatment selection, and may be even more important in the future as a prognostic factor. “Close to 50 percent of never-smoker patients present molecular mutations that may be treatable currently or in the near future via targeted therapies, as compared to potentially 10 percent of ever smokers,” the authors concluded.

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SC trastuzumab as effective as IV

**Naomi Rodrig**

Subcutaneous (SC) trastuzumab has a pharmacokinetic profile and efficacy non-inferior to standard intravenous (IV) administration, offering potential improvements in patient convenience and resource utilization, a study has shown. [Lancet Oncology 2012;13:869-878]

The HannaH study was a phase III, open-label, multicenter trial that compared the two administration modes in patients with HER2-positive early (stage I-III) breast cancer in the neoadjuvant setting. In total, 299 patients were randomly assigned to IV trastuzumab and 297 to SC trastuzumab administered over about 5 minutes. Trastuzumab was given every 3 weeks, together with eight cycles of neoadjuvant chemotherapy. After surgery, patients continued trastuzumab to complete 1 year of treatment. Coprimary endpoints were serum trough concentration ($C_{\text{trough}}$) at pre-dose cycle 8 and pathological complete response (pCR).

The geometric mean ratio of $C_{\text{trough}}$ SC to $C_{\text{trough}}$ IV was 1.33. Overall, 40.7 percent of patients in the IV group and 45.4 percent in the SC group achieved a pCR. “Thus SC trastuzumab was non-inferior to IV trastuzumab for both coprimary endpoints,” the authors wrote.

The incidence of grade 3-5 adverse events was similar between the groups. However, more patients in the SC groups had serious adverse events (21 vs 12 percent), mainly infections and infestations.
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