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Asymptomatic siblings of Chinese colorectal cancer (CRC) patients are at a significantly higher risk of colorectal tumors than matched controls, suggesting they should undergo regular colonoscopy screening, according to a study from the Chinese University of Hong Kong. [Gastroenterology 2013; DOI: 10.1053/j.gastro.2012.11.011]

To assess the prevalence of advanced neoplasms among asymptomatic siblings of patients with CRC, the investigators identified CRC patients at the Prince of Wales Hospital during a period of 10 years (2001-2011).

Colonoscopies were performed in 374 siblings of patients (mean age, 52.5 years) and 374 age- and sex-matched siblings of healthy subjects without history of colorectal tumors (control group). While similar earlier studies mostly used consecutive patients who had undergone colonoscopy as controls, this may not represent a satisfactory control population, according to the authors. “Our study has a unique design,” Dr. Siew C Ng and colleagues wrote. “It offered colonoscopy to siblings of adenoma- and cancer-free patients. The use of such a control group avoids a biased estimate of the association with family history, and removes the acquired or environmental component to this association.”

Advanced neoplasms were defined as cancers or adenomas of ≥10 cm in diameter, high-grade dysplasia, with villous or tubulovillous characteristics.

“We found that siblings of Chinese subjects with CRC have a 3-fold increased risk of advanced colorectal neoplasms including cancers, and a 2-fold increased risk of any colorectal adenomas when compared with siblings of subjects with a normal colonoscopy,” they reported.

The prevalence of advanced neoplasms was 7.5 percent among siblings of CRC patients vs 2.9 percent among controls (matched odds ratio [mOR], 3.07; p=0.002). The risk was even higher when the index case was female (mOR, 4.95), when the index case presented with distal CRC (mOR, 3.10), and when the index case was aged ≥60 years (mOR, 3.09).

The prevalence of adenomas of ≥10 cm was also higher among siblings of patients than controls (5.9 vs 2.1 percent; mOR, 3.34; p=0.004), as was the prevalence of colorectal adenomas (31.0 vs 18.2 percent; mOR, 2.19; p<0.001).
Six adenocarcinomas were detected in siblings of patients vs none among the controls. Two patients had stage 1 cancers, two had stage 2 cancers and two had stage 3 cancers.

The prevalence of hyperplastic polyps was similar between siblings of patients and controls (27.3 vs 21.4 percent; p=0.564).

The investigators noted that these results are consistent with two earlier studies from Italy and France. “Until recently, no local data were available to help in more targeted screening in our population,” they noted. “Information obtained from this study... can provide background against which screening strategies can be formulated.”

Importantly, the Hong Kong findings confirmed that close relatives of CRC patients are not only at increased risk of CRC but also advanced adenomas. “CRC screening with the removal of these premalignant lesions is currently the most effective way to reduce cancer incidence and cancer death, and is strongly indicated in this high-risk group,” they suggested. “Siblings of individuals with CRC deserve screening.”

To screen or not to screen?

Despite new cancer treatments getting faster regulatory green light, cancer screening has remained controversial. Governments and healthcare providers are reluctant to endorse and shoulder the cost of routine screening, especially as recent studies had reported discouraging data. Some publications even suggest that current screening practices for breast cancer or prostate cancer may do more harm than good. Importantly, early detection doesn’t always improve outcomes or prolong survival, raising further doubts as to the utility and cost-effectiveness of universal screening.

The best way to go, experts say, is to target specific at-risk groups. As reported in our cover story, asymptomatic siblings of Chinese colorectal cancer patients are one risk group that should be screened. While this study underscores the role of genetics in cancer etiology, another local study suggests that epigenetic mechanisms may be at play, providing a new target for cancer therapies.

The Editor
Increased contralateral BC risk in BRCA mutation non-carriers

Young breast cancer patients with a family history of the disease who test negative for BRCA1 and BRCA2 mutations are at greater risk of contralateral breast cancer (CBC) than other breast cancer survivors, and the risk varies with age at diagnosis, family history of CBC and degree of relationship to an affected relative. [J Clin Oncol 2013;31:433-439]

Researchers examined the risk of asynchronous CBC in non-carriers of BRCA1 and BRCA2 mutations who had CBC (n=594) or unilateral breast cancer (UBC) (n=1,119).

Results showed that family history of breast cancer was associated with increased CBC risk. The risk was highest among women <45 years of age with first-degree relatives affected at young ages (<45 years; relative risk [RR]=2.5) or women with first-degree relatives with bilateral disease (RR=3.6). Women diagnosed with UBC at age <55 years with a first-degree family history of CBC had a 10-year CBC risk of 15.6 percent. According to the researchers, the findings have important implications for clinical management of breast cancer patients with a family history of the disease.

Pap smear could detect ovarian and endometrial cancers

Pap smear could help detect ovarian and endometrial cancers, recent research suggests. [Sci Transl Med 2013;5:167ra4]

Researchers extended the DNA testing approved for HPV to look for mutations specific to ovarian and endometrial cancers, as these cancers may shed a few cells that trickle down into the cervix. Using a sensitive massively parallel sequencing method, they identified endometrial cancer in 100 percent (24 of 24) and ovarian cancer in 41 percent (9 of 22) of known cancerous Pap smear specimens. Importantly, none of the normal samples showed false positive results.

These findings suggest that Pap smear is a potential option for early and easy detection of endometrial and ovarian cancers, as most endometrial and a fraction of ovarian cancers could be identified in the study.
New ASCO guideline on febrile neutropenia management

The American Society of Clinical Oncology (ASCO) issued a new guideline on the management of fever and neutropenia in cancer patients.

“A priority of this guideline was to help doctors identify patients with febrile neutropenia [FN] who do not need to be hospitalized, sparing selected patients from the discomfort and risks of hospitalization,” said Co-Chair Professor Christopher R. Flowers of the ASCO Expert Panel.

The new guideline describes the application of well-validated scoring systems (eg, Multinational Association for Supportive Care in Cancer [MASCC] score and Talcott’s Rules) in assessing the risk of complications from FN. It also curbs the use of common tests and treatments that are not supported by clinical evidence.

Other highlights include management of and medications for FN at home, prevention of infection for patients with neutropenia but no fever, and initial treatment of FN.
Androgen blockade can be shortened for high-risk prostate cancer

The duration of androgen blockade therapy can be safely halved without affecting survival of patients with high-risk prostate cancer, according to a phase III study.

“Radiotherapy [RT] and long-term androgen blockade is standard treatment for patients with high-risk prostate cancer. While the standard course of androgen blockade is 24-36 months, our study showed that this can be safely shortened to 18 months without compromising survival,” said lead author Dr. Abdenour Nabid of the Centre Hospitalier Universitaire de Sherbrooke in Sherbrooke, Canada.

The study included 630 patients with node-negative high-risk disease (stage T3-4, PSA >20 ng/mL or Gleason score >7). Patients were randomized to receive 36 vs 18 months of androgen blockade therapy before, during and after pelvic RT (whole pelvis 44 Gy/4.5 weeks; prostate 70 Gy/7 weeks). Androgen blockade therapy consisted of bicalutamide 50 mg for 1 month and goserelin 10.8 mg every 3 months for 36 or 18 months.

The primary endpoint of overall survival (OS) did not differ significantly between the two arms. At a median follow-up of 77 months, 77.1 percent of patients in the 36-month arm and 76.2 percent in the 18-month arm were still alive. Five- and 10-year OS rates were 92.1 vs 86.8 percent (p=0.052) and 63.6 vs 63.2 percent (p=0.429), respectively.

“Ten-year disease-specific survival was 87.2 percent for both groups, showing that shortening the duration of androgen blockade to 18 months did not affect the odds of dying of prostate cancer,” reported Nabid. “There were also no significant differences in the rates of biochemical, regional or distant failure between the two arms.”

“For high-risk prostate cancer patients treated with RT and androgen blockade, 18 months of androgen blockade could represent a threshold effect with no further benefit for longer therapy,” he suggested. “Shorter-term hormone therapy could have a big impact on the lives of men with prostate cancer, reducing the quantity and intensity of its unpleasant side effects as well as...
treatment costs. For the benefit of patients, we hope these results will convince doctors that they can stop hormone therapy after 18 months instead of 2-3 years.”

Analysis of treatment impact on quality of life is in progress, marking the longest quality of life follow-up among prostate cancer patients to date.

### Surveillance appropriate for elderly with small renal masses

Surveillance is a reasonable option for older patients with small renal masses who are not candidates for surgery, as it does not appear to adversely affect kidney cancer-specific survival.

“While eight out of 10 small renal masses are malignant tumors, they generally don’t pose an immediate threat because they normally grow slowly and only a small number of them metastasize. Surveillance allows doctors to intervene if the tumor exhibits an aggressive growth rate or reaches a size that indicates a greater potential for spreading,” said lead author Dr. William Huang of the New York University Medical Center in New York, USA. “Based on our analysis, physicians can comfortably tell elderly patients, especially those who are not healthy enough to tolerate general anesthesia and surgery, that the likelihood of dying of kidney cancer is low and that kidney surgery is unlikely to extend their lives.”

In the retrospective cohort study, Huang and colleagues analyzed SEER (Surveillance, Epidemiology, and End Results) cancer registry data linked with Medicare claims for patients aged ≥66 years who were diagnosed with small renal masses (<4 cm) between 2000 and 2007. Of 8,317 patients, 5,706 (70 percent) underwent surgery and 2,611 (31 percent) underwent surveillance. [Abstract 343]

“During a median follow-up of 4.8 years, 3 percent of patients died of kidney cancer. Kidney cancer-specific survival did not differ by treatment approach,” reported Huang.

Surveillance was associated with a significantly lower risk of death from any cause (hazard ratio [HR]: 7-36 months, 0.70; >36 months, 0.37) as well as cardiovascular event (HR, 0.51).

“The percentage of patients managed with surveillance increased from 25 percent in 2000 to 37 percent in 2007,” Huang pointed out. “It appears that doctors are beginning to realize many small tumors do not pose a threat even if they are malignant. There is also increased awareness that removal of the kidney may lead to chronic kidney disease, which is associated with kidney failure, cardiovascular problems, and early death.”

However, as a number of small kidney tumors can become lethal over time, and it is difficult to identify which tumors will become lethal, Huang stressed that surgery remains the treatment of choice for patients who are completely healthy with an extended life expectancy.
Immunotherapy plus sunitinib doubles survival in unfavorable-risk mRCC

Autologous dendritic cell immunotherapy (AGS-003) in combination with sunitinib nearly doubled overall survival (OS) in patients with unfavorable-risk metastatic renal cell carcinoma (mRCC) in a single-arm phase II study.

“While targeted therapies have yielded improved efficacy in treatment of advanced RCC, durable remissions are rare, particularly in unfavorable-risk subjects,” said lead author Dr. Asim Amin of the Carolinas Medical Center and Blumenthal Cancer Center in Charlotte, USA. “In a pivotal trial, sunitinib treatment yielded a median OS of 5.3 months for poor-risk patients and 20.7 months for intermediate-risk patients. Similarly, the validation dataset for the Heng risk model showed a median OS of 8 months for poor-risk and 21 months for intermediate-risk patients treated with VEGF targeted therapies.”

As immunotherapy has shown durable responses in RCC, Amin and colleagues treated 21 patients with poor- and intermediate-risk mRCC with standard 6-week cycles of sunitinib plus AGS-003 (once every 3 weeks x 5 doses, then every 12 weeks until disease progression) and followed them for progression-free survival (PFS) and OS. [Abstract 357]

In the study, tumor response was assessed based on the response evaluation criteria in solid tumors (RECIST). Samples for immune monitoring were taken at screening, baseline, and after the third and fifth doses of AGS-003, and analyzed by multiparametric flow cytometry.

“As reported previously, median PFS was 11.2 months, and the final median OS was 30.2 months,” Amin reported. “When analyzed by baseline Heng risk status, median PFS was 19.4 months for patients with intermediate risk [n=11] and 5.8 months for those with poor risk [n=10]. Median OS was >39.5 months for intermediate-risk patients, and 9.1 months for poor-risk patients. Eight of 21 patients are still alive and continue to be followed.”

“This novel combination therapy using patient-specific immunotherapy plus an oral agent showed significant benefits with a doubling of survival in patients with aggressive mRCC. This is very encouraging and will need to be confirmed in a larger number of patients,” commented Dr. Leonard Gomella of the US Society of Urologic Oncology.

According to Amin, a phase III trial is ongoing to validate the initial clinical and immunologic findings.
S-1 chemo improves survival in Asians with pancreatic cancer

Adjuvant chemotherapy with S-1 significantly improves overall survival (OS) vs gemcitabine in Japanese patients with stage I-III pancreatic adenocarcinoma, the phase III JASPAC-01 study showed.

S-1 is a combination of tegafur (an antimetabolite agent that is converted into 5-FU after absorption), gimeracil (which decreases degradation of 5-FU in the liver), and oteracil (which decreases phosphorylation of 5-FU in the gastrointestinal tract). The oral therapy is approved for treatment of gastric cancer in Japan, South Korea, China, Singapore, Taiwan, Thailand, Hong Kong, Sweden, Denmark, Norway, Finland, UK, Austria, Germany, Bulgaria, and the Netherlands. In Japan, it is also approved for treatment of colorectal, head and neck, non-small cell lung, unresectable or recurrent breast, pancreatic, and biliary cancers. [Taiho Pharmaceutical, http://www.taiho.co.jp/english/news/20130128.html]

“While patients with resected pancreatic cancer typically receive adjuvant gemcitabine, the JASPAC-01 study showed that adjuvant S-1 reduced the risk of death by 44 percent vs the standard treatment [p<0.0001 for non-inferiority and superiority],” reported lead author Dr. Katsuhiko Uesaka of the Shizuoka Cancer Center in Shizuoka, Japan. “At 2 years, OS rate was 70 percent for adjuvant S-1 and 53 percent for adjuvant gemcitabine.” [Abstract 145]

Relapse rates were also lower in the S-1 arm. Two-year relapse-free survival rates were 49 and 29 percent for S-1 and gemcitabine, respectively.

These interim findings led the independent data monitoring committee to recommend early reporting of the results to accelerate adoption of S-1 as the new standard adjuvant treatment for patients with pancreatic cancer.

“Our survival data were much stronger than expected. Based on these results, we hope that guidelines for standard adjuvant therapy for pancreatic cancer in Japan will be changed to replace gemcitabine with S-1 as single-agent therapy,” said Uesaka. “The investigators will continue follow-up of the study participants for at least 5 years.”

The JASPAC-01 study included 385 patients with histologically confirmed ductal adenocarcinoma of the pancreas, R0 or R1 resection, pathological stage I-III with resection of the celiac axis, age >20 years, no prior chemotherapy or radiotherapy in the last 3 years, and adequate organ function. The primary endpoint was OS. Interim analysis was scheduled after 180 deaths.

S-1 was well tolerated in the study, with more than 70 percent of patients completing treatment. “Gastrointestinal side effects of S-1 are more severe in Caucasians than in Asians, requiring the use of lower doses in Caucasian patients. While our findings are not immediately applicable to non-Asian populations, we hope similar studies will soon be conducted in Caucasian patients with adjustment of S-1 dose,” added Uesaka.
Colorectal cancer (CRC) consists of three distinct molecular subtypes that are associated with different prognoses and responses to adjuvant chemotherapy, according to a new study.

In the international study, researchers developed a molecular subtype classification system using gene expression data from 188 patients with stage I-IV CRC. The classification system was subsequently validated in 543 patients with stage II and III disease. [Abstract 333]

“The heterogeneity of the intrinsic subtypes is largely based on three biological hallmarks of the tumor, namely epithelial-to-mesenchymal transition, deficiency in mismatch repair genes that leads to high rates of mutations associated with microsatellite instability [MSI], and cellular proliferation,” reported Dr. Josep Tabernero of the Vall d’Hebron University Hospital in Barcelona, Spain. “In our sample, 21.5 percent belonged to subtype A with a deficient epithelial phenotype, 62 percent belonged to subtype B with a proliferative epithelial phenotype, while 16.5 percent belonged to subtype C with a mesenchymal phenotype.”

Importantly, 10-year follow-up showed that patients with subtype C tumors had the worst outcome and did not benefit from adjuvant 5-FU–based chemotherapy. Outcomes were better for patients with subtype A or B tumors, who benefited from adjuvant chemotherapy.

“We also found that compared with subtype B, subtypes A and C had higher rates of alterations in many genes, such as KRAS, BRAF, and PI3KCA,” Tabernero noted. “Researchers are currently validating this molecular subtype classification system in stage IV CRC. With continued research, we will be able to develop new molecular tests based on this classification system, enabling clinicians to...
identify patients who require more aggressive adjuvant treatment and predict which patients will respond to specific chemotherapies and targeted agents regardless of cancer stage.”

According to the researchers, it is not always clear which CRC patients would benefit from additional therapy to prevent relapse after surgery, especially in stage II, because clinical and pathological poor-prognosis factors do not always identify patients who will relapse. While the recent availability of genomic classifiers can improve identification of high-risk stage II patients, clear recommendations on adjuvant chemotherapy are still lacking. Furthermore, these tests are not useful in patients with later-stage disease who have undergone treatment, nor can they help identify which therapy might be best for the individual patient.

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**Definitive evidence for second-line docetaxel in esophago-gastric cancer**

Results of a phase III study affirm the use of docetaxel in second-line treatment of advanced esophago-gastric cancer, showing markedly improved overall survival (OS) vs active symptom control.

The UK-based COUGAR-02 study included 168 patients with locally advanced or metastatic esophago-gastric adenocarcinoma whose disease progressed within 6 months of first-line platinum/fluoropyrimidine chemotherapy. Patients were randomized to receive docetaxel (up to six cycles) or active symptom control, which could include radiotherapy, steroids and/or supportive medications. [Abstract LBA4]

Median OS was about 50 percent longer in patients who received docetaxel (5.2 months vs 3.6 months with active symptom control; hazard ratio, 0.67; p=0.01). The survival benefit was evident across different tumor sites and stages, and did not differ by patient age or gender.

“The greatest benefit was observed in patients with performance status 0,” noted lead author Dr. Hugo Ford of the Addenbrooke’s Hospital in Cambridge, UK. “Preliminary analysis of overall and disease-specific quality of life suggests that patients receiving
second-line therapy with docetaxel had improved pain scores and no loss in global quality of life.”

“Current practice in the USA and many European countries is to give second-line chemotherapy to patients with esophagogastric cancer, even though the evidence isn’t as strong as we would like. This is the first trial to show that second-line chemotherapy extends survival, without causing deterioration in quality of life,” he continued. “Docetaxel should be a standard second-line treatment for esophago-gastric adenocarcinoma. It is likely to be the standard arm against which future treatments will be compared.”

Patients with esophago-gastric adenocarcinoma have poor outcomes with currently available therapies. All patients who present with advanced disease at diagnosis and 60-70 percent of patients who present with local disease relapse after first-line chemotherapy. Without second-line therapy, median survival is 3 months.
New hypothesis: Antioxidants promote cancer progression

Naomi Rodrig

Contrary to prevalent notions about the health benefits of antioxidants, a novel hypothesis proposed by Professor James D Watson of Cold Spring Harbor Laboratory, USA claims that antioxidants can promote progression of late-stage solid tumors. The paper, titled ‘Oxidants, antioxidants and the current incurability of metastatic cancers’, was published recently online in Open Biology, a journal of the British Royal Society. [Open Biol 2013;3:120144]

Watson, who together with Francis Crick won the 1962 Nobel Prize in Medicine for their discovery of the structure of DNA, counts his new theory “among my most important work since the double helix.”

At the heart of his hypothesis are reactive oxygen species (ROS) – a group of molecules that promote cell apoptosis. “The vast majority of all agents used to directly kill cancer cells [ionizing radiation, most chemotherapeutic agents and some targeted therapies] work through either directly or indirectly generating ROS that block key steps in the cell cycle,” wrote Watson. “This might explain why cancers that become resistant to chemotherapeutic control become equally resistant to ionizing radiotherapy.”

Despite their important apoptosis-inducing role, the ROS also have a negative side, namely their ability to irreversibly damage key proteins and nucleic acid molecules. “So when not needed, they are constantly being neutralized by antioxidant proteins, such as glutathione, superoxide dismutase, catalase and thioredoxin,” he explained.

Therefore, the common perception is that foods rich in antioxidants such as red wine or blueberries further promote ROS neutralization, providing positive health effects.

Watson claims, however, that cancer cells largely driven by mutant proteins such as RAS and MYC are often not responding to treatment because of ROS-destroying antioxidants. “Some epithelial cancers [carcinomas] and effectively all mesenchymal cancers [sarcomas] remain largely incurable,” he wrote, attributing it to their high levels of antioxidants that block ROS-driven apoptosis of tumor cells. “As mesenchymal cancers evolve from their epithelial cell progenitors, they almost inevitably possess much-heightened amounts of antioxidants that effectively block otherwise highly effective oxidant therapies.”

Watson suggests, “the time has come to seriously ask whether antioxidant use much more likely causes than prevents cancer... Blueberries best be eaten because they taste...
good, not because their consumption will lead to less cancer.”

He calls on governments and the scientific community to speed up research towards curing metastatic cancer using RNA interference (RNAi) methodologies. “A billion dollars should suffice to identify all the remaining proteins needed for curing most metastatic cancer,” he wrote. “Unless we can find ways of reducing antioxidant levels, late-stage cancer 10 years from now will be as incurable as it is today.”

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First HK experience with ultrasound-guided transbronchial lung biopsy in cancer diagnosis

Christina Lau

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) provides high diagnostic accuracy and excellent safety, and should be considered one of the upfront investigations of choice for suspected lung cancer in Hong Kong, according to a recent study at the Queen Mary Hospital (QMH).

The prospective case series represents the first local experience with EBUS-TBNA, introduced in Hong Kong in 2005 at the QMH. During the study period (August 2006 to December 2010), 269 EBUS-TBNA procedures were performed in 259 consecutive patients with enlarged (short diameter >1 cm) mediastinal or hilar lesions or lung lesions closely abutting adjacent airways on CT, which were suspected or confirmed to be lung cancer. The objective of the study was to investigate the diagnostic performance and safety of the procedure. [Hong Kong Med J 2013;19:20-26]

In the entire cohort, EBUS-TBNA demonstrated high overall sensitivity (87 percent), specificity (100 percent), negative predictive value (74 percent) and accuracy (91 percent). In the 220 procedures yielding a final diagnosis of malignancy, the respective sensitivity and negative predictive value was 89 and 66 percent. In cases where EBUS-TBNA was used as the first diagnostic test (ie, for tissue sampling; 158 procedures), the sensitivity and negative predictive value was 90 percent and 81 percent, respectively. According to the
authors, the diagnostic yield was similar to most clinical series reported worldwide. [Chest 2012;142:385-393; Lung Cancer 2005;50:347-354]

Importantly, EBUS-TBNA provided adequate tissues for molecular profiling, which is now widely performed to guide personalized therapy of lung adenocarcinoma. Of the 40 patients who had samples sent for epidermal growth factor receptor (EGFR) and/or anaplastic lymphoma kinase (ALK) mutation tests, EBUS-TBNA provided adequate tissues in 38 patients (95 percent).

No significant complications (bleeding, pneumothorax, infection, or respiratory distress) or mortality ensued from the procedures. All patients, including 14 with superior vena caval obstruction and one with severe heart failure, tolerated EBUS-TBNA well with no premature termination of procedure.

“Based on our 4-year experience since 2006, EBUS-TBNA has demonstrated high diagnostic accuracy in providing clear-cut histological classification and molecular profiling that facilitated state-of-the-art treatment for lung cancer,” wrote the authors.

“Previously, surgical intervention such as mediastinoscopy was the only diagnostic modality with access to the mediastinal lymph nodes for tissue sampling, though the hilar area remained a sanctuary site. However, surgical exploration is not usually considered the upfront diagnostic investigation, due to the need for general anesthesia for which most patients with advanced lung cancer are not good candidates. Recourse to EBUS-TBNA opens a new diagnostic paradigm for patients having mediastinal or hilar lymphadenopathy.”
ESMO calls on regulators and hospitals to speed up trial approval

Naomi Rodrig

Following a recent study that looked at the approval process of a large cancer trial, the European Society for Medical Oncology (ESMO) is urging regulatory and hospital authorities to expedite trial approval for the benefit of cancer patients. [doi: 10.1634/theoncologist.2012-0342, epub January 28, 2013]

The study authors analyzed the time that elapsed between the various regulatory steps, including approval from national regulatory authorities, ethics committees and review boards within participating institutions before investigators could start treating patients in the phase III ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial.

ALTTO enrolled over 8,300 women with early-stage HER2-positive breast cancer in 44 countries. Patients were enrolled in the trial between 2007 and 2011, and will be followed up for a total of 10 years.

“As ALTTO is an almost global trial, it allowed a differential analysis of how long the various approval stages took in different geographic and economic regions,” explained ESMO spokesman, Professor Christoph Zie­linski of the Medical University Vienna, Austria. “As expected from previous experience, the time required from one step to the other was not only quite considerable, but also differed from one region to another.”

The data showed that the median approval time was longest in South America – where the regulatory processes took 236 days, followed by Asia-Pacific (62 days), Europe (52 days) and North America (26 days).

Overall, it took an average of 55 days for national regulators to approve the trial protocol, 59 days for approval by ethics committees or institutional review boards (IRB), and 169 days from the IRB approval until the treatment of the first patient, the study showed.

“The slow process obviously constitutes a major obstacle

Zielinski attributed the extended process to the long time needed for negotiations between study sponsors and individual participating hospitals, as well as the time required for drug import regulations. “Once trials were approved and started, recruitment was swift and very effective in almost all geographic regions,” he noted. “This demonstrates the high interest of investigators and the high relevance of the trials for patients.”

“The ALTTO trial is large, and involves many countries. In my opinion, however, the findings are similar to those in trials for other cancers with fewer patients,” added ESMO spokesman Professor Roberto Labianca of the Ospedali Riuniti di Bergamo, Italy. “The slow process obviously constitutes a major obstacle for study initiation, data generation and the translation of study results into everyday, high-quality clinical routine for the benefit of patients.”
RNA editing implicated in HCC

Naomi Rodrig

Pioneering research at the University of Hong Kong (HKU) has demonstrated that a ribonucleic acid (RNA) editing event may be a potential driver in the pathogenesis of human cancers, particularly hepatocellular carcinoma (HCC). [Nature Medicine; DOI: 10.1038/nm.3043]

The study, led by Professor Xin-Yuan Guan, was conducted at HKU’s Cancer Genetic Laboratory of the Department of Clinical Oncology, in collaboration with the Cancer Science Institute of the National Singapore University.

Rather than focusing on genetic (DNA) mutations, which are relatively rare, the researchers looked at RNA – a messenger molecule that passes the genetic information encoded in the DNA to initiate protein synthesis. Modification of the transcribed code at the RNA level (RNA editing) is an epigenetic mechanism leading to variations in the resulting protein.

“Cancer researchers have long focused on the influence of genetic mutation on the formation of tumors while failing to recognize the importance of RNA editing during cancer development. Genetic mutation and RNA editing bring forth similar results as both of them may change protein sequences and functions,” said Guan.

Using transcriptome sequencing, the investigators examined liver cell cultures of 200 HCC patients as well as experimental mouse models of HCC, and found that RNA editing of the AZIN1 gene was increased in HCC specimens. The editing, specifically regulated by ADAR1 (encoding adenosine deaminase acting on RNA-1), altered the protein coding sequence of AZIN1, causing a conformational and functional change in the resulting protein. “[RNA editing] conferred gain-of-function phenotypes that were manifested by augmented tumor-initiating potential and more aggressive behavior,” the authors wrote.

The study also demonstrated that RNA editing triggered the transformation of normal liver cells into malignant cells. Furthermore, clinicopathological data showed that RNA editing was significantly associated
with the presence of liver cirrhosis, tumor recurrence and shorter survival.

With a growing body of evidence supporting the important role of epigenetic mechanisms in tumorigenesis, drug resistance and cancer progression, the findings may prompt the development of targeted drugs that prevent or reverse RNA editing of AZIN1 in HCC.

“In contrast to genetic mutations, which are irreversible and account for only a small proportion of cancer cases, the phenomenon of RNA editing deregulation frequently occurs in a wide range of patients,” stressed Guan. “RNA editing is a potentially adjustable and reversible epigenetic mechanism. Therefore, this study represents a major breakthrough in the field of cancer therapy and brings new ideas for developing targeted drugs.”

Breast-conserving therapy tops mastectomy in early-stage BC

Jackey Suen

Despite the rising use of mastectomy in recent years, a new study has indicated that breast-conserving therapy (BCT) with lumpectomy and adjuvant radiation provides survival benefits over mastectomy in patients with early-stage breast cancer (BC). [Cancer 2012;DOI:10.1002/cncr.27795]

Several reports suggested that the rising use of mastectomy vs BCT in the past few years may be attributed to improvements in reconstruction techniques, as well as common misconceptions. [J Clin Oncol 2010;28:e155-e157; Clin Breast Cancer 2011;11:33-38] “One likely contributing factor leading to increased use of mastectomy is a perception of worse outcomes among women receiving BCT for tumors with unfavorable factors [eg, young age, estrogen receptor-negative, HER2-positive],” the authors explained. “This study determined whether the comparable survival outcome of BCT used in early-stage BC compared with mastectomy as seen in randomized clinical trials could be achieved in the general population.”

A total of 112,154 eligible women from the California Cancer Registry who were diagnosed with stage I/II BC were followed up
for a median of 110.6 months. Fifty-five percent of the patients received BCT (n=61,771) whereas the rest underwent mastectomy (n=50,383).

“Among all patient groups, BCT was consistently associated with improved overall survival [OS] when compared with mastectomy,” the authors reported. The greatest survival benefit with BCT relative to mastectomy was observed in women ≥50 years of age at diagnosis with hormone receptor-positive tumors, although this effect was observed regardless of hormone receptor status and age at diagnosis. The hazard ratios (HRs) of OS and breast cancer-specific survival were 0.81 and 0.87, respectively. BCT prolonged survival vs mastectomy regardless of whether patients had T1 or T2 tumors.

Mortality from several competing causes after BCT or mastectomy was also determined by examining OS, heart disease-specific survival (DSS), breast cancer-specific survival, cerebrovascular DSS and respiratory DSS at 3 years after diagnosis. “BCT was associated with significantly lower 3-year mortality rates from all causes, with the lowest hazard seen for heart DSS [HR=0.51] and respiratory DSS [HR=0.46]. The smallest reduction in hazard was seen for breast cancer-specific survival [HR=0.85],” the authors noted.

“These results provide confidence in the efficacy of BCT even among young patients with hormone-receptor negative disease thought to be at relatively high risk for local failure,” the authors concluded.

Another recent study that investigated the local-regional recurrence (LRR) rate after BCT found that appropriately selected patients can achieve high rates of local-regional control with either upfront surgery or surgery after neoadjuvant chemotherapy. [Ann Surg 2013;257:173-179] “When analyzed according to the type of surgery, BCT vs mastectomy, there were no differences in LRR rates,” the authors wrote. “In appropriately selected patients receiving neoadjuvant chemotherapy, BCT can be performed with low LRR rates. BCT should be limited to patients in whom a segmental mastectomy can be performed with negative margins and should include whole-breast irradiation in all cases with selective use of regional nodal irradiation.”

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**Statins up survival in HCC**

Jackey Suen

Statins could reduce the risk of death in patients with hepatocellular carcinoma (HCC), according to a recent retrospective study. [J Clin Oncol 2012;30(suppl 34): abstract 165]

Given the possible anti-tumor activity of statins and the proven inverse association between statin use and HCC incidence, the study evaluated the effect of statins on the outcome of HCC patients.

A total of 644 patients (mean age, 63.1 years) with confirmed HCC (70.7 percent diagnosed at TNM stage III/IV) were recruited, and 10.7 percent had reported statin use.

The median overall survival (OS) for all patients was 19.2 months. “We observed significant difference in OS between statin
A recent study has revealed the potential of the mitogen-activated protein kinase kinase (MEK) 1 and MEK 2 inhibitor, selumetinib, in reversing refractoriness to radioiodine (iodine-131) treatment in patients with metastatic thyroid cancer. [N Engl J Med 2013;368:623-632]

Although radioiodine therapy has often been used in the treatment of thyroid cancer, metastatic tumors are sometimes refractory to therapy due to impaired iodine uptake in the target tissue, leading to poor prognosis.

Mitogen-activated protein kinase pathway is known to take part in thyroid hormone regulation, and many metastatic thyroid tumors have mutations in genes located upstream of MEK genes, such as the BRAF and RAS gene family. MEK has thus emerged as a potential treatment target in thyroid cancer.

The study included 20 patients (median age, 61 years) with metastatic thyroid cancer. Dosimetry with iodine-124 PET scan was performed at baseline and 4 weeks after treatment with selumetinib (75 mg twice daily). In total, 12 patients had increased iodine-124 uptake (four of nine patients with BRAF mutation and all five patients with NRAS mutation). Eight of those patients had reached the dosimetry threshold for radioiodine therapy, including the five patients with NRAS mutation.

After radioiodine therapy, five patients had confirmed partial responses and three had stable disease. A mean reduction of 89 percent in serum thyroglobulin level was observed in all patients, with no grade ≥3 toxic effects reported.

“Selumetinib produces clinically meaningful increases in iodine uptake and retention in metastatic thyroid cancer refractory to radioiodine. The effectiveness may be greater in patients with RAS-mutant disease,” the authors concluded.
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Oxycodone: Prolonged-release formulations for the management of cancer pain

Speakers at last year’s European Society for Medical Oncology (ESMO) Congress in Vienna, Austria, highlighted the plight of many cancer patients around the world who suffer from severe pain, in large part due to excessive regulatory restrictions on proven and effective pain-relieving opioids. The current report profiles oxycodone, one of the best known opioids used for the management of cancer-related as well as other forms of pain.

Naomi Adam

MSc (Med), Category 1 Accredited Education Provider (Royal Australian College of General Practitioners)

Introduction

Opioid analgesics such as oxycodone are medications that have been associated with controversy. From time to time, media reports highlight some of the unfavorable aspects potentially associated with their use. Chief among these concerns is addiction, that is, compulsive drug use, which is continued despite drug-related harm to self and others. [Drug Safety 1999;21:283-296] This is further complicated by the phenomenon of pseudo-addiction, where patients display behaviors usually associated with addiction (e.g., frequently requesting more medication) because of inadequate pain management. [Sci Am 1990;262:27-33] Other issues with opioids are the development of tolerance (where increasing doses are required to maintain pain control), and physical dependence that leads to withdrawal symptoms if the medication is abruptly discontinued. [In: Smith HS, editor. Drugs for Pain. Philadelphia: Hanley and Belfus, Inc; 2003: 153-156] There is also evidence of diversion of prescription opioids through various pathways, including doctor shopping, thefts from pharmacies and street drug markets, to misuse by recreational users who just want ‘to get high’. [Pain Physician 2012;15(3 Suppl): S191-S203]

On the other hand, according to the International Association for the Study of Pain (IASP) Declaration of Montreal, access to pain management is a fundamental human right. The IASP asserts that in most of the world there is inadequate access to treatment for acute pain, as well as a failure to recognize that chronic pain is a serious health problem. The Declaration concludes that the withholding of pain treatment is profoundly wrong and leads to suffering which is harmful. [Inter-
national Association for the Study of Pain. Declaration of Montreal. http://www.iasp-pain.org/Content/NavigationMenu/Advocacy/DeclarationofMontr233al/default.htm] This statement is underlined by a growing body of evidence that shows untreated or undertreated pain leads to morphological changes in the central nervous system. Ultimately, this can result in peripheral and central sensitization where neuronal activation and inflammation amplifies stimuli (for example hyperalgesia and allodynia).

**Oxycodone**

**Pharmacology**

Oxycodone is a semi-synthetic opioid derived from the opium alkaloid, thebaine. It is structurally related to morphine and shares certain physico-chemical characteristics with other opioids. It provides analgesia with no ceiling effect. Oxycodone is a full opioid agonist with affinity for mu (μ) and kappa (κ) receptors. It has been suggested that activity at the κ receptor may explain its effectiveness in neuropathic pain. [J Pain Symptom Manage 1993;8:63-67, In: Bennett MI, editor. Neuropathic pain. Oxford: Oxford University Press; 2006: 109]

**Pharmacokinetics**

Oxycodone has a high absolute bioavailability of up to 87 percent following oral administration (compared with 30 percent for morphine). Maximal plasma concentrations are reached after 1-1.5 hours with conventional oral formulations of oxycodone (eg, Oxynorm). [Oxynorm Prescribing Information] However, with prolonged-release delivery systems (eg, oxycodone), peak concentration is delayed until 3 hours after dosing. [Oxycodone Prescribing Information] Prolonged-release delivery given every 12 hours provides equivalent peak and trough concentrations of drug to conventional formulation given every 6 hours.

Oxycodone has two principal metabolites – noroxycodone and oxymorphone. The latter has some analgesic activity but is present in plasma in low concentrations and is not considered to contribute to oxycodone’s pharmacological effect. The liver enzymes CYP3A4 and CYP2D6 are involved in the formation of noroxycodone and oxymorphone, respectively.

**Clinical efficacy**

A number of studies (both controlled and non-comparative) have shown that prolonged-release oxycodone is effective in controlling moderate-to-severe cancer pain. Efficacy is comparable to that of prolonged-release morphine or prolonged-release hydromorphone. [Cancer 1997;79:1428-1437; Eur J Pain 1998;2:239-249] Longer-term studies (3 months) have shown that prolonged-release oxycodone provides pain relief for a full 12-hour period in chronic cancer pain. [Cancer Invest 1998;16:562-571] Some investigators have found that there is a subgroup of patients (around a quarter) with cancer pain who get no relief from morphine. A high proportion of these (87 percent) do respond to oxycodone and therefore benefit from the switch to a different opioid. [Supp Care Cancer 2006;14:56-64]

Prolonged-release oxycodone has also been shown to provide pain relief in patients suffering from neuropathic pain conditions, namely post-herpetic neuralgia and painful diabetic neuropathy. In post-herpetic neuralgia, the number-needed-to-treat (NNT) to obtain one patient with >50 percent pain relief with oxycodone is 2.5, whereas for
other treatments the NNT is higher (eg, 2.64 for tricyclic antidepressants [TCAs], 4.39 for gabapentin, and 4.76 for tramadol). [PLoS Med 2005;2:e164] In painful diabetic neuropathy, NNTs are 2.6 for prolonged-release oxycodone, 3.5 for TCAs, 3.8 for gabapentin and 3.1 for tramadol. [Pain 2003;105:71-78]

There is also evidence that prolonged-release oxycodone is effective in post-operative pain due to procedures such as hysterectomy and unilateral total knee arthroplasty. [Eur J Clin Pharmacol 1999;55:425-429; J Bone Joint Surg 2001;83-A:572-576]

**Adverse effects**

The side effect profile of oxycodone is comparable with that of other strong opioids such as morphine. Typical opioid-related side effects should be anticipated and managed appropriately. Typical adverse events include sedation, nausea, vomiting and decreased gastrointestinal motility. There is evidence of the development of tolerance with respect to side effects, as these diminish over time with continued use of oxycodone. Respiratory depression is a potentially serious side effect with all opioid analgesics. However, appropriate monitoring and careful prescribing should minimize the risk.

**Dosing**

It is recommended that as soon as a first-choice weak opioid analgesic has failed, prolonged-release oxycodone should be used 12-hourly for continuous pain relief. The dose should be increased in 25-50 percent increments as necessary until stable pain control is achieved.

**Place within treatment guidelines**

The World Health Organization (WHO) guidelines for the management of cancer pain advocate the use of a stepwise escalation of analgesic medication, according to patient response. [WHO. Cancer pain relief with a guide to opioid availability. 2nd ed. Geneva: The Organization; 1996] The first step of this so-called ‘analgesic ladder’ is a non-opioid with or without adjuvant analgesic. If pain persists or increases, step two is an opioid for mild-to-moderate pain added to the step-one regimen with or without an additional non-opioid analgesic. If pain continues to persist or increase, in step three the opioid is changed to one for moderate-to-severe pain (eg, oxycodone). Regular dosing is clearly easier to achieve with a prolonged-release formulation of a drug because it is taken less frequently.

Further recommendations in the WHO guidelines are that analgesia should be given ‘by the clock’. Analgesics should be administered at regular intervals, rather than on an ‘as required’ basis. The oral route should be used whenever possible, because it is simple, convenient and economical compared with other routes of administration. Dosing should be individualized – the ‘right’ dose is the one that controls the pain. The patient should be well informed of the details of their drug regimen – the doctor should write down the name of each drug, the reason for its use, the dose and the number of times it should be taken each day. This is particularly important when using a prolonged-release formulation, such as those containing oxycodone.
Case Study

Dr. Alex Kwok-Cheung Leung
Specialist in Clinical Oncology

Presentation and history
A 24-year-old Chinese lady with good past health and unremarkable family history presented with an ulcerative left breast mass and hepatomegaly for 2 months in September 2008. Left breast biopsy confirmed invasive ductal carcinoma, estrogen receptor (ER) positive (H-score 200), progesterone receptor (PR) negative, and HER2 2+/FISH negative. The clinical stage was cT4NxM1, with CT scan showing metastasis to the liver, adrenal glands, bone and para-aortic lymph nodes.

She was initially treated in the private sector with one cycle of adriamycin, cyclophosphamide plus bevacizumab (15 mg/kg), followed by three cycles of paclitaxel, carboplatin and bevacizumab every 3 weeks. She was then referred to our department for further management.

Treatment and follow-up
Three more cycles of paclitaxel and carboplatin were given without bevacizumab, as the patient could not afford the cost. Treatment was completed in December 2008. Serial re-assessment PET-CT and ultrasound (U/S) liver showed less than partial response (PR).

She was then given six cycles of 5-FU, adriamycin and cyclophosphamide from January to May 2009. U/S liver showed PR in liver metastasis. She was then put on tamoxifen since June 2009.

The patient became symptomatic in December 2009 with blood-stained discharge from her fungating left breast tumor. A course of palliative radiotherapy (24 Gy/4 fractions) was given. U/S liver in January 2010 showed progressive disease, with the largest liver metastasis measuring 5 x 4.9 x 4.1 cm. She then received 15 cycles of capecitabine (2,500 mg/m² day 1-14 every 3 weeks, with dose reduction to 80 percent in view of fungating left breast ulcer) plus bevacizumab (15 mg/kg every 3 weeks) from January to November 2010. Treatment was well tolerated with no hand-foot syndrome (HFS), diarrhea, bone marrow suppression, proteinuria, hypertension, or significant bleeding event. Clinical response was achieved, with U/S liver in December 2010 revealing a reduction in size of liver metastasis to 2.5 x 2 x 3.9 cm. The left breast mass shrank from 12 cm to 5 cm, and the ulcer resolved. (Figures 1 and 2)

She chose to receive three more cycles of maintenance bevacizumab monotherapy followed by a drug holiday. She received radiotherapy.
for ovarian ablation in January 2011, and started letrozole in April 2011 after confirmation of biochemical menopause.

In September 2011, the patient had progressive disease in the liver while the left breast mass remained static. Letrozole was stopped. Six cycles of vinorelbine and carboplatin were given. In January 2012, she was diagnosed with brain metastasis and was treated with palliative whole-brain radiotherapy. The liver metastasis progressed again in April 2012. Three cycles of gemcitabine were given, but the liver metastasis further progressed. She was started on exemestane in July 2012. Fine needle aspiration of liver metastasis was repeated, this time showing ER positive (H-score 270), PR negative and HER2 3+ disease. Lapatinib was added to exemestane in September 2012. In December 2012, the liver metastasis progressed again. She was then put on weekly paclitaxel with 3-weekly trastuzumab since January 2013.

Discussion

Breast cancer is the most common female cancer in Hong Kong, and was the third leading cause of cancer mortality in 2010. Up to 50 percent of patients develop metastatic disease, with a median survival of 18-30 months.

 Anthracycline and taxane regimens are well established in the initial treatment of metastatic breast cancer. Upon further progression, our patient was treated with capecitabine, an oral drug well accepted for its convenience. Capecitabine is efficacious in heavily pretreated patients. Studies have shown that in patients who failed anthracyclines and taxanes, capecitabine resulted in response rates (RRs) of 20-25 percent, and a RR of 29 percent in the subgroup refractory to both paclitaxel and doxorubicin. Combination with another chemotherapy agent may produce even higher RRs at the expense of greater toxicity.

Capecitabine is generally well tolerated. The most common side effects include HFS, diarrhea and nausea. A local study of Chinese colorectal cancer patients taking adjuvant capecitabine showed no grade 4/5 toxicity, but a higher rate of significant HFS (grade 3, 41.4 percent) and lower rate of severe diarrhea (grade 3, 0 percent) compared to that reported in the X-ACT (Xeloda in Adjuvant Colon Cancer Therapy) trial. The HFS can usually be managed with temporary treatment suspension or dose reduction.

Capecitabine can be given in combination with trastuzumab or lapatinib. Use of bevacizumab in our patient at that time was in line with the initial US FDA accelerated approval in 2008, based on the progression-free survival benefit shown in the ECOG (Eastern Cooperative Oncology Group) 2100 trial. However, more recent studies did not reproduce the same magnitude of benefit. Further studies are in progress to evaluate the role of antiangiogenic treatment in metastatic breast cancer. Another point of note is that the HER2 status of our patient changed from negative to positive. According to the literature, discordance of HER2 status between primary and recurrent disease occurs at a rate of 0.7-10 percent. This could be a result of change in tumor biology, differential eradication of clonal subsets by prior treatment, tumor heterogeneity, and less-than-perfect accuracy of assays.

This case illustrates the successful use of capecitabine after failure of anthracycline and taxane in metastatic breast cancer, achieving good symptom relief and long disease control with minimal side effects.

References:

Sustained benefits of nilotinib in patients with newly diagnosed CML

Long-term trial results of nilotinib (Tasigna®, Novartis) in the treatment of newly diagnosed chronic myeloid leukemia (CML) were presented in December 2012 at the 54th American Society of Hematology (ASH) Meeting, further substantiating the superiority of nilotinib vs imatinib (Glivec®, Novartis). According to the data, patients receiving nilotinib achieved faster and deeper molecular responses (MR), which translated into better clinical outcomes in terms of disease progression and survival.

The ENESTnd trial

Nilotinib – a BCR-ABL tyrosine kinase inhibitor with greater potency and selectivity than imatinib – has demonstrated superior efficacy in the phase III ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients) trial. [N Engl J Med 2010;362:2251-2259]

In the study, 846 patients with newly diagnosed chronic-phase Philadelphia chromosome-positive CML were randomized in a 1:1:1 ratio to receive nilotinib (300 mg or 400 mg, twice daily) or imatinib (400 mg once daily). The primary endpoint was the rate of major molecular response (MMR) at 12 months. MMR is defined as a BCR-ABL transcript level ≤0.1 percent on real-time quantitative polymerase chain reaction (RQ-PCR) assay as expressed on the International Scale (IS).

At 12 months, MMR rates for nilotinib (44 percent for the 300 mg dose, and 43 percent for the 400 mg dose) were nearly twice that for imatinib (22 percent; p<0.001 for both comparisons). The rates of complete cytogenetic response (CCyR) were also significantly higher with nilotinib, and the time to progression to accelerated phase or blast crisis (AP/BC) was significantly longer among patients receiving nilotinib than those on imatinib.

ENESTnd 4-year update

Long-term results of the ENESTnd trial reported at ASH 2012 included efficacy and safety data based on longer follow-up of 4 years (data cutoff, July 2012). The level of MR was defined as MMR, MR⁴ (≤0.01 percent⁵) and MR⁴.⁵ (≤0.0032 percent⁵). [Blood 2012;120:abstract 1676]

Nilotinib continued to demonstrate superior efficacy over imatinib with higher and deeper MR rates, a significantly decreased risk of progression to AP/BC, and higher rates of progression-free survival (PFS), and overall survival (OS).

“Significantly higher rates of MMR, MR⁴ and MR⁴.⁵ were achieved in nilotinib-treated patients,” reported lead investigator Dr. Hagop M. Kantarjian, of the University of Texas MD Anderson Cancer Center, Houston, USA.

By 4 years, significantly more patients in the nilotinib arms (76 percent for the 300 mg dose and 73 percent for the 400 mg
dose) achieved MMR compared with those in the imatinib arm (56 percent). The difference in the rate of MMR continued to be significantly higher for nilotinib from 1 to 4 years. (Figure 1)

According to Kantarjian, no new progressions occurred on core treatment between the 2-year and 4-year analyses. “When events occurring after treatment discontinuation were included, the rates of progression to AP/BC were also significantly lower with nilotinib vs imatinib,” he noted.

He added that nearly twice as many patients had emergent mutations on imatinib vs each nilotinib arm (21 vs 11 in each arm), which may indicate a lower risk of treatment resistance with nilotinib.

The estimated OS rates were similar in all groups at 4 years (94.3 and 96.7 percent for nilotinib 300 mg and 400 mg, respectively, and 93.3 percent for imatinib). However, fewer CML-related deaths occurred in the nilotinib 300 mg and 400 mg arms vs imatinib (5, 4 and 13, respectively).

Both drugs were well tolerated. The main hematologic adverse events included neutropenia, thrombocytopenia and anemia, consistent with previous reports for both agents. No new safety signals were raised, with few adverse events and laboratory abnormalities observed since the previous analysis.

“These long-term data from ENESTnd support the use of nilotinib as a standard-of-care option in newly diagnosed adult patients with Philadelphia chromosome-positive CML in chronic phase, and should be considered to replace imatinib as the standard-of-care frontline therapy for these patients,” concluded Kantarjian.

Deep early response improves outcomes

A poster presentation at ASH 2012 featured an analysis of 4-year data from the ENESTnd trial, focusing on patient outcomes based on early MR and factors associated with early response. [Blood 2012;120: abstract 167]

Earlier data from ENESTnd demonstrated that significantly more patients achieved early MR of both <10 percent and <1 percent BCR-ABLIS at both 3 and 6 months on nilotinib vs imatinib. For the current analysis, patients in the nilotinib 300 mg arm (n=258) and the imatinib arm (n=264) were grouped based on BCR-ABL transcript levels of ≤1 percent, 1≤10 percent, and >10 percent at 3 and 6 months. Rates of MMR and MR4.5 as well as PFS and OS were evaluated according to BCR-ABL transcript levels.

Among evaluable patients at 3 months, 9 percent of patients in the nilotinib arm vs 33 percent in the imatinib arm had poor MR, ie, BCR-ABL transcript levels of >10 percent. Conversely, 90.7 percent of patients in the nilotinib arm achieved BCR-ABL levels of ≤10 percent, and 56.2 percent achieved deep early MR (BCR-ABL levels of ≤1 percent). (Figure 3) Patients with deep early MR response are most likely to achieve MR4.5, a key criterion for potential inclusion in treatment-free remission studies.

Patients with BCR-ABL transcript level of >10 percent at 3 months had a poorer prognosis, including a lower probability of future MMR or MR4.5. For example, 89 percent of patients on nilotinib who achieved BCR-ABL levels of ≤1 percent by 3 months achieved MMR by 2 years. (Figure 4) Results were similar for the 6-month landmark analyses.
PFS rate was higher for nilotinib patients with BCR-ABL levels of ≤ 10 percent than those with >10 percent 3 months (95.2 vs 82.9 percent at 4 years; p=0.0061). The corresponding OS rates at 4 years were 96.7 vs 86.7 percent (p=0.0116).

Reasons for poor response appeared to be related, at least in part, to baseline factors (Sokal risk, spleen size and additional chromosomal abnormalities) and dose intensity.

“Early MR at 3 and 6 months correlated with future MMR and MR45 as well as an increased probability of PFS and OS. Nilotinib frontline therapy allows more patients to achieve deeper responses earlier, associated with improved long-term outcomes vs imatinib,” the authors wrote.

Conclusions

The latest efficacy results and analyses from the ENESTnd trial have confirmed the long-term benefits of nilotinib over imatinib, supporting the frontline use of nilotinib in patients with newly diagnosed chronic-phase Philadelphia chromosome-positive CML.
Survival benefit with bevacizumab in first-line therapy of NSCLC

Non-small cell lung cancer (NSCLC) accounts for most cases of lung cancer, but first-line treatment of metastatic NSCLC with standard platinum-based chemotherapy provides only limited efficacy. At a recent Roche-sponsored symposium in Hong Kong, Professor Roman Perez-Soler of the Albert Einstein College of Medicine, Yeshiva University, New York, USA, reviewed the results of NSCLC chemotherapy trials, focusing on the benefits of adding the angiogenesis inhibitor, bevacizumab (Avastin Roche®, Roche), to standard chemotherapy regimens.

Treatment options for NSCLC

Metastatic NSCLC patients with wild-type epidermal growth factor receptor (EGFR) gene, no translocation of anaplastic lymphoma kinase (ALK) gene and non-squamous histology are usually treated with platinum-based doublet chemotherapy regimens, which include cisplatin or carboplatin combined with a chemotherapeutic drug such as gemcitabine or pemetrexed.

Bevacizumab is a recombinant, humanized, monoclonal antibody against vascular endothelial growth factor (VEGF), a key promoter of angiogenesis and cancer progression. VEGF overexpression is correlated with poor prognosis in NSCLC, and the addition of bevacizumab to chemotherapy regimens has been shown to provide survival benefits and higher response rate (RR), with good tolerability and a consistent safety profile across trials. Hence, bevacizumab has emerged as an additional treatment option for NSCLC.

OS benefit independent of chemochoice

Several studies assessed the efficacy of first-line bevacizumab combined with standard chemotherapy regimens.

In the ECOG (Eastern Cooperative Oncology Group) 4599 study, 878 patients with predominantly non-squamous stage IIIB/IV or recurrent NSCLC were randomized to receive treatment with either standard carboplatin/paclitaxel (CP) chemotherapy for six cycles and bevacizumab 15 mg/kg every 3 weeks until disease progression (DP), or CP chemotherapy alone. The primary endpoint was overall survival (OS). “The median OS with bevacizumab and CP was longer than that with CP alone [12.3 vs 10.3 months],” reported Perez-Soler. [N Engl J Med 2006;355:2542-2550]

In the AVAiL (AVAtin in Lung) study, 1,043 patients with previously untreated, advanced or recurrent non-squamous NSCLC received six cycles of cisplatin/gemcitabine with either bevacizumab 7.5 mg/kg, bevacizumab 15 mg/kg or placebo every 3 weeks until DP. The primary endpoint was progression-free survival (PFS), and OS was a secondary endpoint. Median PFS was 6.7 and 6.5 months for the lower and higher doses of bevacizumab, vs 6.1 months for chemotherapy alone. The respective median OS was 13.6 and 13.4 vs 13.1 months. [Ann Oncol 2010;21:1804-1809]

The SAiL (Safety of Avastin in Lung Cancer)
study enrolled 2,212 patients with stage IIIB/IV or recurrent non-squamous NSCLC. The primary endpoint was safety, and one of the secondary endpoints was OS. Patients received bevacizumab 7.5 mg/kg or 15 mg/kg every 3 weeks plus either carboplatin doublet or cisplatin doublet therapy for up to six cycles, followed by single-agent bevacizumab until DP. The incidence of clinically significant adverse events (AEs), such as thromboembolism, hypertension and hemorrhage, was generally low. Median OS was 14.3 months for bevacizumab plus carboplatin doublet and 14.7 months for bevacizumab plus cisplatin doublet. [Lancet Oncol 2010;11:733-740]

The median OS durations observed in the studies were similar, ranging from 12.3 to 14.6 months. “In the three studies, bevacizumab consistently showed OS benefit of over 1 year in non-squamous NSCLC,” said Perez-Soler. “The benefit applies regardless of the chemotherapy backbone.” (Figure 1)

The POINTBREAK study

Given the proven efficacy of bevacizumab and pemetrexed, the phase III POINTBREAK trial was conducted to evaluate the survival benefit of a combination of the two agents. A total of 939 patients with previously untreated stage IIIB/IV non-squamous NSCLC, performance status 0-1 and median age of 64.7 years were randomized to receive bevacizumab 15 mg/kg, carboplatin AUC 6 and pemetrexed 500 mg/m² (n=472), or bevacizumab 15 mg/kg, carboplatin AUC 6 and paclitaxel 200 mg/m² (n=467). The primary endpoint was OS.

“The result was disappointing,” Perez-Soler said. “The bevacizumab/carboplatin/pemetrexed arm did not show better OS vs bevacizumab/CP, which was contrary to expectations.” The difference in median OS between the control arm (bevacizumab/CP) and bevacizumab/carboplatin/pemetrexed was not statistically significant (13.4 vs 12.6 months; p=0.949). (Figure 2)

“Bevacizumab and pemetrexed will less likely be used together, as the combination does not appear to add efficacy,” he suggested. “Bevacizumab with CP as the control in the POINTBREAK study did very well. I think the first-line treatment of non-squamous NSCLC will be polarizing into two options: either pemetrexed/platinum doublet or bevacizumab/CP.”

Achieving higher RR

“The new approach in NSCLC treatment emphasizes the use of maintenance therapy, which can delay DP,” Perez-Soler explained. “Patients achieving response or stable disease are more likely to be given maintenance therapy. Therefore, the key to achieving maintenance relies on RR.”

A comparison of RR with different drug combinations used in first-line NSCLC treatment demonstrated that >60 percent of patients treated with bevacizumab and standard chemotherapies entered the fifth cycle of first-line therapy or first cycle of maintenance therapy. In contrast, among patients who received chemotherapy without bevacizumab, the rate was <60 percent. (Figure 3) “Adding bevacizumab to standard chemotherapies leads to higher RR. With bevacizumab, more patients entered the fifth cycle of first-line treatment or first cycle of maintenance therapy,” he said.

Well tolerated, consistent safety profile

Due to its anti-VEGF activity, common AEs associated with bevacizumab use include hemorrhage and hypertension. [Lung Cancer 2012;78:1-7] A review of the incidence of grade 3/4 AEs across different bevacizumab
trials showed that <2 percent of patients experienced pulmonary hemorrhage and hemoptysis, while <3 percent had proteinuria. The most common AE was hypertension, ranging from 2.5 percent in the AVAPERL (Avastin With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer) study to 8.5 percent in the AVAiL study. “However, it is rare to interrupt the use of bevacizumab because of hypertension,” Perez-Soler noted. “In general, bevacizumab had a consistent safety profile across trials.”

There were also concerns over the use of bevacizumab in patients with brain metastases, which are present at initial diagnosis in a significant number of cases of advanced NSCLC. A recent review showed no significantly increased risk of brain hemorrhage in patients with NSCLC and emerging or pretreated brain metastases who received bevacizumab treatment. [Lung Cancer 2012;78:1-7] “Basically, bevacizumab is safe for patients with brain metastases,” Perez-Soler said.

**Future prospects**

At present, the only criteria for bevacizumab use are clinical, including nonsquamous histology, no observed hemoptysis, and tumors not invading or abutting major blood vessels. “It is important to study any possible biomarkers for bevacizumab,” suggested Perez-Soler. “With biomarkers, we can show the efficacy of bevacizumab in different NSCLC patients. Ultimately, it would be easier to reach consensus on who should take bevacizumab and who should not.”

Perez-Soler also predicts a wider use of bevacizumab in first-line treatment of NSCLC. “As bevacizumab/carboplatin/pemetrexed did not prolong OS vs bevacizumab/CP in the POINTBREAK study, the bevacizumab/pemetrexed combination will not be used. It is more likely that there will be some increased use of bevacizumab over pemetrexed,” he said.

**Conclusions**

Adding bevacizumab to first-line chemotherapy for NSCLC was shown to provide PFS and OS benefits, independent of the chemotherapy backbone. Bevacizumab-based regimens also allowed more patients to reach the fifth cycle of first-line therapy or first cycle of maintenance therapy, which has been associated with a delay in DP. As demonstrated in the POINTBREAK study, combining pemetrexed and bevacizumab did not prolong OS. Across trials, bevacizumab had a consistent safety profile with a low incidence of AEs.
Patients with indolent non-Hodgkin's lymphoma (NHL) are generally responsive to first-line chemotherapy but are prone to relapses. In contrast, patients with mantle cell lymphoma (MCL) often experience rapid disease progression, and therapeutic options for this subgroup remain limited. At a recent symposium in Hong Kong, Professor Mathias J. Rummel, Medical Director of the Clinic for Hematology and Medical Oncology, Hospital of the Justus-Liebig-University, Giessen, Germany, discussed the treatment options available for the management of these conditions, focusing on the benefits of bendamustine (Treanda®, Teva).

Identifying the ideal treatment strategy

“In many parts of the world, physicians today still employ a watch-and-wait strategy in the management of indolent lymphomas, despite the availability of new therapeutic modalities,” said Rummel. “Nowadays, the goal of treatment for patients with aggressive lymphomas is to prolong remission while minimizing toxicity.”

“Combined immuno-chemotherapy is the standard of care today,” said Rummel. One such approach involves the use of the genetically engineered monoclonal antibody, rituximab. “Rituximab-chemotherapy plus rituximab maintenance appears to be the optimal option for patients with follicular lymphoma,” he said.

More specifically, the combination of bendamustine plus rituximab (B-R) as first-line therapy in patients with advanced follicular lymphoma has been listed as a category 1 recommendation in the USA National Comprehensive Cancer Network (NCCN) guidelines for NHL. [J Natl Compr Canc Netw 2011;9:484-560]

Front-line bendamustine in indolent lymphoma and MCL

“Originally developed in Germany 50 years ago, bendamustine has demonstrated efficacy in the treatment of chronic lymphocytic leukemia, NHL, multiple myeloma and metastatic breast cancer,” said Rummel. Earlier studies have shown that bendamustine exhibits similar or greater potency than cyclophosphamide, and preclinical studies have demonstrated a synergistic interaction when administered with rituximab. [Proc Am Assoc Cancer Res 2004;45:abstract 1215]

In 2000, the German Study Group of indolent Lymphomas (StiL) initiated a phase II trial to evaluate the combination of B-R in patients with mantle cell or low-grade lymphomas who were refractory to or relapsed after previous treatment. “The study endpoints were progression-free survival [PFS], response rate and toxicity,” said Rummel. [J Clin Oncol 2005;23:3383-3389]
At study end, the investigators recorded an overall response rate of 90 percent, with a complete remission (CR) rate of 60 percent. The median PFS was 24 months, and the median overall survival (OS) was not reached. In MCL, the response rate to B-R was 75 percent with a CR rate of 50 percent. Non-hematologic toxicity was generally mild and consisted mainly of WHO grade 1 and 2 events. In their conclusion, the authors noted that B-R was a “highly active regimen in the treatment of low-grade lymphomas and MCLs.”

“Based on those results, we concluded that B-R was a promising combination which needed to be compared with the current standard of care. Therefore, StiL initiated a phase III trial to compare B-R with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) plus rituximab (CHOP-R) as a first-line treatment in patients with indolent lymphoma and MCL,” said Rummel.

**Improved outcomes with B-R vs CHOP-R**

In that phase III study, 549 patients with indolent lymphoma or MCL were randomized to receive B-R or CHOP-R for up to six cycles. Rummel highlighted that the dosage of bendamustine administered was 90 mg/m², which is lower than that recommended in the product information (120 mg/m²). “It is possible to achieve a good result at a lower dosage of 90 mg/m²,” he opined. The primary endpoint of the study was PFS. [Lancet 2013;DOI:10.1016/S0140-6736(12)61763-2]

At the median follow-up of 45 months, PFS was significantly superior for B-R compared with CHOP-R (69.5 vs 31.2 months; p<0.001). (Figure 1) “This PFS figure included all five histologies involved in the study, and it is also important to consider the PFS for each lymphoma histology separately,” stressed Rummel.

“In patients with follicular lymphoma, there was also a clear advantage with B-R,” he said. Median PFS was not reached with B-R whereas it was 40.9 months in the CHOP-R group (p=0.007). (Figure 2) While OS did not differ significantly between treatment arms, Rummel noted that this was because patients with an indolent lymphoma disease could be easily salvaged. “Overall, 103 patients required salvage treatment after B-R, vs 143 after CHOP-R. Of those previously on CHOP-R, 52 received B-R as salvage therapy,” he said.

Rummel also highlighted that in patients with normal lactate dehydrogenase (LDH) levels, PFS was significantly prolonged with B-R compared with CHOP-R (p<0.0001). (Figure 3) In the elevated LDH group, PFS was numerically increased with B-R compared with CHOP-R (p=0.118).

Twenty secondary malignancies were observed in the B-R group vs 23 in the CHOP-R group. Only one hematological malignancy per group was observed (one myelodysplastic syndrome in B-R and one acute myeloid leukemia in CHOP-R). “Neutropenia grade 3–4 was observed in 69 percent of the CHOP-R group, but in only 29 percent of the B-R group,” said Rummel.

The investigators thus concluded that B-R was not only less toxic, but also more effective than the commonly used first-line therapy with CHOP-R. “As such, B-R should be considered as a preferred first-
line therapy for patients with follicular, indolent and MCLs,” noted Rummel. This is in line with the latest NCCN guidelines. [J Natl Compr Canc Netw 2011;9:484-560]

**Better QoL with B-R**

In a separate study, Burke et al compared the efficacy and quality of life (QoL) results between B-R and standard treatment regimes such as CHOP-R and CVP (cyclophosphamide, vincristine and prednisone)-R (CVP-R) in patients with indolent lymphoma or MCL. The primary objective of the study was to compare the CR rate for B-R vs CHOP-R/CVP-R, whereas the secondary objective was to compare the QoL outcomes between the groups.

Focusing on QoL, Rummel highlighted that among all randomized patients, the mean change in Global Health Status (GHS)/QoL score from baseline to final visit was significantly higher for patients treated with B-R than those treated with CHOP-R/CVP-R (3.6 vs -5.1, respectively; p=0.0005), indicating a relative improvement with B-R.

The mean change in GHS/QoL score was also significantly higher in the B-R group for patients with indolent lymphoma (2.1 vs -6.3; p=0.0021), and numerically higher for patients with MCL (10.9 vs 1.6; p=0.0654) as compared with those in the CHOP-R/CVP-R group. [54th American Society of Hematology Annual Meeting and Exposition, abstract 155]

“B-R treatment was also associated with better emotional functioning, less appetite loss and less constipation compared with CHOP-R/CVP-R. In addition, patients on B-R fared better on measurements of dyspnea and fatigue than those who received the standard treatment regimens,” noted Rummel.

“At present, there are several ongoing studies investigating the potential applications of bendamustine as part of a conditioning regimen for resistant or relapsed lymphoma patients. So far, the preliminary results from these studies have been promising,” said Rummel. “For now, we can conclude that treatment with B-R is less toxic and confers better PFS and better improvements in QoL than the current standard treatment regimens.”
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http://www.esmo.org/events/breast-2013-impakt.html

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