Multiple myeloma group to track disease across Asia

Cancer patients suffer from excessive pain due to medication restrictions

Oxycodone: Prolonged-release formulations for the management of cancer pain

Androgen blockade can be shortened for high-risk prostate cancer

Mammographic screening and breast cancer incidence
Multiple myeloma group to track disease across Asia

Radha Chitale

A collaborative effort among multiple myeloma (MM) specialists from around Asia hopes to improve tracking, treatment, and awareness about the cancer, which has seen increased incidence in past decades.

The Asia Network, an initiative of the International Myeloma Foundation, includes representatives from Singapore, Japan, Korea, China, Taiwan, Hong Kong and Thailand and has four main goals.

The initial task, already begun, is to characterize MM in the region and set up registries to track disease incidence and progress.

In Singapore, about 100 cases of MM are diagnosed each year but more detailed data is incomplete. A bone marrow cancer that causes pain and fractures, repeated infections and in severe cases can reduce survival to less than 2 years, MM typically strikes adults over 60. Aging Asian populations suggest a corresponding rise in MM cases.

Much of the existing descriptive data for MM is from North America and Europe. While MM is not very different across ethnicities, Assistant Professor Chng Wee Joo, a senior consultant in the Department of Haematology-Oncology at Singapore’s National University Cancer Institute and one of the founding members of the Asia Network, said the disease incidence is higher in Asia and collecting regional data will be worthwhile.

This step could also help improve patient care by creating risk stratification schemes for appropriate disease management.

For example, patients identified as low risk could be managed with an eye to reducing treatment intensity while those at high risk may need to receive new, aggressive therapies early.

“Not every patient with myeloma is the same, and now that we have more treatment options and the burden of treatment to the patient is getting higher, because these new drugs are not cheap, we need to analyze the situation more closely,” Chng said.

The average cost of MM treatment in Singapore is between S$6,000-S$10,000 per month. A bone marrow transplant can cost S$120,000-S$150,000, plus the costs of follow-up care.

The second goal of the Asia Network is to create opportunities for more MM clinical trials, which would serve the dual purpose of furthering research and improving patient access to expensive therapy.

Lowering the price of treatment is not one of the Asia Network’s goals, partly because the participating countries have a variety of healthcare schemes.

However, the group does plan to bolster patient support and advocacy groups for MM as one of its goals.

The final goal is to raise awareness and educate physicians about MM to improve early diagnosis and begin treatment early.

The initial data-gathering phase should be complete by the end of 2013, said Dr. Daryl Tan, a hematology specialist at the Raffles Cancer Centre in Singapore and a member of the MM Asia Network.

The group plans to expand membership to more countries in Asia at a later time after data gathering and research and trial systems in the existing countries have been established.
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.
Study identifies three CRC molecular subtypes

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

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical feature</th>
<th>Clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient</td>
<td>Baseline good prognosis</td>
<td>5-FU–based treatment or no adjuvant</td>
</tr>
<tr>
<td>epithelial</td>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td>A-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferative</td>
<td>Baseline poor prognosis</td>
<td>chemotherapy</td>
</tr>
<tr>
<td>epithelial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-type</td>
<td>Chemotherapy responsive</td>
<td></td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>Chemotherapy resistant</td>
<td>New targeted therapy? (companion Dx)</td>
</tr>
<tr>
<td>C-type</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Tabernero J, et al. ASCO GI 2013, abstract 333.
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 esophago-gastric 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.
Newer breast cancer screening modalities do not necessarily improve cancer outcomes among older average risk women and may lead to cancer overdiagnosis, a retrospective cohort study shows.

Researchers from the Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center at Yale University in New Haven, Connecticut, US, examined the cost of fee-for-service breast cancer screening and workup from a large database of women over age 66 in the US who were part of a national social insurance program (n=137,274). They also analyzed initial treatment costs for women who did develop cancer. [JAMA Intern Med 2013; doi:10.1001/jamainternmed.2013.1397]

There were significant differences in screening costs across geographic region ranging from US$40 to US$110 per person. The discrepancy was primarily attributed to use of newer, costlier screening methods including digital mammography or computer-aided detection (CAD).

“Newer breast cancer screening technologies... have expanded the options available to clinicians and are diffusing into clinical practice,” the researchers said. “The adoption of these new technologies can increase costs directly through reimbursement for the tests and also lead to higher rates of supplementary imaging, biopsy, or cancer detection.”

Women in high-cost screening areas were up to 78 percent more likely to be diagnosed with breast cancer compared with those in lower-cost areas, and the incidence of early stage cancer was higher.

While the crude incidence difference of early-stage cancer diagnosis between high- and low-cost areas was 1 per 1,000, the difference for stage IV cancer diagnosis was not significant.

“It is clear that the newer modalities pick up more and smaller tumors. These advantages are usually seen in the younger, pre-menopausal women,” said Dr. Ong Kong Wee, senior consultant in the Department of Surgical Oncology at the National Cancer Centre Singapore. “With newer and improved technology, the cost of screening will be expected to rise.”

But the researchers said the findings suggest overdiagnosis of breast cancer in high-cost regions. And more expensive screening methods did not correlate to lower treatment costs at the population level, even with a slight but nonsignificant trend towards higher treatment costs in high screening areas.

“Although our study did not set out to assess the effectiveness of CAD or digital...
Antibody-drug conjugates are new hope in cancer treatment

Rajesh Kumar

Older chemotherapy drugs that are no longer widely used due to their toxicity profiles are finding new uses in cancer treatment, thanks to the development of antibody-drug conjugates.

These will considerably improve survival and the quality of life of cancer patients, said Dr. Deborah Armstrong, associate professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Medicine in Baltimore, Maryland, US. She was a guest speaker at the 3rd Oncology Symposium jointly organized by Tan Tock Seng Hospital and Johns Hopkins in Singapore recently.

Armstrong cited the example of T-DM1 being one such therapy that will add a crucial weapon in the armament against human epidermal growth factor receptor 2 (HER2)-positive breast cancers.

T-DM1 is an antibody-drug conjugate consisting of the antibody trastuzumab (T) attached using a stable linker to the cytotoxic agent emtansine (DM1). It is designed to target and inhibit HER2 signaling and deliver the chemotherapy DM1 directly in tumor cells.

“Researchers have tried linking these to radioisotopes. But T-DM1 is the first one that uses the cell targeting with chemotherapeutic agent...and there’s going to be a big explosion in this type of targeted therapy using different antibodies that target specifically cancer cells with different drugs,” said Armstrong.

In a phase III study, T-DM1 achieved a 32 percent reduction in the risk of death among patients when compared with the standard-of-care arm. The median overall survival rate for T-DM1 patients was 30.9 months, compared with 25.1 months for patients taking a combination of lapatinib and capecitabine.

Based on the trial results, the US FDA has granted priority review for the use of T-DM1 in the treatment of patients with HER2-positive, unresectable locally advanced or metastatic
Singapore researchers identify multiple myeloma biomarker

Radha Chitale

Singaporean researchers identified a new protein that could be both an early sign of multiple myeloma (MM) and a therapeutic target for this cancer of the plasma cells in bone marrow.

The Fas apoptosis inhibitory molecule (FAIM) is a protein that prevents cell death, which is important in maintaining a healthy, functional T-cell population.

The researchers found that FAIM acts on an enzyme that is critical to cancer cell proliferation, although they could not identify the precise mechanism. [J Biol Chem 2010;285:11827–11835]

An analysis of FAIM expression in plasma cell samples from 15 healthy people and 147 people with MM showed that FAIM expression was significantly increased among MM patients, and greater FAIM expression was associated with poor patient outcome.

Silencing FAIM expression destroyed myeloma cells.

“In this study, we identified FAIM as a new biomarker that is associated with poor outcome as well as an important mediator of growth signals in myeloma cells that could

“... The detection of this biomarker will allow us to identify these high-risk patients...”

According to Armstrong, some drugs that work well in ovarian cancer may work in triple-negative breast cancer as well, particularly the platinum drugs. And poly ADP-ribose polymerase (PARP) inhibitors are currently at top of the list of potential solutions.

PARP is a family of proteins involved in a number of cellular processes involving mainly DNA repair and programmed cell death.
lead to drug resistance,” said lead researcher Professor Lam Kong-Peng of the Bioprocessing Technology Institute at Singapore’s Agency for Science, Technology and Research (A*STAR).

“The detection of this biomarker will allow us to identify these high-risk patients and possibly develop treatments that target FAIM to improve their outcome.”

It has been estimated that there are about 80 new cases of MM each year in Singapore. Median survival for MM patients is about 5 years with early treatment, according to the American Cancer Society.

However, patients may not present with symptoms, which can include bone pain, low blood counts and kidney problems, early and may only discover they have the disease when it has progressed. Treatment includes chemotherapy as well as other drugs such as steroids or thalidomide, but the cancer is incurable.

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 fol-
lowed 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 Ziehlinski 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.”

“Once trials were approved and started, recruitment was swift and very effective

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.

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.”

New treatment options for ‘orphan’ blood diseases

Naomi Rodrig

Physicians treating rare blood disorders now have more drug treatments to choose from, which allow patients to avoid demanding surgery and chemotherapy, while bringing huge revenues for pharmaceutical companies who can charge top dollar in these untapped markets, according to a recent report by GBI Research. [http://www.gbiresearch.com/Report.aspx?ID=Acquired-Orphan-Blood-Diseases-Therapeutics-Market-to-2019]

The report looked at the treatment of paroxysmal nocturnal hemoglobinuria (PNH), idiopathic thrombocytopenic purpura (ITP), myelodysplastic syndrome (MDS), myelofibrosis
(MF) and polycythemia vera (PV). Treatments for these conditions are often limited to symptom management and improvement of quality of life, with risky surgical procedures offering the only alternative.

“This bleak outlook makes the orphan blood disease market a great opportunity for drug discovery and development, as patient populations are small but untapped,” the authors wrote.

A case in point is eculizumab (Soliris®, Alexion) – a first-in-class humanized monoclonal antibody that reduces hemolysis and the risk of thrombosis associated with PNH by modifying the activity of the immune system. It is the first therapy approved for the treatment of PNH; at US$ 600,000 per year per patient, it is also the most expensive drug in the world. “Due to the market dominance of Soliris®, the PNH pipeline is very weak, so Alexion Pharmaceuticals look set to continue to benefit from this high pricing,” the report predicted.

MF is another acquired orphan blood disease with limited treatment options. Stem cell transplantation is the only curative treatment, but it is highly risky and often only leads to remission rather than cure. Symptomatic treatments include blood transfusions, androgen therapy, chemotherapy and radiotherapy.

Ruxolitinib (Jakafi®, Incyte Pharmaceuticals and Novartis) is a JAK inhibitor which targets the genes believed to cause MF, approved by the FDA in November 2011 for the treatment of intermediate- or high-risk MF.

Other drugs with the same mechanism of action are currently in the development pipeline, as other companies fight for the market share. For example, lestaurtinib (developed by Cephalon), is in clinical trials for myeloproliferative disorders and acute myelogenous leukemia (AML).

Two drugs approved in 2008 for the treatment of ITP—romiplostim (Nplate®, Amgen and Kyowa Kirin) and eltrombopag (Revolade®, GSK) – are also doing well in the market, as Medicare in the USA covers most of the cost of these treatments. Meanwhile, a small phase II study has shown promising results for the experimental kinase inhibitor fostamatinib (Rigel Pharmaceuticals) in ITP patients refractory to other treatments.

Screening advocated for siblings of CRC patients

Naomi Rodrig

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 pre-malignant 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.”
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.”

Cancer patients suffer from excessive pain due to medication restrictions

Alexandra Kirsten

Adequate relief of cancer pain is recognized as a patient right, however many around the world suffer needlessly due to excessive regulatory restrictions of opioids.

“Unrelieved cancer pain is a cause of major worldwide suffering, not because we don’t have the tools necessary to relieve pain, but because most patients don’t have access to the essential pain-relieving medication,” said Professor Nathan Cherny, from Shaare Ze-dek Medical Center, Jerusalem, Israel, while speaking at last year’s European Society for Medical Oncology (ESMO) held in Vienna, Austria.

Cherny reported the findings of a Europe-wide study which found that very few countries provide all seven opioids on the essential
drug list of the International Association for Hospice and Palliative Care (IAHPC). Those medications include codeine, immediate and slow release oral morphine, oral oxycodone, and transdermal fentanyl.

The study, initiated by ESMO and the World Health Organization (WHO), was conducted by the International Collaborative Project to Evaluate the Availability and Accessibility of Opioids for the Management of Cancer Pain and included reports from several international oncology and palliative care organizations. [Ann Oncol 2010;21:615-626]

Additional worldwide data was collected between December 2010 and July 2012, with 156 reports submitted by experts in 76 countries and 19 Indian states. [ESMO Abstract 1707 PR]

“This pandemic affects literally billions of people. Not only are the patients suffering often terrible unrelieved pain, but their family members are often permanently scarred by the memories of witnessing such suffering in their loved ones,” Cherny said.

In many countries, less than three essential drugs for the relief of cancer pain are available. Often those medications are either not or partially subsidized by the government and availability can be limited. Furthermore, many countries have highly restrictive regulations that limit cancer patients entitled to medication from receiving prescriptions and increase the bureaucratic burden of the prescribing and dispensing process. Regarding this worldwide problem, the authors said that “the under-treatment of pain and the suffering that ensues is a public health catastrophe. There is an urgent need to examine drug control policies and repeal excessive restrictions which impede this most fundamental aspect of cancer care.”

“The study has provided an unprecedented wealth of knowledge that will be an essential tool in lobbying to reformulate national plans for the treatment of cancer pain,” Cherny said. Advocacy initiatives by stakeholder and international organizations partnering with authorities and regulators have demonstrated that a regulatory reform is possible.

“Urgent and intensive efforts are needed to expand this process, particularly in the countries with the most severe restrictions of availability and accessibility,” the authors concluded.
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 (eg, 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. [International 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 postoperative 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.

**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.
Radiotherapy after radical prostatectomy – 10-year results

The EORTC trial, reported in 2005, showed that postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer improved the rate of progression-free survival after an average follow-up of 5 years. Now the 10-year results have been reported.

A total of 1,005 patients aged up to 75 years with prostate cancer and capsular perforation, positive surgical margins or invasion of seminal vesicles, were randomized to receive postoperative radiotherapy either immediately or only after a significant increase in prostate specific antigen (PSA) levels. Median follow-up was 10.6 years (range 2 months to 16.6 years). Biochemical or clinical progression or death occurred in 198/502 (39.4 percent) in the immediate radiotherapy group vs 311/503 (61.8 percent) in the ‘wait-and-see’ group, a highly significant difference. Late adverse events occurred significantly more often in the immediate radiotherapy group (70.8 percent vs 59.7 percent). Death from prostate cancer occurred in 5.0 percent vs 6.8 percent, a nonsignificant difference.

Postoperative radiotherapy improved local control and biochemical progression-free survival at 10 years, but not prostate cancer specific mortality. Further analysis suggested that postoperative radiotherapy might benefit patients younger than 70, but harm older patients, and it might also benefit patients with positive surgical margins.


Global burden of cancer in 2008

Advances in cancer prevention and treatment have led to a fall in cancer mortality in richer countries, but poorer countries have yet to realize this improvement and, in fact, have increasing cancer mortality rates. Available population data have been used to assess the burden of cancer worldwide in 2008.

Data were gathered from 184 countries in 12 world regions. It was estimated that around the world a total of 169 million years of healthy life were lost to cancer in 2008. Colorectal, lung, breast and prostate cancers caused 18 to 50 percent of the cancer burden. Infection-related cancers (liver, stomach, cervix) added an additional 25 percent to the cancer burden in sub-Saharan Africa and an additional 27 percent in East Asia. Years of life lost (YLLs) contributed >90 percent to the total burden and were the most important part of disability-adjusted life-years (DALYs). In poorer countries YLLs contributed to a greater proportion of DALYs than in richer countries, indicating a poorer prognosis after diagnosis in poorer countries.

Improvements in cancer prevention and care are needed in lower-income countries.

Mammographic screening and breast cancer incidence

Data from the nine ‘Surveillance, Epidemiology, and End Results’ areas in the US, including about 10 percent of the US population, have provided information about the value of mammographic screening for breast cancer from 1976 to 2008.

During this time the annual incidence of early-stage breast cancer among women aged 40 years or older increased from 112 to 234 cases per 100,000 women. Over the same period the rate of presentation with late-stage breast cancer fell from 102 to 94 cases per 100,000 women. It is therefore presumed that only eight of the 122 extra cases per year would proceed to advanced disease. It is calculated that breast cancer was overdiagnosed (harmless tumors detected on screening) in 1.3 million US women in the last 30 years. In 2008, overdiagnosis affected >70,000 US women and accounted for 31 percent of all diagnoses of breast cancer.

It is concluded that there is substantial overdiagnosis of breast cancer with mammographic screening and that screening has, at best, only a small effect on breast cancer mortality.

Cancers of early onset are more likely than late-onset cancers to be familial. Now a Swedish study has shown that cancers at any age may be familial and early or late onset may be familial features.

The Swedish Familial-Cancer Database is a national register that includes all Swedes born after 1931 and their parents. The familial-cancer study included >12.2 million people and >1.1 million cases of a first primary cancer with follow up from 1961 to 2008. The risk of occurrence of the same type of cancer in parent and child was significantly increased (2-to 3-fold) for colorectal, lung, breast, prostate and bladder cancers, melanoma, squamous cell skin cancer, and non-Hodgkin’s lymphoma, at whatever age the cancer developed in the parent. With the parental cancer diagnosed at age 90 or older there was still an increased risk in the offspring for colorectal, breast, and prostate cancers. When the parental cancer diagnosis was at a younger age (<40 years) there was no increase in risk to offspring at the ages of 60 to 70 years. The highest risk was among younger offspring after an early-age diagnosis in a parent. The highest risk of all was a 5.3-fold increase in risk of prostate cancer among men whose father developed prostate cancer age 40 to 49 years.

Cancers may be familial at any age of onset in a parent but the greatest risk was of early onset cancer in both parent and child.

Ponatinib for Ph-positive leukemias

BCR-ABL, a fusion product of the Philadelphia chromosome (Ph) is a tyrosine kinase implicated in the pathogenesis of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL). Resistance to tyrosine kinase inhibitors such as imatinib, dasatinib or nilotinib is often caused by mutations in the BCR-ABL kinase domain. Ponatinib is an orally available tyrosine kinase inhibitor that blocks both native and mutated BCR-ABL. A multicenter US phase I study has shown that ponatinib is highly active against Ph-positive leukemias.

The study included 81 patients with treatment-resistant hematological cancers, including 65 Ph-positive leukemias (60 CML and five Ph-positive ALL). Among the 65 patients with Ph-positive leukemias 33 (51 percent) had received all three currently approved tyrosine kinase inhibitors and 26 (40 percent) had received two. Among the 43 patients with chronic-phase CML, 42 (98 percent) had a complete hematological response to ponatinib, 31 (72 percent) had a major cytogenetic response, and 19 (44 percent) had a major molecular response. Twelve patients had chronic-phase CML with the BCR-ABL T3151 mutation, which is resistant to current tyrosine kinase inhibitors: all 12 had a complete hematological response and 11 (92 percent) had a major cytogenetic response. Of the 13 patients with chronic-phase CML without detected mutations, all had a complete hematological response and eight (62 percent) had a major cytogenetic response. The responses in patients with chronic-phase CML were durable. Among the 22 patients with accelerated-phase or blast-phase CML or Ph-positive ALL, eight (36 percent) had a major hematological response and seven (32 percent) had a major cytogenetic response. Eleven (14 percent) of the 81 patients developed pancreatitis, serious in 8 cases, and 22 patients (27 percent) developed thrombocytopenia, serious in 1 case. Rash, myelosuppression and constitutional symptoms were common and raised levels of lipase or amylase (and pancreatitis) were dose-limiting.

Ponatinib is highly active against Ph-positive leukemias resistant to current tyrosine kinase inhibitors, including patients with the BCR-ABL T3151 mutation, other mutations, or no mutations.

13th St. Gallen International Breast Cancer Conference 2013
13/3/2013 to 16/3/2013
St. Gallen, Switzerland
Info: Q Events AG
Tel: +041 71 228 58 08
Fax: +041 71 228 58 09
E-mail: bcc@qevent.to.s.biz
http://www.oncoconferences.ch/dynasite.cfm?dsmid=111783

1st International Congress on Oncological Perspectives of Fertility Preservation: Gynecological & Breast Cancer
21/3/2013 to 23/3/2013
Berlin, Germany
Tel: +972 3 5666166
Fax: +972 3 5666177
E-mail: info@comtecmed.com

EORTC/EANO/ESMO 2013 – Trends in Central Nervous System Malignancies
22/3/2013 to 23/3/2013
Prague, Czech Republic
Tel: +032 2 775 02 01
Fax: +032 2 775 02 00
E-mail: eortceanoesmo@ecco-org.eu
http://www.ecco-org.eu/Conferences/Conferences/EORTC_EANO_ESMO.aspx

8th International European Federation for ColoRectal (EFR) Cancer Congress
Vienna, Austria
Tel: +001 319 76 90
Fax: +001 319 11 80
E-mail: efr2013@at.kuoni.com
http://www.efrcancer.org

2nd International Symposium on Thoracic and Upper Aerodigestive Malignancies
Athens, Greece
Info: Scientific – Cultural Events and Publications
Tel: +030 210 7240039/ 210 7240608
Fax: +030 210 7240139
E-mail: scep_ath@otenet.gr
http://thorhnc2.com/

American Association for Cancer Research Annual Meeting 2013
Washington DC, USA
Tel: +001 708 486 0720
E-mail: aacr@compusystems.com
http://www.aacr.org/home/scientists/meetings--workshops/aacr-annual-meeting-2013.aspx

7th Conference on Experimental and Translational Oncology – CETO
20/4/2013 to 24/4/2013
Portoroz, Slovenia
Info: Association of Radiology and Oncology
E-mail: info@ceto.si
http://www.ceto.si/

26th Annual Meeting of the American Society of Pediatric Hematology/Oncology
24/4/2013 to 27/4/2013
Miami, USA
Tel: +001 847 375 4716
Fax: +001 847 375 6483
E-mail: info@aspho.org
http://www.aspho.org/education/content/meeting.html

Tumor Imaging in Cancer Drug Development
30/4/2013 to 2/5/2013
Boston, USA
Tel: +001 212 537 5898
E-mail: register@hansonwade.com
http://tumor-imaging.com/

5th IMPAKT Breast Cancer Conference
2/5/2013 to 4/5/2013
Brussels, Belgium
Info: Nicole Bullo
Tel: +041 91 973 19 39
Fax: +041 91 973 19 18
http://www.esmo.org/events/breast-2013-impakt.html

European Multidisciplinary Conference in Thoracic Oncology 2013 (EMCTO)
9/5/2013 to 11/5/2013
Lugano, Switzerland
Tel: +041 91 973 19 25
Fax: +041 91 973 19 18
http://www.esmo.org/events/lung-2013-EMCTO.html
2013 ASCO Annual Meeting
31/5/2013 to 4/6/2013
Chicago, USA
Tel: +001 703 449 6418
Fax: +001 703 563 2715
E-mail: ascoregistration@jspargo.com
http://chicago2013.asco.org/

18th Congress of the European Hematology Association (EHA)
13/6/2013 to 16/6/2013
Stockholm, Sweden
Tel: +031 20 679 3411
E-mail: eha@mci.group.com
http://ehaweb.org/congress-and-events/18th-congress/key-information/

10th International Gastric Cancer Congress (IGCC)
19/6/2013 to 22/6/2013
Verona, Italy
Tel: +039 045 830 3646
E-mail: info@10igcc.com / meeting@studioventisette.net
http://www.10igcc.com/

15th World Congress on Gastrointestinal Cancer
3/7/2013 to 6/7/2013
Barcelona, Spain
Info: Imedex
Tel: +001 678 242 0906
Fax: +001 770 751 7334
E-mail: registration@imedex.com

JPOG is NOW CME-Accredited...
in Hong Kong, Indonesia, Malaysia and Singapore

For over 35 years, JPOG has been the only regional, peer-reviewed journal of paediatrics, obstetrics and gynaecology in Asia. The bimonthly journal is proud to announce its CME-accreditation in the following Asian countries: HONG KONG, INDONESIA, MALAYSIA and SINGAPORE.

From the research bench to your patient’s bedside – JPOG raises the quality of life of women and children in Asia. Pick up a copy today and start earning CME points.
For further details, visit www.jpog.com today.
### Editorial Advisory Board – Singapore

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Goh Boon Cher</td>
<td>National University Cancer Institute Singapore</td>
</tr>
<tr>
<td>Prof. Pierce Chow</td>
<td>Duke-NUS Graduate Medical School</td>
</tr>
<tr>
<td>Asst. Prof. Jeffrey Low</td>
<td>National University Cancer Institute Singapore</td>
</tr>
<tr>
<td>Asst. Prof. Jiade J. Lu</td>
<td>National University Cancer Institute Singapore</td>
</tr>
<tr>
<td>Dr. Khoo Kei Siong</td>
<td>Parkway Cancer Centre</td>
</tr>
<tr>
<td>Dr. Tan Yew Oo</td>
<td>Consultant Medical Oncologist</td>
</tr>
<tr>
<td>Dr. Eng-Hseon Tay</td>
<td>Novena Medical Centre</td>
</tr>
<tr>
<td>Dr. Wong Seng Weng</td>
<td>The Cancer Centre</td>
</tr>
</tbody>
</table>

**Oncology Tribune** contains articles from Cancer Network, under license from UBM Medica LLC. Copyright © 2013 UBM Medica LLC.

**Oncology Tribune** is published 6 times a year by UBM Medica, a division of United Business Media. **Oncology Tribune** is a controlled circulation publication to medical practitioners in Asia. It is also available on subscription to members of allied professions. The price per annum is US$48 (surface mail) and US$60 (overseas airmail); back issues at US$5 per copy. Editorial matter published herein has been prepared by professional editorial staff. Views expressed are not necessarily those of UBM Medica. Although great effort has been made in compiling and checking the information given in this publication to ensure that it is accurate, the authors, the publisher and their servants or agents shall not be responsible or in any way liable for the continued currency of the information or for any errors, omissions or inaccuracies in this publication whether arising from negligence or otherwise howsoever, or for any consequences arising therefrom. The inclusion or exclusion of any product does not mean that the publisher advocates or rejects its use either generally or in any particular field or fields. The information contained within should not be relied upon solely for final treatment decisions.

© 2013 UBM Medica. All rights reserved. No part of this publication may be reproduced in any language, stored in or introduced into a retrieval system, or transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise), without the written consent of the copyright owner. Permission to reprint must be obtained from the publisher. Advertisements are subject to editorial acceptance and have no influence on editorial content or presentation. UBM Medica does not guarantee, directly or indirectly, the quality or efficacy of any product or service described in the advertisements or other material which is commercial in nature. Printed by KHL Printing Co Pte Ltd, 57 Loyang Drive, Singapore 508968.

ISSN: 2078-2535