Malay ethnicity linked to lower OS in breast cancer

Elvira Manzano

Malay ethnicity was associated with poorer survival outcomes compared with other Asian ethnicities in a large study involving Asian patients with breast cancer.

In the study, which included 5,264 women, 5-year overall survival (OS) was lowest among Malay women (58.5 percent), followed by Indian and Chinese women (66 and 75.8 percent, respectively). Malay ethnicity was also associated with a significantly higher risk of death from all causes (hazard ratio [HR], 1.34; 95% confidence interval [CI], 1.19 to 1.51) independent of age, stage and tumor characteristics, and treatment. [PLoS One 2012;7:e30995]

“The underlying reasons for this association are unclear,” said study author Assistant Professor Mikael Hartmann, of the National University of Singapore’s Saw Swee Hock School of Public Health. “Further research in Asian women is thus critical to investigate possible variations in tumor biology, treatment responsiveness and lifestyle after diagnosis.”

Using a large multicenter hospital-based cohort of breast cancer patients, Hartmann and colleagues retrospectively analyzed the impact of ethnicity on survival after breast cancer among Malay, Indian and Chinese women listed in the Singapore-Malaysia breast cancer registry, a merger between the National University Hospital and the University Malaya Medical Center breast cancer registries.

In the cohort, nearly 72 percent of the study cohort were Chinese (n=3,767), 18 percent were Malays (n=968), and 10 percent were Indians (n=529). Median age was 50 years. After 30,882 person-years of follow-up, 1,690 deaths from all causes had occurred. Five-year overall OS was highest in Chinese women and lowest among Malay women. Malay women were significantly younger at diagnosis, with larger tumors and a more aggressive tumor biology compared with the comparator groups (p<0.001).

Among women with non-metastatic breast cancer, the Malays were least likely to receive complete loco-regional treatment. Within the subgroup who underwent breast-conserving surgery, a higher percentage were Malays (34.2 percent) compared with Chinese and Indian women (23.7 percent and 25.6 percent, respectively; p<0.001). Overall, Malay women were significantly more likely to receive chemotherapy.

“This is the first large study to shed light on the impact of ethnicity on the survival of women following breast cancer in the Asian context,” said the authors. “Ethnic differences in co-morbidity and life expectancy may partly explain the observed ethnic disparities in survival.”

Nevertheless, the differences in life expectancy are unlikely to completely explain the results. A variety of factors such as differences in socio-economic status and cultural values, tumor biology, response to treatment and lifestyle may explain the ethnic disparities in breast cancer survival, they said.

In recent years, the incidence of breast cancer in Asia has been on the increase. This is in contrast to many western countries where it appears to have plateaued or decreased. Over the last 10 years, breast cancer rates have risen by up to 30 percent in China and India, and doubled or tripled in Japan, Korea and Singapore. While ethnicity has been implicated as a predictor of survival in the West, it has not been studied in Asian settings prior to this study.
Report highlights recent advances in oncology

Naomi Rodrig

Last month, the American Society of Clinical Oncology (ASCO) released its annual report on the top cancer advances of 2012, highlighting major achievements in precision medicine, cancer screening and overcoming treatment resistance.

Clinical Cancer Advances (CCA), now in its 8th year, was developed under the guidance of a 21-person editorial board of renowned experts in specific fields of cancer research. The editors reviewed studies published in peer-reviewed scientific or medical journals and presented at major scientific meetings over a 1-year period (October 2011-September 2012). Reviewed research covers the full range of clinical research disciplines: epidemiology, prevention, screening, early detection, treatment, patient care, biomarkers, tumor biology, and cancer disparities.

The 2012 CCA features a total of 87 studies, 17 of which are considered major, meaning they represent practice-changing results published in a peer-reviewed journal, and/or reports on treatments that received US FDA approval in the past year.

“Consistent, significant achievements are being made in oncology care with novel therapeutics, even in malignancies that have previously had few treatment options, as well as defining factors that will predict for response to treatment. ASCO’s report distills the most significant of these advances that are impacting the lives of cancer patients today,” said Dr. Bruce Roth, MD, Co-Executive Editor of the report.

• Two new therapies which delay progression of advanced breast cancer:
  - Adding targeted therapy to hormonal therapy delays disease progression in postmenopausal women with advanced hormone receptor-positive breast cancer.
  - Use of an ‘armed’ antibody, trastuzumab emtansine (TDM-1), to selectively deliver medicine to HER2-positive breast cancer cells without affecting normal cells.
• Preoperative chemotherapy and radiation improves survival for patients with esophageal cancer.
• Screening with flexible sigmoidoscopy reduces colorectal cancer incidence and mortality.
• A new targeted treatment extends survival for patients with advanced melanoma.

Many of the top clinical research advances of 2012 involve therapeutic approaches that stem from a growing understanding of the complex biology of cancer, which enables development of targeted drugs and treatments tailored to molecular characteristics of individual patients and their tumors. This research has led to new FDA approvals for anticancer agents in 2012, some of which are for treatment-resistant tumor types.

Between October 2011 and October 2012, the regulatory agency approved seven new anticancer drugs and expanded indications for five existing agents to provide new treatment options for patients with certain forms of myeloma (carfilzomib), leukemia (liposomal vincristine), breast cancer (pertuzumab and everolimus), skin cancer (vismodegib), prostate cancer (enzalutamide), gastrointestinal stromal tumors (imatinib mesylate), colorectal cancer (regorafenib), kidney cancer (axitinib), and soft tissue sarcoma (pazopanib).

Almost all of the newly approved drugs are targeted agents. Vismodegib marks the first FDA approval of a drug targeting the hedgehog signaling pathway, which plays an important role in tissue growth and repair. It is now being evaluated in clinical trials for cutaneous, stomach, and pancreatic cancers.

In addition, new data from The Cancer Genome Atlas Project identify potential new drug targets in colorectal cancer, reveal that epigenetic regulation is critical for cancer cell survival, and propose innovative technologies for predicting chemotherapy response in patients with ovarian cancer.

Dr. Several other studies featured in the report address the need to identify treatment-resistant patients early, so they can be directed to alternative, potentially effective treatments while being spared the adverse effects of regimens that are not likely to benefit them.

Referring to the impending spending cuts for cancer research, ASCO President Dr. Susan Blackwell remarked, “We offer, again, an inspiring perspective on clinical cancer advances over the past year, but with a cautionary note: if current threats to federal funding materialize, future progress in cancer research will be seriously undermined.”

“To conquer cancer, we need to build bridges to the future: Bridges that will get scientific advances to the patient’s bedside quicker; bridges that will enable us to share information and learn what works in real time; bridges that will improve care for all patients, around the world, she added.

Mammography screening: Debate ongoing

Naomi Rodrig

Routine mammography screening has led to substantial overdiagnosis of breast cancer in the USA while having only a small effect on mortality from the disease, a recent study found. [Int J Epidemiol Med 2012;367:1998-2005]

The findings provoked a strong public reaction, with some patient groups blaming the overdiagnosis for making women unnecessary testing and treatment.

Using the Surveillance, Epidemiology and End Results (SEER) database, the study investigated examining women from 1976 through 2008 in the incidence of ductal carcinoma in situ and late-stage breast cancer among women >40 years of age.

They estimated that 1.3 million women were mistakenly diagnosed with breast cancer, when in fact they only had early-stage tumors which would not progress to advanced disease, and did not require treatment. Among women aged 60 and above, breast cancer was ‘over-diagnosed’ in >70,000 women, accounting for about one-third of all diagnosed cases.

Conversely, mammography screening has only marginally reduced the rate of advanced cancer presentation (by 8 percent) during the 3 decades despite substantial increases in the detection of early-stage cases. The authors concluded that “screening is having, at best, only a small effect on the rate of death from breast cancer.”

However, the American College of Radiology (ACR) disputes the findings, arguing that the article was “deeply flawed and misleading” and based on false assumptions. Specifically, the baseline incidence of breast cancer was incorrect determined, according to the ACR, which warned, “If such misinformation is used to determine screening guidelines and recommendations, the cost may be lost lives.” [http://www.acr.org/NR/rdonlyres/7228F6F4-86C3-4F9D-A412-8C2B06E34DFD/0/News_Publications%2FNews_Articles%2F2012%2FQuality_Care%2F20121112-ACRBSI-Bleyer-and-Welch-Breast-Cancer-Screening%2C+accessed+19+December+2012]

With such strong opinions for and against mass screening, it seems the question will remain open for some time.

Singapore study seeks genetic clues to lymphoma in Asian patients

Continued from page 1

By molecular profiling and immunohistochemistry, a research team including Lim recently identified a novel biomarker for type II enteropathy associated T-cell lymphoma. [Cancer Discov 2012;2:591-597]

Further validation studies to discover additional novel biomarkers for different subtypes of T-cell lymphoma are now underway. In addition, the group is generating lymphoma cell lines and model systems to screen for effective therapeutic agents.

The TRP aims to translate new scientific insights into advances that can be quickly applied in the clinic, from cancer detection, diagnosis, monitoring to treatment. The research team consists of practicing oncologists, pathologists and scientists and has extensive international collaborations including with the National Cancer Institute, US, and The Cancer Genome Atlas (TCGA) lymphoma program.
Women opt for screening, surgery with inconclusive BRCA tests

Radha Chitale

Women who receive uninformative BRCA gene test results were more likely to undergo invasive surgeries to remove their ovaries as well as cancer screening tests of questionable benefit, a study shows.

Data from 1,077 survey respondents who had been tested for BRCA gene mutations a median of 3.7 years prior showed that, of the 773 women (71.8 percent) who received uninformative results – neither definitively positive nor negative – 12.3 percent had risk-reducing salpingo-oophorectomy (RRSO) to remove an ovary plus fallopian tube. [Arch Intern Med 2012;Dec 17:1-8. doi:10.1001/2013.1] Without official guidelines, what to do in the case of inconclusive BRCA tests is largely in the hands of physician and patient.


“Psychiatric patients are no more likely than the general population to develop cancer but are more likely to die of it,” the study researchers said.

The study also showed that a higher proportion of psychiatric patients presented with metastasized cancer (7.1 percent) compared with the general population (6.1 percent). Psychiatric patients were also less likely to have had surgery (HR: males, 1.52; females, 1.29). [Arch Gen Psychiatry 2012;Dec 17:1-9. doi:10.1001/jama psychiatry.2013.278]

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The study also showed that a higher proportion of psychiatric patients presented with metastasized cancer (7.1 percent) compared with the general population (6.1 percent). Psychiatric patients were also less likely to have had surgery (HR, 0.81), including resection of colorectal, breast and cervical cancers. Psychiatric patients received less radiotherapy for these cancers as well as fewer sessions of chemotherapy (mean, 10.3 sessions vs 12.4 sessions). Dementia and schizophrenia were associated with a reduced risk of cancer while depression, neurotic disorder, and alcohol or drug disorders were associated with an increased risk of cancer.

Professor Ranga Krishnan, dean of the Duke-NUS (National University of Singapore) Graduate Medical School and professor of the Neuroscience and Behavioral Disorders Program, suggested that mental illness may result in patient apathy and reduced compliance and willingness to follow through with cancer treatment.

“There are studies suggesting that depression worsens the prognosis of these patients,” he said. “[But] many of the treatments for cancer can aggravate their psychiatric condition and this, coupled with the stress of coping with the illness, makes it a challenge to manage these patients.”

Physicians must be aware and rely on their own judgment in order to treat and manage psychiatric patients with cancer, Krishnan said, noting that treating the mental disease in addition to the cancer, rather than attributing it to the coping process, is important.

“There are no specific procedures except a recognition of the nature of illness and interaction with treatment.”

The study did not include information on the medication of the psychiatric patients, nor did it include demographic data or information on cancer staging.

While the lifetime risk of ovarian cancer is 1-2 percent in the general population, the risk of cancer is up to 40 percent in women with BRCA gene mutations. RRSO is known to significantly reduce the risk of ovarian cancer, breast cancer and related or all-cause mortality.

Where family history indicates cancer risk, monitoring and screening tests such as serum CA-125 or trans-vaginal ultrasound are reasonable, although the authors noted there is little evidence to support that these tests are linked to survival benefits.

“[Research] shows that genetic testing, even if negative, does not always allay deep-seated fears of cancer,” Grann and Ashby-Thompson wrote. “The challenge of the field is to identify persons needing additional or different treatment without scaring those who do not into additional interventions.”

Psychiatric patients with cancer have increased mortality, less intervention

Metastases occurred more frequently in psychiatric patients with cancer while the rate of surgical treatment or other intervention was lower, according to an analysis of over 6,000 psychiatric patients with a cancer diagnosis.

Among 6,586 psychiatric patients in Western Australia with new cancers, cancer incidence was lower in psychiatric patients compared with a matched data set from the general population (hazard ratio [HR]: males, 0.86; females, 0.92) while mortality was higher (HR: males, 1.52; females, 1.29). [Arch Gen Psychiatry 2012;Dec 17:1-9. doi:10.1001/jamapsychiatry.2013.278]

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HPV infection linked to laryngeal cancer

Rajesh Kumar

Human papillomavirus (HPV) infection was strongly associated with the risk of laryngeal squamous cell carcinoma in a systematic review and meta-analysis. Researchers from China analyzed pooled data from 55 studies and found HPV prevalence in 28.0 percent of laryngeal cancer tissues (95% confidence interval [CI], 22.3%-32.9%). A total of 26.6 percent laryngeal cancer patients were infected with high-risk type HPV only, HPV-16 being the most common one with 19.8 percent prevalence (95% CI, 15.7%-24.6%). [J Infect Dis 2013;207:479-488] Of the 55 studies included in the meta-analysis, 12 were case-control studies. When examined on their own, these suggested a strong association between HPV infection and laryngeal squamous cell carcinoma, with an odds ratio (OR) of 5.39 (95% CI, 3.25-8.94).

Oral sex is believed to be a common mode of HPV transmission. Previous research has suggested that a rise in this form of transmission is partly due to the commonly held misconception that unprotected oral sex does not pose a risk of sexually transmitted infections. “With respect to sexually transmitted HPV and its related cancers, we think [the issue] needs more attention,” said study co-author Associate Professor Lei Gao of the Institute of Pathogen Biology, Chinese Academy of Medical Sciences in Beijing, China. “We are trying to find more evidence to support the association between HPV and oral and head cancers.”

Assistant Professor Jeeve Kanagalalingam, head and neck surgeon and director at The ENT Practice, Mt. Elizabeth Novena Specialist Centre, Singapore, termed the findings extremely interesting. “The odds ratio of 5.39 makes the association quite strong,” said Kanagalalingam.

When asked to explain the clinical relevance of such findings, he said: “Going forward, the key question is whether these HPV-related tumors have a different biological behavior, making them more radio-sensitive like HPV-positive oropharyngeal tumors. This could give us a biomarker to select advanced laryngeal tumors that may benefit from an organ-preservation treatment strategy, rather than laryngectomy.”

Meanwhile, as part of the larger body of work on HPV and related cancers, the researchers conducted yet another meta-analysis of 60 published studies probing the link between HPV infection and esophageal cancer, considering the upper gastrointestinal tract could be exposed to HPV through oral transmission. This study also found a strong association, particularly between the high-risk type HPV-16 and esophageal cancer, with a summarized estimation to be 24.8 percent (95% CI, 20.1%-30.3%). [J Infect Dis. In press]

However, the researchers expressed the need for further studies to verify the relationship between HPV infection and laryngeal and esophageal cancers, and to explore the exact underlying mechanisms of their association.

Acupuncture relieves radiation-induced xerostomia

Eight weekly sessions of acupuncture provided significantly better relief from the symptoms of chronic radiation-induced xerostomia than conventional oral care in patients of head and neck cancer in a UK study.

The randomized crossover study recruited 145 patients with chronic radiation-induced xerostomia more than 18 months after radiation treatments. All participants received two group sessions of oral care education and eight 20-minute sessions of acupuncture. Patient-reported outcome measures were completed at baseline and weeks 5, 9, 13, 17, and 21. [Ann Oncol 2012; doi:10.1093/annonc/mds515]

The primary outcome was improvement in dry mouth, and objective saliva measurements were taken using Schirmer strips. Acupuncture compared with conventional oral care produced significant reductions in patient reports of severe dry mouth [hazard ratio (HR), 2.01; p=0.031] and objective saliva [HR, 1.67; p=0.048].

“Xerostomia is therefore an entirely subjective symptom – it is what the patient says it is, regardless of salivary measurement.”

The profound impact that xerostomia exerts on functions such as eating, talking and sleeping, which were relieved by acupuncture, means that if it is a placebo effect then this is a pretty powerful placebo, said Dr. Valerie Jenkins, Deputy Director of Sussex Health Outcomes Research & Education in Cancer (SHORE-C) at Brighton & Sussex Medical School, who supervised the research.

“The skepticism that exists about complementary therapies (such as acupuncture) is often due to inadequately designed and reported studies. This was a well-controlled, randomized trial conducted in major cancer centers in the UK with good governance and reporting of adverse events.”

The researchers said further studies are needed to refine the acupuncture technique and discover how long its effect lasts and whether booster sessions might be required. They believed it could be easily incorporated into the care of patients with xerostomia, a common chronic side effect of radiotherapy due to damage to salivary glands with few effective treatments.

The acupuncture intervention was designed in a way that allowed it to be delivered simply and cheaply in normal hospital surroundings, producing a significant benefit for patients with chronic symptoms, said the researchers.
Extending tamoxifen use improves breast cancer outcomes

Naomi Rodrig

Treating women with estrogen receptor (ER)-positive breast cancer for 10 years reduced the rates of late recurrence and breast cancer mortality compared with the current standard of 5 years, according to the international ATLAS (Adjuvant Tamoxifen - Longer Against Shorter) study.

“The five years of adjuvant tamoxifen is already an excellent treatment that substantially reduces the 15-year risk for recurrence and death from ER-positive breast cancer. [Lancet 2011;378:771-784] ATLAS now shows that 10 years of tamoxifen is even more effective,” said Dr. Christina Davies, Oxford University, UK, who presented the results at the 2012 CTBC-AACR® San Antonio Breast Cancer Symposium last month. The study was simultaneously published in The Lancet. [doi:10.1016/S0140-6736(12)61963-1]

The investigators enrolled 6,846 women with ER-positive breast cancer between 1996 and 2005. Half had node-positive disease. All the women had been using tamoxifen for 5 years, and were then randomly assigned to continue treatment for another 5 years or stop.

After about 8 years of follow-up, there were 1,329 breast cancer recurrences and 728 deaths after recurrence. Treatment allocation had little effect on either recurrence or death rates during the period of 5 to 9 years after diagnosis.

However, during the second decade following diagnosis, the women who continued tamoxifen had a significantly lower recurrence rate (617 recurrences in 3,428 women allocated to continue vs 711 in 3,418 controls; p=0.002) and a 29 percent reduction in the risk of death. Additionally, 397 deaths; p=0.01) than those who stopped.

The greatest benefit was observed during 10 to 14 years after diagnosis.

Choice of tamoxifen or any other endocrine treatment after 5 years was based on patient preference, with no apparent excess of endometrial cancer.

The ATLAS study included a large number of postmenopausal women (median age, 61 years) from 128 centers in 17 countries with estrogen receptor-positive advanced breast cancer that recurred or progressed following endocrine therapy. Women were randomized to one of the two doses of fulvestrant and followed until progression or death.

On the basis of these results, “whenever fulvestrant is considered for the treatment of metastatic hormone-sensitive breast cancer improved survival without increasing toxicity risk, according to updated results from the phase III CONFIRM® trial. Median overall survival (OS) was longer by more than 4 months among women treated with a 500-mg dose of fulvestrant compared with those treated with the standard 250-mg dose (26.4 vs 22.3 months). The difference translates to a 15 percent reduction in the risk of death. Additionally, both doses had similar toxicity profile. [Abstract S1-4].

Promising results with higher dosing of fulvestrant in breast cancer

Elvira Manzano

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On the basis of these results, the recommended dose is 500 mg.

“ATLAS showed that protection against breast cancer recurrence and death is greater with 10 years than with 5 years of tamoxifen use. Women and their doctors should be aware of this evidence when deciding how long to continue tamoxifen, or any other endocrine treatment.”

Rates of drug-related serious adverse events were 2.2 percent for the high-dose group and 1.1 percent for the low-dose group. Adverse events proved fatal in five patients treated with the 500-mg dose compared with seven in the 250-mg group. Di Leo said the next step is to investigate 500-mg fulvestrant in combination with other agents such as PI3K inhibitors or anti-HER2 agents.
Novel targeted therapy with quizar-tinib has shown promising results in a phase II clinical trial involving patients with a hard-to-treat subtype of acute myeloid leukemia (AML).

Researchers enrolled 137 AML patients, 99 of them with FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) mutation within their leukemia cells. The gene produces an enzyme that signals bone marrow stem cells to divide and replenish. In about a quarter of patients with AML, the disease mutates FLT3 so that the enzyme stays permanently on, causing rapid growth of leukemia cells instead.

The enrolled patients had either relapsed or did not respond to second-line chemotherapy or hematopoietic stem cell transplantation. They were given quizar-tinib at a starting dose of 80 mg/day for women and 135 mg/day for men for 28-day cycles.

Forty-four of the 99 participants with a FLT3-ITD mutation (44 percent) experienced some form of complete remission wherein leukemia was cleared from the bone marrow, although the patients still needed blood and platelet transfusions. But only 13 (34 percent) of the patients without the gene mutation had the same outcome.

“We can put two-thirds to three-quarters of adults with AML into remission with chemotherapy, but there’s a 50 percent chance of the disease coming back, which usually ends up being fatal,” said lead investigator Dr. Mark Levis, associate professor of oncology and medicine at Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland, US.

“Many patients in this trial were able to go on to receive a potentially life-saving bone marrow transplant. It caught us by surprise how well it works,” said Levis.

“A FLT3-ITD mutation tells us that, typically, patients will need very intensive chemotherapy just to achieve a remission, and then the disease will regrow quickly,” Levis said. “So, we have learned to try to perform a bone marrow transplant soon after we get the patient into remission, before the cancer relapses.”

Quizartinib blocks the FLT3 enzyme and is available in liquid oral form. It typically starts working in 2 days, though it may take up to 60 days to completely eliminate AML cells from the bone marrow, said Levis.

The common side effects with quizar-tinib were nausea (38 percent), anemia (29 percent), QT prolongation (26 percent), vomiting (26 percent), febrile neutropenia (25 percent), diarrhea (20 percent), and fatigue (20 percent). Fourteen patients (10 percent) experienced side effects severe enough to discontinue the drug.

Investigators are now testing lower doses of the medication since the trial to reduce side effects, Levis said.

Long-term survival from quizar-tinib therapy is still unknown, but of the 137 patients, 47 (34 percent) were able to receive a bone marrow transplant after responding to quizar-tinib. Some of these patients have survived 2 years after treatment with no disease recurrence, said Levis.

Based on the results, the drug manufacturer is planning larger phase III trials in which patients who have the FLT3 mutation will be randomized to receive either quizar-tinib or chemotherapy.

“These data represent the highest level of single agent activity observed to date for FLT3-targeted therapy in FLT3-ITD positive relapsed/refractory AML,” said the researchers.

“Of clinical significance in this heavily pretreated population, approximately one-third of the patients were successfully bridged to potentially curative hematopoietic stem cell transplantation, and many patients who were refractory to prior therapy responded to quizar-tinib.”

**Sulforaphane compound stems ALL in the lab**

Radha Chitale

Sulforaphane, a natural compound common to cruciferous vegetables such as broccoli and cabbage, attenuated the growth of acute lymphoblastic leukemia (ALL) cells in an in vivo study.

“Sulforaphane is endowed with both preventive and therapeutic activities in solid tumors,” the researchers said.

ALL is a cancer of the white blood cells and primarily affects children. If untreated, ALL can be fatal. “There is about an 80 percent cure rate, but some children don’t respond to treatment,” said Dr. Daniel Lacorazza, assistant professor of pathology and immunology at the Baylor College of Medicine in Houston, Texas, US. “For those cases, we are in need of alternative treatments.”

The researchers noted that epidemiological studies have shown cruciferous vegetable consumption to be linked to a lower incidence of breast, lung, prostate, colon and bladder cancers.

In their study, leukemic cell lines, cancerous cells and healthy cells were incubated with quantities of sulforaphane. Sulforaphane appeared to induce apoptosis and cell cycle arrest in the cancerous cells but had no effect on healthy cells. Similar effects were observed in preclinical mouse models. [PLoS ONE 7(12):e51254]

“Collectively, our preclinical studies showed that sulforaphane can inhibit the expansion of leukemic cells in vivo, which supports future clinical trials of this compound as an adjunctive agent,” the researchers said.

Eating more cruciferous vegetables would have however supply enough sulforaphane to have a clinical effect, the researchers noted, due to the bioavailability of the compound.

“Cooked broccoli demonstrated lower serum concentrations compared with raw broccoli,” they said. “However, oral administration of sulforaphane led to a significant reduction in the expansion of leukemic cells in a model for pre-established lymphoma tumors.”

**Consider a patient’s age when selecting CLL therapy**

Radha Chitale

AGE is not usually considered when deciding a treatment approach for patients with chronic lymphocytic leukemia (CLL), but new research suggests that it should be.

An analysis of 663 patients with CLL enrolled in four sequential CLL trials found that first-line therapy with fludarabine significantly improved progression-free survival (PFS) and overall survival (OS) compared with chlorambucil in patients aged <70 years (hazard ratios [HR] 0.6 and 0.7, respectively), but not in patients older than 70 (HR, 1.0). [JCO 2012; doi:10.1200/JCO.2011.41.5646]

In contrast, first-line therapy with rituximab combined with fludarabine improved PFS and OS in both younger and older patients compared with fludarabine alone, whereas alemtuzumab consolidation therapy after chemotherapy or chemoimmunotherapy did not cause improvement in either group.

“We hope this study will shape future research by highlighting the importance of enrolling older patients in clinical trials and of developing trials that specifically target older patients,” said lead author Dr. Jennifer Woyach, assistant professor of hematology at the Ohio State University Comprehensive Cancer Center in Columbus, Ohio, US.

Principal investigator Dr. John Byrd, a CLL specialist and professor of medicine at the cancer center, said the findings apply to routine care of CLL patients 70 years and older and to future CLL trials.

CLL most often occurs in people older than age 65; the average at diagnosis is 72. Yet, most CLL clinical-trial participants are in their early 60s.

“These data also show that future treatment trials for older adults with CLL should build on CD20 antibody therapies such as rituximab and ofatumumab, but not on fludarabine or alemtuzumab,” said Byrd.

– RK 01
Ponatinib active in drug-resistant CML and ALL, gets FDA nod

Christina Lau

Ponatinib, a new oral tyrosine-kinase inhibitor (TKI), has demonstrated activity in drug-resistant chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphocytic leukemia (Ph+ ALL) in adults in a pivotal phase II trial. [Abstract 135]

The positive results have led to an accelerated approval by the US FDA 3 months ahead of its official deadline for a decision on the drug.

Ponatinib is a pan-BCR-ABL.TKI with potent activity against native and mutant forms of the BCR-ABL protein and other kinases. It targets cells with the "gatekeeper" T315I mutation, which confers resistance to other TKIs for CML and Ph+ ALL and is found in 5-20 percent of patients.

In the phase III PACE Ponatinib Ph+ ALL and CML Evaluation) trial, researchers assessed ponatinib in 499 patients with CML and Ph+ ALL who were either resistant to or intolerant of dasatinib or nilotinib (R/I patients) or had the T315I mutation. Nearly all patients were previously treated with ≥2 available TKIs (imatinib, dasatinib, and/or nilotinib).

"We now have strong evidence that reducing the amount of chemotherapy initially administered to these children, who constitute the majority of ALL patients, does not negatively affect their immediate outcome," said study author Dr. Andre Baruchel of the Robert Debré University Hospital in Paris, France. "Perhaps more importantly, we now know that eliminating harmful chemotherapy from their treatment can help minimize their risk of heart damage later in life."

"There is no difference in complete remission rate, MRD levels, EFS, OS, cumulative incidence of relapse [or] secondary malignancy in the randomized population," Baruchel said. "We conclude that daunorubicin is dispensable during induction therapy in children with standard-risk B-cell ALL with good early response to vincristine, dexmethasone and asparaginase."

Commenting on the study, ASH President Dr. Arnaud Keating of the University of Toronto, Canada, said the study is important as the complication can be devastating in some patients. "Some eventually succumb to heart failure and may even become candidates for a heart transplant."
Studies investigate EBV-targeted therapies for NPC

Christina Lau

Recent understanding of the role of Epstein-Barr virus (EBV) infection in nasopharyngeal carcinoma (NPC) has led researchers to develop EBV-targeted therapies for nasopharyngeal carcinoma (NPC).

“Globally, around 2 million cancer cases per year are attributable to infections. Of these cases, 10.3 percent are EBV-associated lymphomas and carcinomas,” said Professor Lawrence Young of the University of Birmingham, UK.

According to Young, EBV infects more than 90 percent of human population. The infection is predominantly asymptomatic with the virus establishing a lifelong infection in the memory B-cell compartment.

“What EBV wants to do is to persist in a normal host and replicate. The development of EBV-associated cancer is an accident,” he said. “In normal differentiating epithelial cells, the virus is able to replicate after epithelial infection. If epithelial cells are unable to differentiate, however, EBV may remain latent, occasionally leading to the development of malignancies in the epithelium.”

As the EBV replication cycle is controlled by T cells, Young suggested that anything affecting T cell immune response could allow EBV to replicate more and infect more cells, increasing the chances of developing EBV-associated malignancies.

“Studies have shown that EBV adopts different forms of latent gene expression in different malignancies. These include EBV nuclear antigens [EBNAs] and latent membrane proteins [LMPs],” Young noted. “Based on understanding of the impact of EBV latent gene expression, researchers have started to develop EBV-targeted therapies that aim to activate the latent virus and then kill it when it replicates.”

A Dutch team, for example, has developed a cytolytic virus activation (CLVA) therapy for NPC. The therapy involves the use of gemcitabine and valproic acid to induce EBV lytic cycle, followed by the antiviral drug ganciclovir to block EBV replication and kill proliferating EBV-infected cells. In three patients with refractory NPC, CLVA therapy led to disease stabilization with the gene expression in different malignancies. These studies have shown that EBV adopts different forms of latent gene expression.

“Efficacy shown in subgroup analyses of the AVAGAST and REAL-3 trials suggests that it is possible to achieve significant benefit by refining patient selection,” she said. [J Clin Oncol 2012;30(suppl 4): abstract 5; Waddell TS et al, ESMO 2012]

There is currently little evidence on the prospective selection of patients for targeted therapy, especially since we have no validated, accessible and predictive biomarker for direct patient selection to date except HER2,” she said.

“In addition, intratumoral heterogeneity of HER2 overexpression/amplification is of particular therapeutic relevance. Studies have shown discordance within or between sections of the primary tumor in up to 79 percent of HER2-positive cases, while discordance between metastasis and primary tumor and between immunohistochemistry and FISH assays is also common,” she continued. “Clarification of the correlation between molecular profile, intratumoral heterogeneity and clinicopathological characteristics will provide insights into tumor biology and facilitate clinical selection of patients for targeted therapy.”

SIRT and TomoTherapy for HCC: Asian perspective

SIRT in combination with sorafenib has demonstrated encouraging results in a recent study of Asian patients with non-resectable hepatocellular carcinoma (HCC), while data from Korea suggest that TomoTherapy is more effective than 3D conformal RT in locally advanced HCC.

“SIRT with yttrium-90 is indicated for inoperable larger or multifocal HCC, including HCC with portal vein involve-ment, as well as refractory colorectal cancer liver metastases and neuroendocrine tumor metastases. The disease control rate is approximately 80 percent, compared with 40 percent with transarterial chemoembolization [TACE],” said Professor Pierce Chow of the National University of Singapore and Singapore General Hospital.

The phase 1/II trial, known as AHCC005, included 34 patients with BCLC B or C HCC. “Tumor response was encouraging, with 12 percent of patients achieving complete regression, 23.5 percent achieving partial regression, and 44 percent achieving stable disease. Tumor response rate was 53.5 percent, while disease control rate was 79.5 percent,” reported Chow. “The median time to progression was 39 weeks. Median survival was 26.0 months for patients with BCLC B disease, and 8.2 months for those with BCLC C disease.”

“As there is currently no established first-line therapy for inoperable HCC without metastasis, the HCC Trials Group has started a phase III randomized controlled trial to compare SIRT with sorafenib in patients with locally advanced HCC,” he continued. “Recruitment is ongoing, and patients previously treated with surgery, TACE or radiofrequency ablation are eligible.”

In another study (n=106), researchers from the Yonsei University, Korea have shown significantly longer overall survival (OS) (1-year: 81.1 vs 52.8 percent; 2-year: 42.2 vs 30.2 percent; 3-year: 31.6 vs 25.9 percent) with TomoTherapy vs 3D conformal RT in patients with locally advanced HCC.

“While the two modalities showed similar progression-free survival [PFS] and OS in tumors ≤5 cm, significant benefits in PFS and OS were seen in tumors larger than 5 cm,” said investigator Professor Jinil Seong. “We therefore strongly suggest TomoTherapy for locally advanced HCC patients with tumors larger than 5 cm.”
Hematological malignancies: Platelet transfusion as needed

There has long been debate about whether patients with hypoprothrombinemia should be given platelet transfusions prophylactically or only as needed for bleeding. The results of a study in Germany provide ‘guarded’ support to the as-needed strategy. Conducted at eight centers, the study included 396 patients aged 16–80 years undergoing either intensive chemotherapy for acute myeloid leukemia or autologous hematopoietic stem-cell transplantation for hematological cancers. Randomization was to platelet transfusion when bleeding occurred (as necessary) or when the morning platelet count was 10 x 10^9 per L or lower (prophylactic). The mean number of platelet transfusions during 14 days of observation was 1.63 (as-needed strategy) vs 2.44 (prophylactic), an overall reduction of 33.5 percent with the as-needed strategy. This reduction was 31.6 percent for patients treated for acute myeloid leukemia and 34.2 percent among those given a stem-cell transplantation. In patients with acute myeloid leukemia the as-needed strategy was associated with an increased risk of non-fatal grade 4 (mostly CNS) bleeding. In patients who had stem-cell transplantation there was no increase in risk of non-fatal hemorrhage with this strategy. The two patients who died of cerebral hemorrhage were both in the as-needed treatment group.

It is concluded that the prophylactic platelet transfusion strategy should be used for patients with acute myeloid leukemia. For patients having stem-cell transplantation the as-needed strategy could be used, but only in centers with well-trained and experienced staff.

Trastuzumab emtansine for HER2-positive advanced breast cancer

Trastuzumab emtansine (T-DM1) consists of the human epidermal growth factor receptor 2 (HER2)-targeted antibody trastuzumab, conjugated with a cytotoxic agent, derivative of maytansine (DM1), allowing intracellular delivery of DM1 specifically to HER2-positive cells. A multinational trial has shown T-DM1 to be effective treatment for HER2-positive advanced breast cancer.

A total of 991 patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane were randomized to T-DM1 or lapatinib plus capecitabine. Median progression-free survival was 9.6 months (T-DM1) vs 6.4 months (lapatinib-capecitabine), a significant 35 percent reduction in death or progression with T-DM1. Median overall survival was 30.9 months vs 25.1 months, a significant 32 percent reduction in death or progression with T-DM1. Median overall survival was 30.9 months vs 25.1 months, a significant 32 percent reduction in mortality. The objective response rate was 43.6 percent vs 30.8 percent. Toxicity was less with T-DM1 (grade 3 or 4 adverse effects, 41 percent vs 37 percent). Thrombocytopenia and severe neutropenia were more common with lapatinib-capecitabine. T-DM1 prolonged survival in women with advanced HER2-positive breast cancer and was less toxic than lapatinib-capecitabine. At present there are about 25 antibody-drug conjugates (ADCs) undergoing clinical trials as anticancer agents.

Aspirin in colorectal cancer: Only ‘effective’ with tumor gene mutation

Aspirin has been shown to protect against colorectal cancer and improves the prognosis for some patients with the disease. Tumor expression of prostaglandin-endoperoxide synthase 2 (PTGS2 or cyclooxygenase 2) regulates the effect of aspirin on survival of patients after diagnosis. Tumor PTGS2 is difficult to measure in a standardized way but a US study has now linked aspirin use to prolonged survival from colorectal cancer when the tumor cells have a mutated PIK3CA gene (the phosphatidylinositol-4, 5-bisphosphate-3-kinase, catalytic subunit alpha polypeptide gene). Data on 964 patients with colorectal cancer were obtained from the Nurses’ Health Study and the Health Professionals Follow-up Study. Among patients with tumors with a PIK3CA mutation, regular use of aspirin was associated with a reduction in cancer-related mortality by 82 percent and overall mortality by 46 percent. Among patients without this mutation aspirin did not affect cancer-specific or overall survival.

Regular use of aspirin after diagnosis improves survival only among patients whose tumors have the mutated PIK3CA gene. The mutation may serve as a marker predicting response to aspirin. It is present in more than one in six colorectal cancers.


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Epidemiology of PTCL

“PTCL represents 10–15 percent of non-Hodgkin's lymphoma (NHL) cases per year,” commented Dr. Won Seog Kim of the Division of Hematology-Oncology, Samsung Medical Center, Seoul, Korea. [Curr Oncol Rep 2008;10:404–411] By some estimates, the incidence of PTCL is growing significantly in developed populations. [Lymphoma 2008;9:1509–1517] Overall survival (OS) in PTCL varies according to subtype and the median ranges from 1-3 years. [J Clin Oncol 2006;24:1373–1403] The most common subtype is the diffuse large B lymphoma, comprising 44.2 percent of NHL cases,” Kim added. [Korean J Pathol] 2011;45:254–260] Overall survival (OS) in PTCL varies according to subtype and the median ranges from 1-3 years. [J Clin Oncol 2006;24:1373–1403] The most common subtype is the diffuse large B lymphoma, comprising 44.2 percent of NHL cases. [Korean J Pathol] 2011;29:4410-4416] Alternatively, the consolidation (HSCT) is particularly recommended for patients with PTCL who are in complete remission. [Blood 2010;116:Abstract 1753] Hematopoietic stem cell transplantation (HSCT) is particularly recommended for patients with PTCL who are in complete remission. [Blood 2010;116:Abstract 1753] HSCT is the first approved treatment by the US FDA for relapsed or refractory PTCL. It is an antifolate, or dihydrofolate reductase (DHFR) inhibitor that exhibits high affinity for reduced folate carrier 1 (RFC-1), a protein overexpressed by tumor or embryonic tissues. [Blood 2008;10:404–411] Patients with progressive disease after at least 3 chemotherapy cycles or combination chemotherapy of CHOP (NCCN) Guidelines recommend clinical trials or combination chemotherapy of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) as the frontline treatment. [NCCN, NHL Clinical Practice Guidelines, version 1, 2011] “However, the CHOP and CHOP-like regimens may cause severe toxicities in patients,” Kim warned. For NK/ TCL, concurrent chemoradiotherapy (CCT) followed by etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) is favored as it improved progression-free survival (PFS) and OS rates compared to a clinical trial. [J Clin Oncol 2009;27:6027-6032] The combination of steroid dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) is an emerging chemotherapeutic regimen for the treatment of relapsed or refractory NK/TCL. In a phase I study, patients who received SMILE had a 67 percent overall response rate (ORR) and a 50 percent complete response rate (CR). [Cancer Sci 2008;99:1016-1020] “The subsequent phase II study of this regimen resulted in ORR and CR of 79 percent and 45 percent, respectively,” Kim added. [J Clin Oncol 2011;29:4410-4416] Patients with progressive disease after at least one prior treatment received pralatrexate intravenously at 30 mg/m^2 per week for 6 weeks followed by 1 week rest in 2-week cycles. Primary assessment of response was performed by independent central pathology review using radiology, skin photography, and other relevant clinical data. The primary endpoint was ORR. Secondary endpoints included duration of response (DOR), PFS, and OS. [J Clin Oncol 2011;29:1182-1198] In the PROPEL study, assessment of responses performed by independent central review found an ORR of 29 percent. Approximately 11 percent of patients achieved complete response (CR), 18 percent achieved partial response (PR), and 19 percent had stable disease. The median DoR was 10.1 months and the median PFS was 3.5 months. Finally, the median OS was 14.5 months. In summary, pralatrexate, in the PROPEL study, induced durable responses in relapsed or refractory PTCL irrespective of age, histologic subtypes, amount of prior therapy, prior methotrexate, and prior autologous stem-cell transplant. [J Clin Oncol 2011;29:1182-1198] In patients who received pralatrexate as second-line therapy after CHOP failure, the ORR was 47 percent. Approximately 20 percent of patients achieved CR and 27 percent achieved PR. [Blood 2010;116:Abstract 4882] In patients who received pralatrexate after ifosfamide, carboplatin, and etoposide (ICE)-based regimen failure, ORR was 40 percent, CR was 25 percent, PR was 15 percent, and DoR was 16.2 months, all by central review assessment. “It goes to show that taking a new good drug, and using it earlier in the disease stage will give you more benefit,” O’Connor expounded. [Blood 2010;116:Abstract 1753] The most common adverse events reported with pralatrexate use were mucositis and thrombocytopenia. Nonetheless, these toxicities appeared reversible upon dose modification. [J Clin Oncol 2011;29:1182-1198] According to O’Connor, doses should be omitted or reduced based on patient tolerance of the drug and grade of mucositis. “I now adapt a strategy where I start at 10 mg/m^2 to 20 mg/m^2 to 30 mg/m^2, or keeping patients at 20 mg/m^2 if mucositis occurs,” O’Connor suggested. Recently, oral leucovorin 3-6 days post pralatrexate is recommended to further reduce the risk of mucositis.

Future management of PTCL

“For the past 30 years, we have seen no progress in the OS of PTCL patients,” commented Dr. Thomas Mehling, Director of Oncology at Mundipharma International. Existing evidence has demonstrated less than satisfactory response with CHOP and CHOP-like induction treatments. Pralatrexate, however, has recently shown promise in PTCL, resulting in prolonged OS benefit. Strategies are currently being directed to evaluate combining regimens, ie, pralatrexate with bortezomib and vorinostat, forodesine, belinostat, or romidepsin. Currently, a number of clinical trials are conducted to test the potential synergism of these combinations. “With these advances in PTCL therapy, we may see new hope on the horizon,” Mehling concluded.
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