HPV検査単独の方がパップ検査よりも優れているようである（Abstract No.1506）

ほとんどの女性はHPVスクリーニングを3年ごとに延長しても安全である

Most women can safely extend HPV screening to every three years

通常の臨床現場における子宮頸がんスクリーニングとしてのヒトパピローマウイルス（HPV）検査とパップ検査の両者に関する初めての大規模スタディの結果、スクリーニング間隔を1年から3年に延長しても安全であることが確認された。HPV検査はまた子宮頸がんハイリスク女性をパップ検査よりも多く検出したと第47回American Society of Clinical Oncology（ASCO）学会で発表された。研究者らは30歳以上の女性331,818人を追跡した。パップ検査で正常でありHPV陰性女性の5年間のがんリスクは非常に低く10万人当たり3.2人であった。個々の検査を観察すると、HPV陰性女性はパップ検査正常女性と比較しがんのリスクが半分であり（10万人当たり3.8人対7.5人）、HPV検査単独の方がパップ検査よりも正確であり、HPVとパップ検査併用と比較しHPV検査のみを行うことによるがんのリスクは同様に低い（10万人当たり3.8対3.2）ことが示唆された。組み入れ時HPV陽性であった女性（パップの検査結果に関係なく）はHPVの結果に関係なくパップ検査で異常であった女性と比較し、5年間の子宮頸がんまたは前がん状態リスクが高かった（年間1.5対0.9）。

Full Text

The first large-scale study of both human papillomavirus (HPV) testing and Pap test for cervical cancer screening in routine clinical practice confirms that women can safely extend their screening intervals from one to three years. The study also found that HPV testing may be more accurate than conventional Pap test in determining cervical cancer risk.

"Our results are a formal confirmation that the three-year follow-up is appropriate and safe for women who have a negative HPV test and normal Pap result," said lead author Hormuzd Katki, Ph.D., principal investigator in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute. "These results also suggest that an HPV-negative test result alone could be enough to give a high level of security for extending the testing interval to every three years, but we'll need additional evidence from routine clinical practice, and formal recommendations from guideline panels before that can be routinely recommended."

Cervical cancer is caused by infection with HPV, which is sexually transmitted and can be detected by testing a sample of cervical cells for viral DNA. HPV infection is almost always cleared by the body, but if not, cancer may develop, typically decades after initial infection. While Pap testing has dramatically reduced cervical cancer rates, incorporating HPV testing into screening programs could reduce cancer rates even further. Screening guidelines from American medical organizations such as the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) have endorsed the use of concurrent HPV testing with Pap tests as a safe alternative to Pap testing alone for women 30 and older, recommending co-testing every three years for women who are HPV-negative and have a normal Pap test. However, co-testing has not been widely adopted by physicians and women, many of whom are unsure about the safety of extending testing intervals for more than one year. This study provides substantial data from routine practice confirming that the practice is safe.

In the study, researchers followed 331,818 women ages 30 and older who enrolled in Kaiser Permanente Northern California's co-testing program between 2003 and 2005 for five years. The researchers found that the five-year cancer risk for women who had both a normal Pap test and tested negative for HPV was very low: 3.2 per 100,000 women per year.

Looking at each test individually, HPV-negative women had half the cancer risk of women with a normal Pap test (3.8 per 100,000 women per year compared to 7.5 per 100,000), suggesting that HPV testing alone is more accurate than Pap testing alone, and that the cancer risk for HPV testing alone was similarly low, compared with HPV and Pap testing together (3.8 versus 3.2 per 100,000).

HPV testing also identified more women at high risk for cervical cancer than Pap tests. Women who tested HPV-positive at enrollment (regardless of Pap test results) had higher five-year risks of cervical cancer or pre-cancer than women with an abnormal Pap test at enrollment regardless of HPV test results (1.5 percent per year versus 0.9 percent per year). By finding, at enrollment, more women at risk for cancer, HPV testing facilitated earlier intervention to prevent cancer.

However, according to Dr. Katki, Pap tests remain important for determining which women who tested HPV-positive should have further screening. HPV-positive women who had an abnormal Pap test were more likely to have - or soon develop - cancer or precancer than HPV-positive women with a normal Pap test.

ASCO2011特集

新たな複数分子を標的とした分子標的薬は骨転移病変を縮小または除去する（Abstract No.3010）

経口METおよびVEGFR2阻害薬は複数の進行固形がんに対し有意な有効性を有する

An oral inhibitor of MET and VEGFR2 has significant effect on several advanced solid tumors

経口METおよびVEGFR2（多くのがんの発現や増殖に関係するキナーゼ）阻害薬Cabozantinib（XL184）は様々な進行がんを有する患者において強力な有効性を有することが、第47回ASCOで発表されたPhase IIトライアルの結果示された。骨転移を有するまたは有さない進行固形がん患者がcabozantinibを12週間にわたり内服した。このトライアルは、部分寛解をした患者は内服を継続し、疾患が安定している患者はcabozantinibまたはプラセボに無作為に割り付けられ、疾患が進行した患者はトライアルから外れるといった、“中断”トライアルとしてデザインされた。様々なタイプのがんを有する評価可能であった患者398人における奏効率は9%（398人中34人）であった。12週後のコントロール率（部分寛解および疾患の安定）が最も高かったのは肝がんの76%（29人中22人）であり、前立腺がんで71%（100人中71人）、卵巣がんでは58%（51人中32人）であった。骨転移を有する68人（乳がん、前立腺がんおよびメラノーマ）中59人が部分寛解または、しばしば有意な疼痛軽減や他のがん関連症状の改善に結びつく骨スキャン上の完全な病変消失を来した。

Full Text

Cabozantinib (XL184) - an oral inhibitor of MET and VEGFR2, kinases involved in the development and progression of many cancers - showed strong responses in patients with various advanced cancers in a Phase II trial. The drug demonstrated particularly high rates of disease control for advanced prostate, ovarian and liver cancers, which are historically resistant to available therapies. The drug also fully or partially eliminated bone metastases in patients with breast and prostate cancers and melanoma.

"Cabozantinib appears to have significant effects on several treatment-resistant tumors, as well as impressive effects on bone metastases. In addition, these effects are associated with rapid improvement in pain, a reduction in opiate narcotic requirements and improvement in anemia," said lead author Michael S. Gordon, M.D., a medical oncologist at Pinnacle Oncology Hematology in Scottsdale, AZ. "The implications of these results are very exciting-it is unusual to find a targeted therapy, absent of a molecular mutation in tumors, that works in bony disease and has this activity."

To be eligible for the study, patients had to have advanced, progressive solid tumors, with or without bone metastases. Of 398 evaluable patients (of 483 enrolled in the trial), 39 percent had bone metastases at baseline. Patients received cabozantinib over 12 weeks. The trial was designed as a "discontinuation" trial, in which those who had partial responses stayed on the drug; those with stable disease were randomized to cabozantinib or placebo; and patients with progressive disease were removed from the trial. This novel type of clinical trial design more quickly evaluates the disease-stabilizing activity of growth-inhibitory agents like cabozantinib, compared to the traditional model of randomizing all patients to either the experimental arm or placebo.

Among 398 patients evaluable with all types of cancer included in the trial, the response rate was 9 percent (34 of 398). The highest disease control rates (partial response and stable disease) at week 12 were 76 percent for liver cancer (22 of 29 patients), 71 percent for prostate cancer (71 of 100 patients), and 58 percent for ovarian cancer (32 of 51 patients).

Fifty-nine of 68 patients with bone metastases (including patients with breast and prostate cancers and melanoma) experienced either partial or complete disappearance of the cancer on bone scans, often with significant pain relief and other improved cancer-related symptoms.

The reduction of bone metastases and pain relief was an unexpected finding in this study, Dr. Gordon said. Independent review by radiologists confirmed that bone metastases disappeared in the majority of patients who had bone metastases when they entered the study. The majority of these patients had castration-resistant prostate cancer (CRPC), but patients with breast cancer and melanoma also had disappearance of bone metastases. Bone metastases greatly contribute to morbidity and mortality in patients with these types of cancer, which typically spread to the bone.

Due to these results, the study has been expanded to include more CRPC patients. Similarly, the high rate of lasting responses in ovarian cancer patients led researchers to also expand the study to evaluate the drug's effect on patients with a particularly resistant form of the disease known as platinum resistant/refractory ovarian cancer.

This study expansion results will help determine the design of future Phase III trials, which will assess whether the drug extends patients lives or has other longer-term benefits among patients with specific cancer types. At present, cabozantinib is being investigated for use as a single agent. Additional studies will evaluate the efficacy and tolerability of appropriate combinations with other agents for future indications.

The most common grade three or above adverse events were fatigue (9 percent) and hand-foot syndrome (8 percent). Dose reductions were required in 41 percent of patients due to side effects; 12 percent were removed from the trial for adverse events.

ASCO2011特集

全ての男性が頻回のPSAスクリーニングを必要とするわけではない（Abstract No. 4512）

新たなスクリーニング法の結果、PSAレベルにより転移性前立腺がんまたは前立腺がん死のリスクを予測できる可能性が示唆された

Novel-screening approach suggests PSA levels may predict risk of metastatic prostate cancer or prostate cancer-related death

過去にスクリーニングを受けていないスウェーデン男性における大規模レトロスペクティブケースコントロールスタディの結果、44～50歳の男性における初回スクリーニング時の前立腺特異抗原（PSA）により、最大30年後の前立腺がん死または転移性前立腺がん発症のリスクが予測できることが示されたとの研究結果が第47回ASCOで発表された。このスタディでは、44～50歳の時点で計測したPSAレベルが上位 10%（>1.6ng/ml）であった男性の44%が前立腺がんにより死亡した。結果として、この少人数の男性集団においては、前立腺がん死の半分近くが集中的な調査により予防できる可能性があったと筆者らは述べている。さらに、同年齢層に比してPSA値の低い男性は数十年後の転移性前立腺がん発症または前立腺がん死リスクが比較的低く（28～0.5%）、生涯において3回の検査しか必要でない可能性がある。この結果は、頻回にスクリーニングを行う必要のある人を決定するのに重要な意味をもつ可能性がある。

Full Text

A large retrospective, case control study of previously unscreened Swedish men showed that prostate specific antigen (PSA) levels at the time of initial screening among men aged 44 to 50 can accurately predict the risk that a man will die of prostate cancer or develop metastatic prostate cancer up to 30 years later. The authors suggest that the initial PSA test result for men in this age group could enable approximately 50 percent of men to undergo just three PSA tests in their lifetime.

The study found that 44 percent of prostate cancer deaths occurred in men who had the top 10 percent of PSA levels (greater than 1.6 ng/ml) when they were tested between the ages of 44 and 50. As a result, the authors say, nearly half of all prostate cancer deaths could potentially be prevented by intense surveillance of this small group of men. In addition, they found that men with low PSA values for their age group are at comparatively lower risk (28 percent to 0.5 percent) of developing metastatic prostate cancer or dying of prostate cancer decades later and may only need to be tested three times in their lifetime. The findings could have important implications in deciding who should be screened with frequency.

"Doctors have urgently needed an effective PSA testing strategy that accurately distinguishes men at high risk for prostate cancer who need aggressive monitoring from those at low-risk of the disease, who can be safely spared from frequent testing. If confirmed in prospective trials, this approach could have a significant impact on future prostate cancer screening programs," said lead author Hans Lilja, M.D., Ph.D., attending research clinical chemist at Memorial Sloan-Kettering Cancer Center in New York. "Our results appear to identify a subgroup of relatively young men at very high risk of aggressive prostate cancer who would likely benefit from close monitoring as they age."

In the study, researchers analyzed PSA in archived blood samples from 12,090 men provided between 1974 and 1986, and 4,999 repeat samples six years later as part of the Swedish Malmo Preventive Project67 men provided blood samples at age 60.

Using these samples, the investigators assessed the median PSA levels for ages 44 to 50, 51 to 55 and 60.

These median levels at baseline served as the base to distinguish men at high or low risk of dying of prostate cancer or developing metastatic prostate cancer. As men aged, if their PSA level remained below the median for the population in their age group, the risk of death from metastatic prostate cancer progressively declined. They found that 28 percent of metastases or deaths from prostate cancer over the next 27 years occurred in men ages 44 to 50 who had a PSA below the median in the population (0.7 ng/ml). For men ages 51 to 55 with a PSA less than the median, 0.8, the risk of metastatic prostate cancer or death was lower - only 18 percent. At age 60, only 0.5 percent of deaths or metastases occurred in men with a PSA less than median for that age, 1.1 ng/ml.

While these figures - 28 percent and 18 percent - may seem high, Dr. Lilja said, the short-term risk (15 years) of metastatic prostate cancer or dying from prostate cancer is very low. Based on progressively declining risks, the researchers conclude that men with PSAs below population median in each age group remain at increasingly lower risk for dying of prostate cancer as they age. As a result, testing three times between ages 44 and 60 could be recommended for 50 percent of men. The other half of men with PSAs above the median would be followed more closely.

"Such a scenario could avoid more intense, costly PSA testing that could result in over-diagnosis and unnecessary treatment that potentially has little benefit, since they would be at extremely low risk," Dr. Lilja said.

ASCO2011特集

CA-125と経膣エコーによるスクリーニング法は有効ではない（Abstract No. 5001）

CA-125と経膣エコーを用いたスクリーニングは卵巣がん死亡率を減少させず偽陽性率を上昇させる結果になる

Screening with CA-125 and transvaginal ultrasound does not reduce ovarian cancer death rate, results in more false positives

80,000人近くの女性を対象とした無作為化多施設スクリーニングスタディの結果、卵巣がん早期発見目的の血中CA-125検査と経膣エコーの併用は卵巣がん死亡率を減少させず、多数の偽陽性およびそれに基づく生検例さらにフォローアップ検査を産出する結果となることが第47回ASCOで発表され、JAMA 6月8日号に掲載される。55～74歳の女性を年1回のスクリーニング（39,105人）または通常の管理（39,111人）を受ける群に無作為に割り付けた。スクリーニング群の女性は年1回のCA-125検査および経膣エコー検査（それぞれ6年間と4年間）を受け、13年間追跡調査された。通常管理群の女性はこれらのスクリーニング検査は要求されなかった。これらの2群間において卵巣がん発現率または死亡率に統計学的有意差は認められなかった。しかし、スクリーニング群女性においては、真陽性が212例であったのに対し、多くの偽陽性－3,285例が認められた。偽陽性であった女性において1,080人が生検のために手術を施行された；うち163人において重篤な合併症が発生した。筆者らは、これらの検査はすでに卵巣がんと診断された患者においては適切に使用されているが、一般の人々におけるスクリーニング法としては有用ではないと結論付けている。

Full Text

A randomized, multicenter screening study of nearly 80,000 women in the general population showed that using a CA-125 blood test and transvaginal ultrasound for early detection of ovarian cancer did not reduce the risk of dying from the disease, and resulted in a large number of false positives and related biopsies and follow-up procedures. The results indicate that while these tests are widely and appropriately used to evaluate symptoms, and to gauge disease status and effectiveness of treatment in women already diagnosed with ovarian cancer, they are not useful in screening the general population.

"There hasn't been a good method for the early detection of ovarian cancer, and our hypothesis was that CA-125 and transvaginal ultrasound, which are useful in measuring disease, would also identify ovarian cancer early, at a stage in which it is more likely to be cured," said lead author Saundra Buys, M.D., professor of medicine at the University of Utah and Huntsman Cancer Institute in Salt Lake City. "The results were disappointing, but not necessarily surprising. The study shows that the available tests are not effective and may actually cause harm because of the high number of false positives. These results point to the continued need for more precise and effective screening tools for this disease."

In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, 78,216 women ages 55 to 74 were assigned to either annual screening (39,105 women) or usual care (39,111 women) between 1993 and 2001. Women in the screening arm were offered annual CA-125 testing for six years and transvaginal ultrasound for four, and followed for up to 13 years. Those in the usual care arm were not offered the screening tests.

The results showed no statistically significant difference in ovarian cancer cases or mortality between the two arms. Ovarian cancer was diagnosed in 212 women in the screening group arm compared to 176 in the usual care arm; 118 women in the screening arm died from ovarian cancer, while 100 died from ovarian cancer in the usual care group.

Among women in the screening arm, there were a high number of false positives - 3,285 false positives, compared to just 212 true positives. Of women who had a false positive test, 1,080 underwent surgery for biopsy - the procedure generally required to evaluate positive test results; 163 of them had serious complications.

The authors emphasized that the study results don't apply to screening women with symptoms or abnormal findings on physical examination. Physical examination based on symptoms and appropriate follow-up testing remains the best available approach for ovarian cancer detection.

ASCO2011特集

喫煙の乳がんに対するリスクのエビデンスがさらに得られた（Abstract No.1505）

中等度の飲酒はしなくとも長期喫煙することにより、乳がん高リスク女性において複数の一般的ながんのリスクが上昇する

Long-term smoking, but not moderate alcohol use, linked to increased risk of multiple common cancers among women at high risk of breast cancer

13,000人以上の健康な女性を対象とした大規模前向き研究の結果、長期喫煙歴のある女性において浸潤性乳、肺、および大腸がんリスクが有意に高いことが示されたと第47回ASCOで発表された。喫煙歴のない女性と比較し、35年以上の喫煙歴のある女性は浸潤性がんのリスクが60%高く、喫煙歴が15～35年の女性では34%高かった。喫煙歴が35年以上の女性においては喫煙歴のない女性と比較し、大腸がんのリスクが4倍以上であった；喫煙歴が15～35年の女性では7%高かった。1日1箱のタバコを35年以上吸っていた女性は喫煙歴のない女性と比較し肺がんリスクが30倍高かった。1日1箱未満の喫煙を35年以上継続した女性は肺がんリスクが13倍高かった。身体活動が低いことと子宮体がんリスクとの関連も認められた。しかし、飲酒によるがんのリスク上昇は認められなかった。

Full Text

A large prospective study of more than 13,000 healthy women at high risk of breast cancer identified several important lifestyle factors associated with cancer risk. The study reported that the risks of invasive breast, lung and colon cancers were significantly higher in women with long smoking histories, compared to women who did not smoke or had shorter smoking histories.

Investigators also found a significant association between low levels of physical activity and endometrial cancer risk. Use of alcohol, however, was not associated with increased cancer risk.

"The NSABP study was the first large study to prospectively examine the impact of smoking in women at high risk of breast cancer," said Stephanie Land, Ph.D., study author and Research Associate Professor in the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh. "Our results showed an even greater increase in risk than has been shown in previous studies, suggesting that for women who are at risk of breast cancer because of family history or other factors, smoking cigarettes is even more risky than for other women. It sends a very important message for women with family histories of breast cancer about the long-term risks of smoking, as well as the importance of staying physically active. We're seeing again that smoking cessation is one of the most effective tools we have for reducing risk of many cancers."

The study analyzed the risk of several common cancers in 13,388 women at increased risk for breast cancer (as defined by age, a diagnosis of lobular carcinoma in situ, family history, or other factors) who participated in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial, based on their baseline self-reported smoking, alcohol use, and physical activity.

The study found that the risk of invasive breast cancer was higher in smokers than in non-smokers, and increased with more years of cigarette smoking. Compared to women who never smoked, those who smoked at least 35 years had a 60 percent higher risk of invasive breast cancer, and those who smoked between 15 and 35 years had a 34 percent higher risk. Those who smoked less than 15 years had no increased risk of breast cancer. This is the third large, prospective study to report a strong association between smoking and breast cancer, and is the first to show further elevation of cancer risk in women already at high risk of breast cancer.

The incidence of colon cancer was also significantly higher for women with long histories of cigarette smoking. The risk of getting colon cancer was over four times higher for women who smoked more than 35 years versus those who had never smoked; risk was 7 percent higher for women who smoked for 15 to 35 years. This result confirmed findings of previous studies of women already at high risk of breast cancer.

Similarly, women who smoked had a significantly higher risk of lung cancer, a finding that confirms many previous studies. Those who smoked more than one pack of cigarettes per day for over 35 years had a risk that was 30 times higher than women who never smoked. Women who smoked less than one pack per day for over 35 years had a 13-fold increase in lung cancer risk.

Alcohol use was not associated with breast cancer risk in this study. Moderate alcohol consumption of up to one drink a day was associated with a 60 percent decreased risk of colon cancer compared to those who did not drink. Several factors might have been different in this study from past studies that have shown associations between alcohol use and cancer risk, Dr. Land said. In particular, there were fewer heavy drinkers enrolled in this study, compared to other studies. Also, the results of this study are based on a one-time self-report of alcohol drinking habits.

Low physical activity was not associated with breast, lung or colon cancer risk, though it was associated with a 70 percent increased risk of endometrial cancer. Investigators said this may be due to the association between fitness and obesity, also a risk factor for endometrial cancer.

ASCO2011特集

PARP阻害薬は再発性卵巣がんの生存率を改善する（Abstract No.5003）

維持療法およびPARP阻害薬は再発性卵巣がん治療において重要な役割を果たす可能性がある

Maintenance therapy and PARP inhibitors could play important roles in treatment of relapsed ovarian cancer

第47回ASCOで発表されたphase II無作為化トライアルの結果、経口PARP阻害薬を用いた維持療法により最も一般的なタイプの卵巣がん患者の無増悪生存期間が4ヵ月延長したことが示された。この多施設国際スタディでは高悪性度の重症卵巣がん患者265人をolaparibまたはプラセボ投与群に無作為に割り付けた。患者はプラチナ製剤を基本とした治療により完全寛解または部分寛解を達成した後、8週以内にトライアルに組み入れられた。無増悪生存期間（PFS）はolaparib投与群において生存期間中央値8.4ヵ月とプラセボ投与群の4.8ヵ月よりも有意に長かった。データ解析の時点で、olaparib群に割り付けられた患者の半分（68人）が再発せず内服を継続していたのに対し、プラセボ群のうちプラセボ内服を継続していたのはわずか16%（21人）であった―したがって、全生存期間データはまだ解析として使用できていない。嘔気、倦怠感、嘔吐、および貧血などの有害事象はolaparib群においてプラセボ群よりも多く認められたが、これらの多くは重度ではなかった。副作用を軽減するための投与量減量がこのスタディでは認められており、それはolaparib群において（23%）プラセボ群（7%）よりも多く認められた。

Full Text

A Phase II randomized trial showed that maintenance treatment with the oral PARP inhibitor drug olaparib improved progression-free survival by about four months in women with the most common type of relapsed ovarian cancer. This is the first randomized trial to demonstrate a benefit for maintenance therapy for recurrent ovarian cancer, and the first randomized trial in ovarian cancer of a PARP inhibitor - a novel class of molecularly targeted drugs.

The results of this study, if confirmed in larger trials, could lead to a new treatment approach for recurrent ovarian cancer in which drugs like olaparib are given over a long period of time to prevent recurrences or prolong remissions. This somewhat novel approach, called maintenance therapy, has already proven useful in lung cancer. Standard treatment for ovarian cancer includes platinum-based chemotherapy. After this regimen, patients are observed until recurrence, and then treated with another course of chemotherapy. While some tumors respond well to chemotherapy, the regimens are too toxic for patients to take continuously, and clinical trials haven't shown any benefit for extended courses of chemotherapy.

"A well-tolerated antitumor agent that could be used for months or perhaps years as maintenance therapy after standard chemotherapy could be a big step forward and ultimately extend survival," said lead author Jonathan A. Ledermann, M.D., principal investigator of the study and Professor of Medical Oncology at UCL Cancer Institute, University College London. "This study demonstrates proof of principle for the concept of maintenance therapy in ovarian cancer using a PARP inhibitor. Our progression-free survival difference was very impressive and better than we anticipated."

The multicenter, international study randomized 265 women with high-grade serous ovarian cancer to either olaparib or placebo. Patients were enrolled in the trial within 8 weeks of having achieved either a complete or partial response to platinum-based treatment. PARP inhibitors have been shown to work better in patients whose tumors have responded to platinum.

In the study, the progression-free survival (PFS) - the amount of time during and after treatment in which the cancer does not return - was significantly longer in the group receiving olaparib than the placebo group, with a median of 8.4 months versus 4.8 months. At the time of data analysis, half the patients randomized to olaparib (68 patients) had not relapsed and were still receiving the drug, while only 16 percent (21 patients) remained on placebo - so overall survival data were not yet available for analysis.

Adverse events were more commonly reported in the group receiving olaparib than placebo, including nausea, fatigue, vomiting, and anemia, but the majority of these were not severe. Dose reductions to manage side effects were allowed in the study and were more prevalent in the olaparib group (23 percent) compared to the placebo group (7 percent).

Olaparib inhibits the enzyme Poly ADP ribose polymerase (PARP), which is involved in DNA repair. Up to half of women with high-grade serous ovarian cancer - the most common type of ovarian cancer - may have a DNA repair deficiency that makes them more susceptible to treatment with PARP inhibitors.

A number of PARP inhibitors are in Phase II and Phase III clinical trials as single agents and in combination with standard chemotherapies and radiation in some types of breast and ovarian cancers believed to have DNA repair defects.

ASCO2011特集

新たな化学療法レジメンにより高リスクALLの生存率が改善する（Abstract No.3）

メトトレキサート大量療法はB前駆細胞性急性リンパ性白血病の小児および若年成人の無イベント生存率を上昇させる

High-dose methotrexate boosts event-free survival for children and young adults with B-precursor acute lymphoblastic leukemia

高リスクB前駆細胞性急性リンパ性白血病（ALL）の小児および若年成人においてメトトレキサート大量療法は標準的なメトトレキサート 漸増療法よりも優れているとのスタディ結果が第47回ASCOで発表された。このPhase IIIスタディは高リスクB前駆細胞性ALLと新たに診断された1～30歳の患者2,426人を、標準的な導入化学療法および地固め化学療法後の2ヵ月の中間維持治療期間中にメトトレキサート大量療法群またはメトトレキサート漸増とアスパラギナーゼの併用群に無作為に割り付けた。計画されていた中間解析における5年間の無イベント生存率は、メトトレキサート大量療法群で**82%**でありメトトレキサート漸増療法群においては75%であった。骨髄およびCNS再発もまた大量療法群において有意に少なかった（それぞれ42対68および22対32）。発熱性好中球減少症発現率は大量療法群で低かった（5.2%対8.2%；P=.005）。その他の有意な毒性に関して差はなかった。登録は早期に中止され、メトトレキサート大量療法の適応である患者はその後、大量療法レジメンを受けることができた。

Full Text

A randomized Phase III Children's Oncology Group study shows that a high-dose methotrexate regimen is superior to the standard regimen of escalating methotrexate for children and young adults with high risk B-precursor acute lymphoblastic leukemia. This regimen improved five-year event-free survival and had no greater significant side effects compared to the standard regimen. The trial establishes a new standard treatment for these patients.

"Pediatric ALL was once a deadly form of leukemia, and now it's one of the most curable. This trial helps us address an important need for patients with this disease. With these results, we now have an approach that will raise cure rates even higher," said Eric C. Larsen, M.D., principal investigator of the study and director of the Maine Children's Cancer Program and the Division of Pediatric Hematology/Oncology at the Barbara Bush Children's Hospital at Maine Medical Center. "Based on the findings from this trial all current and upcoming treatment protocols for children with newly diagnosed high risk B-precursor ALL will use this regimen."

Methotrexate has been an essential component in the treatment of children with ALL for more than 50 years, but the optimal dose and schedule has been a matter of debate and clinical research. Escalating intravenous methotrexate followed by a second chemotherapy drug called asparaginase (together known as the Capizzi regimen) has been an effective standard treatment for ALL for approximately two decades. This approach involves starting at a low dose of methotrexate and gradually increasing the dose depending on a patient's tolerance.

The escalating methotrexate regimen has led to improved cure rates for ALL, by decreasing relapses in the bone marrow, where the disease initially occurs. Relapse rates in the central nervous system (CNS) have not declined as significantly, representing an ongoing need for better treatment options. To reduce these CNS relapses, this study tested a methotrexate regimen, which delivers a dose 50 times the starting dose of the escalating regimen. The high-dose regimen has a greater potential to reach tumor cells in the central nervous system.

The Phase III study randomized 2,426 patients ages 1 to 30 with newly diagnosed high-risk B-precursor ALL to high-dose methotrexate versus escalating methotrexate plus asparaginase during a two-month interim maintenance phase of therapy following standard induction and consolidation chemotherapy. At a planned interim analysis, the five-year, event-free survival for patients who received high-dose methotrexate was 82 percent, compared to 75 percent for patients on the escalating methotrexate regimen.

There were also significantly fewer bone marrow and CNS relapses in the high-dose group. Enrollment was halted early as a result, and certain patients were eligible to then receive the high dose methotrexate regimen.

The investigators were initially concerned that there might be more side effects in the group receiving high-dose methotrexate, however these patients actually had a lower incidence of febrile neutropenia than those on the standard regimen. There were no differences in other significant toxicities.

The National Institutes of Health funded the study.

ASCO2011特集

長期のイマチニブ投与により高リスクGIST患者の生存期間が延長される（Abstract No.LBA1）

イマチニブを用いたエクステンディドアジュバント療法は高リスク消化管間質腫瘍患者の生存期間を改善する

Extended adjuvant therapy with imatinib improves survival for patients with high-risk gastrointestinal stromal tumors

2011年ASCOで発表された前向き無作為化多施設Phase IIIトライアルの結果、高リスク消化管間質腫瘍（GIST）術後3年間のイマチニブ治療により1年間のイマチニブ治療と比較し、全生存期間および無再発生存期間の改善が示された。このスタディにおいて再発リスクの高いGIST患者400人が術後1年または3年間のイマチニブ投与を受ける群に無作為に割り付けられた。フォローアップ期間中央値54ヵ月後の5年無再発生存期間は1年治療群（47.9%）と比較し3年治療群（65.6%）で高かった。同様に、5年生存率もアジュバントイマチニブ療法による1年治療群と比較し3年治療群において高かった。イマチニブの忍容性は全般的に良好であり多くの副作用はこの薬剤を投与された患者において典型的に認められるものであった。しかし、1年治療群患者の7.7%および3年治療群の13.7%が副作用のために治療を中断した。このスタディ結果から、3年間にわたる治療コースが再発リスクの高いGIST患者の新たな標準治療となりつつある。

Full Text

A prospective, randomized, multicenter, Phase III trial showed that three years of treatment with imatinib (Gleevec) after surgery in patients with high-risk gastrointestinal stromal tumors (GIST) improved overall and recurrence-free survival compared to one year of treatment. The findings could result in the three-year course of therapy becoming the new standard of care for those patients who are at risk for relapse.

"Earlier studies have shown an improvement in recurrence-free survival with one year of adjuvant imatinib treatment, but we were surprised to also see better numbers with overall survival after three years of therapy," said lead author Heikki Joensuu, M.D., professor of oncology at Helsinki University Central Hospital in Helsinki, Finland. "This might be the first example of long-term adjuvant therapy with a targeted small molecule tyrosine kinase inhibitor, and it's likely to become standard treatment."

GIST tumors, which usually begin in the stomach or intestine, are a type of soft-tissue sarcoma. Imatinib targets the abnormal proteins encoded by mutated KIT and PDGFR-alpha genes, which are found in approximately 90 percent of GIST. One year of imatinib is now considered the standard adjuvant treatment for operable GIST. Approximately 85 percent of patients who have advanced GIST respond to imatinib, with partial remission or stable disease lasting a median of two years.

In the study 400 patients with GIST who were at high risk for recurrence were randomized to either one or three years of imatinib after surgery. After a median follow up time of 54 months, the investigators found that five-year recurrence-free survival was higher in the three-year group (65.6 percent) compared to patients treated for one year (47.9 percent). Similarly, the five-year overall survival for the three-year group was higher - 92.0 percent - compared to 81.7 percent of patients who received adjuvant imatinib for only one year.

Imatinib was generally well tolerated and the majority of side effects were typical of patients receiving the drug: anemia, fatigue, nausea, diarrhea and muscle cramps. However, 7.7 percent of the patients in the one-year group and 13.7 percent of the patients who received three years of adjuvant therapy halted treatment because of adverse events.

Few patients developed resistance to adjuvant imatinib, which is in line with previous studies. Only 2 percent (4) and 6.1 percent (12) of patients in the 12- and 36-month groups, respectively, stopped treatment due to GIST recurrence while receiving imatinib.

Dr. Joensuu stressed the need for continued monitoring of the trial participants, in addition to new research aimed at better identifying patients who could benefit from long-term adjuvant imatinib. Studies analyzing GIST risk factors and addressing longer treatment times with adjuvant imatinib - including a single-arm, non-randomized study examining 5-year adjuvant treatment - are currently underway.

The study was funded by Novartis, and also received academic funding.

ASCO2011特集

BRAF阻害剤は転移性メラノーマの生存率を改善する（Abstract No.LBA4）

Vemurafenibは進行メラノーマ患者の無増悪生存期間を改善する初めての薬剤である

Vemurafenib first drug to improve progression-free survival in patients with advanced melanoma

第47回ASCOで発表されNew England Journal of Medicineオンライン版に掲載された無作為化国際Phase IIIトライアルの結果、BRAF遺伝子のV600E変異を標的とするvemurafenib（PLX4032）は進行メラノーマ患者において標準的治療と比較し全生存期間を改善した初めての薬剤である。このトライアルでは、治療歴のない手術不能なステージIIICまたはステージIVの転移性メラノーマを有しBRAF遺伝子にV600E変異のある患者675人において、zvemurafenibを用いた治療と化学療法薬dacarbazineを比較した。計画されていた3ヵ月後の中間解析において、vemurafenib投与患者はdacarbazine投与患者と比較し死亡リスクが63%低かった（hazard ratio [HR]0.37；P<0.001）。Vemurafenib群はまたdacarbazine群よりも疾患進行（または死亡）リスクが74%低く（HR 0.26、P<0.001）奏効率が高かった(48.3vs5.5%、P<0.001)。最も多い副作用は発疹、光線過敏症、肝酵素上昇、および関節痛であった。これらの副作用のうちグレードIII以上であったのは10%未満であった。

Full Text

A randomized, international Phase III trial showed that vemurafenib (also known as PLX4032), which targets the V600E mutations in the BRAF gene, is the first drug to improve overall survival when compared to standard chemotherapy in patients with advanced melanoma. It is also the first drug to improve progression-free survival (PFS) and response proportion in these patients. If approved by the U.S. Food and Drug Administration, vemurafenib could become a new standard treatment for patients with melanoma who have this gene mutation. The drug has received extensive attention as a result of striking results from earlier-stage trials. This study is the first to demonstrate conclusively that the drug significantly improves survival better than the current standard.

"This is really a huge step toward personalized care in melanoma," said lead author Paul Chapman, M.D., attending physician in the melanoma/sarcoma service at Memorial Sloan-Kettering Cancer Center in New York. "This is the first successful melanoma treatment tailored to patients who carry a specific gene mutation in their tumor, and could eventually become one of only two drugs available that improves overall survival in advanced cancers." The other drug, ipilumumab, is an immune therapy also featured in ASCO's 2011 Annual Meeting plenary session.

Approximately half of all melanomas harbor a V600E mutation in the BRAF gene. The trial compared the effectiveness - overall survival and progression-free survival - of treatment with vemurafenib to the chemotherapy drug dacarbazine in 675 patients with previously untreated, inoperable stage IIIC or stage IV metastatic melanoma and a V600E mutation in the BRAF gene.

At the planned interim analysis at median three months, patients receiving vemurafenib had a 63 percent reduction in risk of death compared to those receiving dacarbazine. Those who received vemurafenib also had a 74 percent reduction in the risk of progression (or death) compared to dacarbazine. In addition, the researchers found that those receiving vemurafenib had a 48.4 percent response rate compared to 5.5 percent for the dacarbazine group. At the first trial interim analysis, it was recommended that those patients receiving dacarbazine switch to vemurafenib.

The most common side effects of vemurafenib were skin rashes, photosensitivity, elevated liver enzymes, and joint pain. Fewer than 10 percent of these side effects were grade three or worse. In addition, 18 percent of patients developed a low-grade non-melanoma skin tumor.

Dr. Chapman said that because the study findings showed improvements in PFS and response rate along with greater overall survival, PFS may now become a validated study endpoint for future trials with similarly targeted therapies in melanoma.

The researchers plan to next test vemurafenib in combination with other agents in patients with advanced melanoma. A Phase I trial has already begun with vemurafenib and ipilimumab, which received approval from the U.S. Food and Drug Administration earlier this year.

The study was sponsored by Hoffman-La Roche.

ASCO2011特集

治療により小児神経芽腫の生存率が改善する（Abstract No.2）

新たな高用量化学療法レジメンにより難治性神経芽腫の小児の生存率が改善する

New high-dose chemotherapy regimen improves survival in children with hard-to-treat neuroblastoma

高リスク神経芽腫の小児における骨髄破壊的化学療法薬ブスルファンとメルファランの併用（BuMel）による無イベント生存率および生存率は、カルボプラチン、エトポシドおよびメルファラン（CEM）の3種類の化学療法薬による異なる骨髄破壊的療法と比較し良好であるとのスタディ結果が2011年ASCOで発表された。ヨーロッパSIOP神経芽腫グループが行ったHR-NLB1トライアルはこれら2種類の高用量骨髄破壊的化学療法レジメンの有効性を比較した。このトライアルではステージIVの遠隔転移またはMYCN腫瘍遺伝子増幅を有する高リスクの小児563人（年齢中央値3歳）を、BuMel（281人）またはCEM（282人）投与群に無作為に割り付けた。3年後の無イベント生存率はBuMel群で49%であったのに対しCEM群では33%であった。3年後の全生存率はBuMel投与群の60%に対し、免疫療法を行わないCEM群では48%であり、ブスルファン群の方が再発および進行率が低かった（47%対60%）。しかし、神経芽腫の治療にはリスクを伴わないわけではない。治療関連死はBuMel群で3%であり、CEM群で5%であった。これらの結果に基づき、無作為化は早期に中止された。

Full Text

A randomized Phase III trial showed that children with high-risk neuroblastoma had better event-free and overall survival with a combination of the myeloablative chemotherapy drugs busulphan and melphalan (BuMel) compared to a different myeloablative regimen of three chemotherapy drugs, carboplatin, etoposide and melphalan (CEM). These results establish a new standard of care for children with high-risk disease, of whom previously only 30 percent survive long-term. Myeloablative chemotherapy is high-dose chemotherapy that kills cells in the bone marrow, including cancer cells.

"The study's results are important for patients with this extremely difficult to treat disease," said lead author Ruth Ladenstein, M.D., MBA, associate professor of pediatrics at the University of Vienna and St. Anna Children's Cancer Research Institute in Vienna. "These results, combined with the recent report that an anti-GD2 ch14.18 antibody-based immune therapy can increase event-free and overall survival by 20 percent in high-risk patients, mean that we could potentially improve overall prognosis by up to 35 percent in the future. Thus, we overcome the 50 percent threshold in survival rates by choosing the right high-dose myeloablative regimen for these patients."

Neuroblastoma is a rare cancer of specialized nerve cells, but it is the most common cancer in the first year of life and accounts for approximately 15 percent of childhood cancer deaths. About 650 cases are diagnosed each year in the United States, with about 40 percent that are considered high-risk, meaning they are very likely to recur or progress, despite therapy. The typical therapy for these patients includes intense upfront chemotherapy to induce remission, surgery, radiotherapy, myeloablative therapy to kill the cancer cells remaining in the bone marrow combined with stem cell transplantation, and followed by minimal residual disease treatment with 13 cis retinoid acid, as well as immunotherapy if available.

The HR-NLB1 trial of the European SIOP Neuroblastoma Group compared the effectiveness of two high-dose myeloablative chemotherapy regimens. In the trial, 563 children (median age three) with stage IV, high-risk disease with distant metastases or local disease with MYCN oncogene amplification were randomized to receive either BuMel (281) or CEM (282). After three years, the event-free survival for BuMel was 49 percent compared to 33 percent for the CEM group. The overall survival after three years was 60 percent for those who received BuMel compared to 48 percent in the CEM group without immunotherapy, and the busulphan group had lower rates of relapse and progression (47 percent versus 60 percent). Based on the results, the randomization was stopped early.

Treatment for neuroblastoma is not without risk. The treatment-related death rate was 3 percent for the busulphan regimen and 5 percent for CEM.

ASCO2011特集

メラノーマのファーストライン治療としてipilimumabは有効である（Abstract No.LBA5）

モノクローナル抗体ipilimumabと化学療法の併用は転移性メラノーマの全生存率を改善する

Monoclonal antibody ipilimumab plus chemotherapy improves overall survival in metastatic melanoma

2011年ASCOで発表されNew England Journal of Medicineオンライン版に掲載されたPhase III無作為化スタディの結果、免疫療法薬ipilimumabと標準的な化学療法薬dacarbazineの併用によるファーストライン治療により未治療の転移性メラノーマ患者の全生存率が改善することが示された。昨年の2010年の学会において、ipilimumabはメラノーマワクチンgp100と比較し生存率を改善することが示された。今回のスタディにおいて転移性メラノーマ患者502人がipilimumabとdacarbazine併用群（250人）またはプラセボとdacarbazine投与群（252人）に無作為に割り付けられた。1年後の全生存率は併用療法群において47.3%であったのに対しdacarbazine単独療法群では36.3%であった。2年後の全生存率は2剤併用群で28.5%であったのに対しdacarbazine単独群では17.9%であった。3年後の総生存率は2剤併用群で20.8%であったのに対し化学療法単独群では12.2%であった。全生存率中央値はipilimumabとdacarbazine投与群で11.2ヵ月であったのに対しdacarbazine単独投与群においては9.1ヵ月であった（死亡のハザード比[HR] 0.72）。無増悪生存期間中央値は併用療法の2.8ヵ月に対しdacarbazine単独群では2.6ヵ月であり、ほぼ同等であった。

Full Text

A Phase III randomized study found that first-line treatment with a combination of the immunotherapy drug ipilimumab (Yervoy) and the standard chemotherapy drug dacarbazine (DTIC) improves overall survival in patients with previously untreated metastatic melanoma. It is the first study to show that combining chemotherapy and immunotherapy is safe and effective for patients with advanced melanoma. At the 2010 Annual Meeting, ipilumumab was shown to improve survival when compared to a melanoma vaccine, gp100.

"These findings show the same kind of important results announced last year with the use of ipilimumab alone in improving overall survival in metastatic melanoma," said lead author Jedd Wolchok, M.D., director of immunotherapy clinical trials and associate attending physician at Memorial Sloan-Kettering Cancer Center in New York. "This trial's three-year endpoint is significant. No randomized trial for metastatic melanoma has followed patients for this long, and it demonstrates the durability of this survival benefit, now out to three years in this population, and even four years in some cases. It's one of the advantages of immunotherapy. The immune system is a 'living drug,' able to adapt itself to changes in the tumor that might otherwise lead to resistance when treated with chemotherapy or a pathway inhibitor."

Advanced melanoma is one of the most deadly forms of cancer, and over the past three decades, melanoma incidence has climbed faster than any other cancer type. Ipilimumab is a monoclonal antibody that represents a new class of drugs that activate the immune system's T cells, which then seek and destroy melanoma cells. The drug targets the cytotoxic T-lymphocyte associated antigen 4, which acts like a brake on the T-cell. Ipilimumab removes this brake, enabling T cells to attack the cancer.

In this study, 502 patients with metastatic melanoma were randomized to ipilimumab plus dacarbazine (250) or placebo and dacarbazine (252). The overall survival rate for the combination after one year was 47.3 percent compared to 36.3 percent for DTIC alone. After two years, the overall survival rate was 28.5 percent for the two drugs, versus 17.9 percent for DTIC alone. At three years, overall survival was 20.8 percent for the combination compared to12.2 percent for chemotherapy alone.

Investigators found that the median overall survival was 11.2 months for patients who received ipilimumab and DTIC versus 9.1 months for those given only DTIC. The median progression-free survival times, however, were nearly the same: 2.8 months for the combination compared to 2.6 months for DTIC. Dr. Wolchok attributed this finding to the way ipilimumab - and immunotherapy - may work. The effects of immunotherapy treatment can take much longer to be seen than those from traditional chemotherapy or targeted therapies, and patients' scans may accurate way to gauge treatment effectiveness than progression-free survival.

The combination of ipilimumab and dacarbazine had a good safety profile, with no gastrointestinal perforations and a lower rate of colitis than was expected based upon prior studies with ipilimumab alone. Still, approximately 56 percent of patients in the ipilimumab-DTIC group and 27 percent of those who received only DTIC had significant grade 3/4 adverse events from their therapy, including elevated liver enzymes.

The next step in the research, according to Dr. Wolchok, is to investigate combinations of different therapies with ipilimumab, such as the targeted drug vemurafenib in melanoma patients with BRAF mutations, and to test other combinations of targeted agents and immune-modifying agents together as well.

The study was sponsored by Bristol-Myers Squibb.

ASCO2011特集

エキセメスタンは健常女性の乳がんリスクを軽減させる（Abstract No.LBA504）

アロマターゼ阻害薬は高リスクの閉経後女性における浸潤性乳がんリスクを軽減する

Aromatase inhibitor significantly reduces risk of invasive breast cancer in high-risk, postmenopausal women

2011年ASCOで発表されNew England Journal of Medicineオンライン版に掲載された大規模無作為化二重盲検Phase IIIトライアルの結果、乳がん発症リスクの高い閉経後女性においてアロマターゼ阻害薬エキセメスタンが乳がん発症リスクを65%低下させることが示された。MAP.3（乳がん予防トライアル：Mammary Prevention Trial-.3）スタディは健常女性におけるアロマターゼ阻害薬の乳がん予防効果を評価した初めての無作為化トライアルである。このトライアルは、リスクファクター（60歳以上；5年Gailリスクスコア1.66%超；異型乳管または小葉過形成または上皮内小葉がんの既往；または乳房切除術後の上皮内乳管がん）を1つ以上有する閉経後女性4,560人を組み入れた。フォローアップ期間中央値3年後に、浸潤性がんはエキセメスタン群において65%少なかった（浸潤性乳がんはエキセメスタン群で11人に対しプラセボ群で32人）。このトライアルの患者66症例において浸潤性乳がんと前浸潤性DCISが60%減少した。重要なことに、異型乳管または異型小葉過形成などの前駆病変もエキセメスタン群において少なかった。

Full Text

A large randomized double-blind phase III trial led by Canada's NCIC Clinical Trials Group (NCIC CTG) has shown that in postmenopausal women who are at increased risk of developing breast cancer, the aromatase inhibitor (AI) exemestane (Aromasin) reduces this risk by 65 percent compared with placebo.

"The potential public health impact of these findings is important. Worldwide it is estimated that 1.3 million women are diagnosed with breast cancer each year and nearly 500,000 women die of the disease. Results from the MAP.3 trial indicate that exemestane is a promising new way to prevent breast cancer in menopausal women most commonly affected with breast cancer," said Paul E. Goss, M.D., Ph.D., lead study author and professor of medicine at Harvard Medical School and Massachusetts General Hospital in Boston, MA.

"The reduction in breast cancers of 65 percent we demonstrated was exactly in line with our expectations," Dr. Goss continued. "The numbers of tumors are small but there also appeared to be fewer of the more aggressive tumors on exemestane. Our study not only showed an impressive reduction in breast cancers, but also an excellent side effect profile, although my cautionary note is that average follow-up to date has been only 3 years."

Estrogens have been implicated in causing breast cancer. The anti-estrogens tamoxifen and raloxifene are FDA approved preventatives of breast cancer in women at high risk. However, it has been estimated that rare but serious uterine cancer and blood clots which can be fatal, have limited the acceptance of tamoxifen to only 4 percent of high risk women and 0.08 percent of all women in the U.S. There is a need for highly effective and safer options for breast cancer prevention.

Aromatase inhibitors (AIs) powerfully prevent estrogen synthesis and are distinct from tamoxifen in the way they counteract estrogen. AIs are superior to tamoxifen in preventing recurrences in early breast cancer patients, including the prevention of new breast cancers. The investigators predicted from laboratory experiments and clinical results that AIs would prevent breast cancer without the serious toxicities seen with tamoxifen.

The MAP.3 (Mammary Prevention Trial-.3) study, led and coordinated by the NCIC CTG, is the first randomized trial to assess an aromatase inhibitor as a breast cancer preventative in healthy women. Exemestane is an AI approved by the U.S. Food and Drug Administration for use in early breast cancer patients. The trial enrolled 4,560 women from the U.S., Canada, Spain and France.

Eligible postmenopausal women had at least one of these risk factors: age greater than or equal to 60 years; five-year Gail risk score greater than 1.66 percent; prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ; or ductal carcinoma in situ with prior mastectomy.

At a median follow up of three years, the group receiving exemestane had a 65 percent reduction in invasive cancers (11 invasive breast cancers in the exemestane group compared to 32 in the placebo group). There was also a 60 percent reduction of invasive breast cancer plus pre-invasive DCIS among the 66 cases in the women on the trial. Importantly, there were fewer cases of cancer precursor lesions such as atypical ductal and atypical lobular hyperplasia in the group receiving exemestane.

The investigators reported symptoms such as hot flashes, fatigue sweating, insomnia and arthralgia were frequent in all women on study but predictably slightly more common on exemestane. However, these symptoms did not appear to affect self-reports of overall health-related quality of life on exemestane.

More serious adverse events including bone fractures, osteoporosis, hypercholesterolemia, adverse cardiovascular events and other non-breast cancers were equal in both groups.

"After unblinding, women on active therapy will be offered exemestane to complete five years, and MAP.3 sites will have the option of offering five years of exemestane to those initially allocated to placebo. We and others are conducting placebo-controlled trials in healthy women and early breast cancer patients of AIs in menopausal women of similar age and results from these ongoing trials will contribute to our understanding of long term efficacies and toxicities of aromatase inhibitors," Dr. Goss said. "Long-term results in women with early breast cancer show durable long-term reductions in new breast cancers with exemestane without accumulation of late toxicities. So we are hopeful and optimistic that this will be the case in this prevention setting."

The study was supported by the Canadian Cancer Society; Pfizer Inc. PEG supported in part by Avon Foundation.

ASCO2011特集

卵巣がんにおけるbevacizumabの治療ベネフィット（Abstract No. LBA5006 and5007）

新たに診断された卵巣がんに対するbevacizumab使用に関する初期データから再発リスクの高い女性の生存率に関する有益性が示唆された

Initial data on use of bevacizumab for newly diagnosed ovarian cancer suggests survival benefit for women at high risk of recurrence

第47回ASCOで報告された無作為化Phase IIIトライアルの生存率に関する中間データから、新たに診断された卵巣がん患者に対する標準的なカルボプラチンおよびパクリタキセル化学療法へのbevacizumab併用は、特により進行の速い患者において、化学療法のみの治療と比較し有益である可能性が示唆された。ICON7スタディにおいて、新たに診断された、高リスクまたは進行上皮性卵巣がん、原発性腹膜がん、または卵管がん患者を6サイクルの化学療法単独、または同様の化学療法とbevacizumabの同時併用を受けその後ベバシズマブ単独療法を12ヵ月受ける群に無作為に割り付けた。フォローアップ期間中央値28ヵ月後、死亡は標準治療群よりもbevacizumab群において少なかった（それぞれ178対200、p=0.11）。再発リスクの最も高い患者においてあらかじめ計画されていたサブグループ解析では、36%の死亡リスク低下が認められた（p=0.0002）。やはりASCO学会で発表されたOCEANSスタディでは、bevacizumabとプラチナ製剤ベースの化学療法の併用により、再発性卵巣がん、腹膜がん、および卵管がんの無増悪生存期間が延長した。

Full Text

Interim survival data from a randomized Phase III trial reported at the American Society of Clinical Oncology's 47th Annual Meeting suggested that adding bevacizumab (Avastin) to standard carboplatin and paclitaxel chemotherapy for treatment of newly diagnosed ovarian cancer patients may offer benefit over treatment with chemotherapy alone, particularly for patients with more aggressive disease.

In the ICON7 study, 1,528 women with newly diagnosed high-risk or advanced epithelial ovarian, primary peritoneal or fallopian tube cancer were randomized to receive 6 cycles of chemotherapy alone, or the same chemotherapy concurrently with bevacizumab followed by single agent of bevacizumab for a total duration of 12 months. First results presented at last year's ESMO Annual Meeting reported a progression-free survival (PFS) benefit for adding bevacizumab to standard chemotherapy.

To further inform consideration of a licensing application, an interim analysis of overall survival was requested by regulatory authorities - the U.S. Food and Drug Administration and the European Medicines Agency. After a median follow-up of 28 months, there were fewer deaths in the bevacizumab group than the standard therapy group (178 versus 200, respectively). This represents a 15 percent overall reduction in risk of death, but was not statistically significant.

The ICON7 investigators also conducted a planned subgroup analysis looking at the results in patients at highest risk of recurrence - those with stage III ovarian cancer who were left with more than 1 cm of tumor after surgery and all stage IV patients who had surgery. In this subgroup, the reduction in risk of death was 36 percent (79 deaths versus 109 deaths in the standard therapy group). This result reached statistical significance (P=.0002).

"It's too early to reach firm conclusions about the full extent of the overall survival benefit of adding bevacizumab to the treatment regimen for newly diagnosed ovarian cancer, but it does seem very promising, particularly for patients at high risk of recurrence," said Gunnar Kristensen, M.D., Ph.D., one of the lead investigators of this study and Senior Consultant in the Department for Gynecologic Oncology, Norwegian Radium Hospital, Oslo, Norway. "We don't have complete answers to all our questions today; we will have to wait for final results of the trial which are expected in about two years."

In another trial also presented at ASCO, the randomized Phase III OCEANS study of bevacizumab in combination with platinum-based chemotherapy showed that women with recurrent ovarian cancer who took bevacizumab lived significantly longer without their disease getting worse. A 52% reduction in the risk of disease progression was seen.

"Women taking bevacizumab lived for longer periods without disease progression and without having to go back on chemotherapy," said Carol Aghajanian, M.D., lead study author and Chief, Gynecologic Medical Oncology Service, Memorial Sloan-Kettering Cancer Center in New York. "This is good news for women with these cancers, as we are increasingly able to treat ovarian cancer as a chronic disease."

The results from OCEANS show that after a median follow-up of 24 months, median progression-free survival was 12.4 months for the patients in the bevacizumab group, compared to 8.4 months for patients who had chemotherapy alone. In addition, 79 percent of women treated with bevacizumab in combination with chemotherapy had significant tumor shrinkage, compared to 57 percent treated with chemotherapy alone. The duration of response was also longer for the patients in the bevacizumab group (10.4 months versus 7.4 months).

The multicenter study randomized 484 patients to receive bevacizumab, an anti-VEGF monoclonal antibody, and chemotherapy (carboplatin and gemcitabine) or a placebo and the same chemotherapy regimen. Bevacizumab or placebo was continued after the completion of chemotherapy until the time of disease progression.

The side effects of bevacizumab were consistent with those seen in previous studies. No gastrointestinal perforations were seen in the OCEANS trial.

The investigators said the next step in this work is to evaluate the role of bevacizumab in combination with chemotherapy for platinum-resistant disease, and to combine bevacizumab with other emerging novel therapies such as PARP inhibitors.

"The data from OCEANS demonstrate a clear response from bevacizumab in these cancers," Dr. Aghajanian said. "These are very meaningful results for patients for whom there are currently limited treatment options available."

ASCO2011特集

前立腺がん循環腫瘍細胞は生存期間と相関する（Abstract No. LBA4517）

前立腺がん循環腫瘍細胞は生存期間のサロゲートバイオマーカーとなりうる

Prostate cancer circulating tumor cells could be used as surrogate biomarker for survival

転移性去勢抵抗性前立腺がん（mCRPC）の全生存期間延長に対するabiraterone acetateの有効性を示した前向き無作為化Phase IIIトライアルの解析から、循環腫瘍細胞（CTCs）レベルは生存期間と相関があることも明らかにされたと2011年ASCOで発表された。1,195人の患者を対象としたPhase III COU-AA-301トライアルにおいてabiraterone療法はmCRPCの全生存期間を有意に改善した（abirateroneおよびプレドニゾン投与群で15.8ヵ月に対しプレドニゾンおよびプラセボ投与群で11.2ヵ月、p<0.0001）。このトライアルにおいて研究者らは972人の患者においてベースライン時に、723人においては3ヵ月後にもCTC数計測を行い、abiraterone療法によりCTCs数が減少し、好ましくない計測数（CTC≥5）から好ましい計測数（CTC<5）に“変換”したことを確認した。この結果は治療後4ヵ月ほどの早期の予後および全生存期間が良好であることの予測因子であった。これらの初期結果から、CTCsを去勢抵抗性疾患に関する臨床試験の生存期間のバイオマーカーパネルの一部として使用する研究が導かれた。過去のスタディでは、mCRPCにおいてCTCs数減少により全生存期間が改善し、一部の症例においてはPSAよりもより強力な生存期間の早期予測因子であることが示されていた。

Full Text

An analysis of a prospective, randomized Phase III trial showing the effectiveness of a drug in extending overall survival in metastatic castration-resistant prostate cancer (mCRPC) also has found that the level of circulating tumor cells (CTCs) correlated with survival according to researchers at ASCO's 2011 annual meeting. These initial results have led to the investigation of the use of CTCs as part of a biomarker panel for survival in clinical trials for castration-resistant disease.

A problem plaguing the prostate cancer field is the identification of reliable early indicators that a drug can prolong life. Such surrogates can be used in lieu of a survival endpoint in clinical trials, allowing drugs to be tested in smaller, less costly trials that could potentially enable faster approvals by the U.S. Food and Drug Administration. Changes in prostate specific antigen (PSA) have not been shown to be surrogates for survival in prospective trials and cannot be used for regulatory approvals.

In the Phase III COU-AA-301 trial, a study of 1,195 patients showed that the drug abiraterone acetate (Zytiga) significantly improved overall survival in mCRPC (15.8 months for those on abiraterone and prednisone versus 11.2 months for those on prednisone and placebo). In this trial, investigators evaluated CTC counts in 972 patients at baseline, and in 723 patients after three months, finding that the abiraterone therapy reduced the number of CTCs, "converting" them from unfavorable (CTC greater than or equal to five) to favorable (CTC less than five) counts. This was predictive of a better prognosis and overall survival as early as four weeks after treatment. According to lead author Howard I. Scher, M.D., the D. Wayne Calloway Chair in Urologic Oncology and chief of the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center in New York, studies have linked declining numbers of CTCs with improved overall survival in mCRPC, and in some cases, have been shown to be a more powerful early predictor of survival than PSA among men with prostate cancer.

"The ultimate goal of these studies is to develop a biomarker panel that includes CTCs that can be used in Phase III trials instead of a survival endpoint," said Dr. Scher. "This trial was the first to show a survival benefit with the CTC question embedded, and which is part of a formal collaboration with the FDA. Preliminary results show that CTC and lactate dehydrogenase (LDH) are prognostic, confirming previous studies. This trial becomes the basis for a biomarker panel that we will create, which will then be tested prospectively in subsequent trials. To establish a surrogate for survival is a multistep process that requires consistent results in multiple Phase III studies and which have the CTC biomarker question embedded. Our results are very encouraging for the use of CTCs."

Dr. Scher added that while favorable changes in CTC are associated with a better prognosis, the results cannot be used alone to guide treatment decisions for an individual patient. Testing whether changes in CTC can be used to manage individual patients "will require a new, dedicated trial that specifically asks this question."

The researchers are continuing their work to define a biomarker panel that is most strongly associated with overall survival in mCRPC.

ASCO2011特集

リンパ節への放射線照射は早期乳がんの予後を改善する（Abstract No. LBA1003）

局所リンパ節放射線照射を追加することにより早期乳がん女性の再発が減少する

Adding regional nodal irradiation decreases recurrences in women with early breast cancer

2011年ASCOで報告された無作為化Phase IIIトライアルの中間解析のデータから、リンパ節転移陽性または高リスクのリンパ節転移陰性乳がん患者において、局所リンパ節放射線照射（RNI）を併用することにより無病生存期間が改善し、腫瘍部位の近辺および他の身体部位のがん再発が減少することが報告された。このスタディは1,832人の女性を組み入れた。そのうちほとんど（85%）が1～3個のリンパ節転移を有しており、高リスクでリンパ節転移陰性の乳がんを有している割合（10%）は少なかった。全員が乳房温存術およびアジュバント化学療法または内分泌療法による治療を過去に受けており、その後、全乳房照射（WBI）単独またはWBIとRNI併用群に無作為に割り付けられた。フォローアップ期間中央値62ヵ月の後、RNIも受けた患者の無病生存率は33%改善した（WBI単独の84%からRNI併用療法89.7%、ハザード比0.67；p=0.003）。これには孤立性局所無病生存率の41%低下（5.5%から5年後3.2%、p=0.02）、および遠隔無病生存率の36%低下（13%から5年後7.6%、p=0.002）が含まれた。全死亡率はRNI群において24%低下した（p=0.07）。

Full Text

Interim analysis data from a randomized Phase III trial reported at the American Society of Clinical Oncology's 47th Annual Meeting showed that, in women with node-positive or high-risk node-negative breast cancer, additional regional nodal irradiation (RNI), improves disease-free survival, reducing cancer recurrences both near the tumor site and in other parts of the body. In addition, overall mortality was reduced by 24 percent in the group receiving RNI, but this did not reach statistical significance.

"These results are potentially practice-changing. They will encourage physicians to offer all women with node-positive disease the option of receiving regional nodal irradiation," said Dr. Timothy J. Whelan, BM BCh, lead study investigator for the NCIC Clinical Trials Group and a professor of oncology and Division Head of Radiation Oncology at McMaster University and the Juravinski Cancer Centre, Hamilton, Ontario. "Adding regional nodal irradiation improved disease-free survival, lowered the risk of recurrences, and there was a positive trend toward improved overall survival, while not greatly increasing toxicities."

Women with node-positive breast cancer are treated with breast-conserving surgery plus axillary lymph node dissection, followed by whole breast irradiation (WBI). If a woman's cancer has high-risk features, such as a tumor larger than 5 cm or more than three positive axillary nodes, she often receives regional nodal irradiation, or RNI. However, for women with one to three positive nodes, the benefit of adding RNI has been unclear.

The study enrolled 1,832 women, most of whom (85 percent) had one to three positive lymph nodes, and a smaller proportion of women (10 percent) who had high-risk, node-negative breast cancer. All women had been treated with breast-conserving surgery and adjuvant chemotherapy or endocrine therapy. The participants were randomized to receive either WBI alone or WBI plus RNI.

A protocol specified interim analysis of the data conducted in March 2011 found that after a median follow up of 62 months, there were statistically significant benefits for the group receiving the added RNI therapy. These included a greater than 30 percent improvement in disease free survival (from 84 percent for those who received WBI to 89.7 percent for those who also got RNI at 5 years), as a result of a 41 percent lower rate of recurrences near the tumor site (from 5.5 percent to 3.2 percent at 5 years), and a 36 percent lower rate of cancer recurrences in other parts of the body (from 13 percent to 7.6 percent at 5 years).

The patients who received the added RNI had a low but statistically significant increased risk of grade 2 or greater pneumonitis and lymphedema.

ASCO2011特集

肺がんに対する維持療法は無増悪生存期間を改善する（Abstract No. CRA7510）

ペメトレキセドによる維持療法を拡大することにより進行肺がん患者の無増悪生存期間が改善する

Extending pemetrexed treatment as maintenance therapy improves progression-free survival in patients with advanced lung cancer

2011年ASCOで発表されたPhase III無作為化トライアルの結果、化学療法薬ペメトレキセドを用いた維持療法により、初回化学療法の一部としてもペメトレキセド投与を受けた進行非扁平上皮非小細胞肺がん患者の無増悪生存期間（PFS）が改善することが示された。PARAMOUNTは、非常に難治性の非小細胞肺がん患者の無増悪生存期間を維持療法の継続により上昇させうることを示した初めての大規模トライアルである。このスタディにおいて939人の患者が、ペメトレキセドおよびシスプラチンを用いて疾患の寛解導入を試みる標準的な4コースのファーストライン寛解導入療法を受けた。これらの患者のうちがんが進行しなかった患者539人がペメトレキセド維持療法および最適な支持療法を受ける群（359人）またはプラセボと最適な支持療法を受ける群（180人）に無作為に割り付けられた。最適な支持療法とは、例えば疼痛や感染症を軽減したり食欲を刺激したりするなどの非抗がん療法である。ペメトレキセド維持療法により疾患進行リスクが38%低下した（p=0.00025）。PFS中央値はペメトレキセド群で4.1ヵ月であったのに対しプラセボ群では2.8ヵ月であった。疾患コントロール率はペメトレキセド群で71.8%であったのに対しプラセボ群では59.6%であった（p=0.009）。

Full Text

A Phase III, randomized trial showed that maintenance therapy with the chemotherapy drug pemetrexed (Alimta) improves progression-free survival (PFS) in patients with advanced nonsquamous non-small cell lung cancer who also received pemetrexed as part of their initial chemotherapy regimen. PARAMOUNT is the first large trial to demonstrate that continuation maintenance can increase progression-free survival in advanced non-small cell lung cancer, an extremely difficult disease to treat. The study provides physicians with a new treatment option after first-line therapy with pemetrexed.

"Cisplatin-pemetrexed therapy is an effective induction therapy for advanced disease. But after the fourth course, we typically stop treatment, and eventually need to go to a second-line therapy when the disease progresses again," said lead author Luis Paz-Ares, M.D., Ph.D., chair of oncology at Seville University Hospital in Seville, Spain. "This cancer doesn't have many treatment options, and we don't want to fire all of our treatment bullets at once. These results suggest that patients can still continue to benefit from the use of the same drug. This could change the standard of care for these patients, at least in terms of maintenance treatment."

In the study 939 patients were given the standard four courses of first-line induction treatment with pemetrexed and cisplatin to attempt to induce disease remission. Of those, 539 patients whose cancer did not progress were randomized to maintenance pemetrexed and best supportive care (359) or placebo and best supportive care (180) until disease progression. Best supportive care entails non-anti-cancer therapy, including treatment to reduce pain and infections, for example, and stimulate appetite.

The investigators found that pemetrexed maintenance resulted in a 38 percent reduction in the risk of disease progression. The median PFS was 4.1 months for those in the pemetrexed group compared to 2.8 months in the placebo group. The disease control rate was 71.8 percent in the pemetrexed arm compared to 59.6 percent on placebo.

The toxicity profile of maintenance therapy was very favorable and in accordance with previous single agent pemetrexed.

Maintenance therapy isn't mandatory for every patient, Dr. Paz-Ares noted. "Some may have significant toxicity during induction treatment, and it may be worth having a treatment break. On the other hand, a patient who is having a good response in the absence of significant toxicity may be a good candidate for maintenance therapy. A lot of factors go into the treatment decision, and each patient should be informed."

ASCO2011特集

アジュバント化学療法を早く開始するのが最適なようである（Abstract No. 6125）

大腸がん手術後の化学療法開始時期が遅延するほど生存率が低下する

Following colorectal cancer surgery, longer delay to beginning chemotherapy associated with worse survival

過去に公表されたスタディのデータ解析から、大腸がん（CRC）の術後アジュバント化学療法（AC）開始までの期間が長いほど生存率が低いことが示されたとのメタ解析の結果が2011年ASCOで発表されJAMA 6月8日号に掲載された。研究者らは計15,410人の患者を対象としたスタディの組み入れ条件を満たす10のスタディ（雑誌に掲載された論文7本とアブストラクト3本）を特定した。ACまでの期間が4週間増加すると全生存期間および無増悪生存期間が有意に低下した（14%）。術後どれ位経過した後に化学療法を始めたら有益性が限られてしまうかとの論点に関して筆者らは、彼らの研究結果から4週後ではなく12週後に化学療法を開始した場合の生存率が48%であったことが示されたことから、12週後に化学療法を開始しても何らかの有益性が得られることが示唆され、したがって妥当な有効期間は4〜5ヵ月の単位であろうと述べている。これらの結果から、CRC患者の管理および予後においてACのタイミングが重要な役割を果たしており、医師らが化学療法開始の遅延を避けることは賢明であることが示唆された。

Full Text

An analysis of data from previously published studies indicates that longer time to beginning adjuvant chemotherapy after surgery for colorectal cancer is associated with worse survival, according to a study presented at the ASCO 2011 Annual Meeting and published in the June 8 issue of JAMA, a theme issue on cancer. The study is being published early online to coincide with its presentation at the American Society of Clinical Oncology 2011 Annual Meeting.

"Colorectal cancer (CRC) is the third leading cause of cancer mortality in the Western world. While surgical resection remains the cornerstone of management for patients with stage I-III disease, a considerable proportion of patients will ultimately relapse and die from their disease," according to background information in the article. "Adjuvant chemotherapy [AC] improves survival among patients with resected colorectal cancer. However, the optimal timing from surgery to initiation of AC is unknown." There is also a question of the benefit of beginning chemotherapy after a certain time period, typically believed to be 12 weeks.

James J. Biagi, M.D., of Queen's University, Kingston, Ontario, Canada, and colleagues conducted a review and meta-analysis of studies that assessed the relationship between time to AC and survival in CRC. Studies were only included if relevant prognostic factors were adequately described and either comparative groups were balanced or results adjusted for these prognostic factors. The researchers identified 10 eligible studies involving 15,410 patients (7 published articles, 3 abstracts) that met study criteria for inclusion. Nine of the studies were cohort or population based and 1 was a secondary analysis from a randomized trial of chemotherapy.

The researchers found that meta-analysis indicated that a 4-week increase in time to AC was associated with a significant decrease (14 percent) in both overall survival and disease-free survival. There was no significant heterogeneity among included studies. Results remained significant after adjustment for potential publication bias and when the analysis was repeated to exclude studies of largest weight.

"The effect of AC on survival is thought to be eradication of micro-metastatic deposits in a proportion of patients who would otherwise be destined to have cancer recurrence. There is a substantial theoretical rationale to initiate AC promptly after curative surgery," the authors write.

Regarding the question of after what time period would beginning chemotherapy appear to be of limited benefit, the authors found that their results indicate survival of 48 percent if chemotherapy is administered at 12 weeks instead of 4 weeks, suggesting there may be some benefit to chemotherapy beyond a 12-week window, and that a reasonable limit may be more in the order of 4 to 5 months.

These findings suggest that timing of AC plays a critical role in the management and outcomes of patients with CRC and that it would be prudent for clinicians and jurisdictions to avoid delays in access to chemotherapy, the researchers write. "Our results indicate that at a population level, the effect of delays might be substantial. With approximately 140,000 new cases of CRC diagnosed in the United States in 2009, of which roughly 35 percent or 49,000 had stage III disease, the population at risk is sizeable."

"In conclusion, our results demonstrate a significant adverse association between time to AC and survival in CRC, supporting a position that clinicians and jurisdictions need to optimize patient flow logistics to minimize time to AC," the authors write. "Our results provide further validation of the intuitive concept of early time to AC. Physicians may need to more carefully consider timing when discussing AC with patients."

ASCO2011特集

薬物により骨髄線維症の奏効率が改善する（Abstract No. LBA6501）

JAK阻害薬は高リスク骨髄線維症患者の奏効率を改善する

JAK inhibitor improves response rate for patients with high-risk myelofibrosis

あるヨーロッパの無作為化Phase IIIトライアルの結果、Janusキナーゼ（JAK）阻害薬ruxolitinibが、しばしば白血病に到る致死的な可能性のある骨髄疾患である骨髄線維症の3つの型の治療の奏効率を顕著に改善することが示されたと第47回ASCOで発表された。全ての患者においてJAKシグナリングパスウェイが活性化していたが、JAK2遺伝子の変異を有していたのは全体の約半数であった。RuxolitinibはJAK阻害薬でありJAK2変異の有無にかかわらず有効である。COMFORT IIトライアルは、原発性骨髄線維症、真性多血症後骨髄線維症または本態性血小板血症後骨髄線維症の成人患者におけるruxolitinibの有効性、安全性および忍容性を現在可能な最適な治療法と比較調査した。このスタディでは中等度または高リスクの患者をruxolitinib（146人）または可能な最適な治療法（73人）に無作為に割り付け、有効性のエンドポイントは脾臓サイズの35%以上の減少とした。Ruxolitinib群では24週後に31.9%の患者が、48週後には28.5%がこのエンドポイントを達成した。可能な最適な治療を受けたコントロール群患者においてはこのレベルの脾臓サイズの縮小を認めた者はいなかった。

Full Text

A randomized Phase III European trial showed that the Janus kinase (JAK) inhibitor ruxolitinib resulted in dramatically improved response rates in treating three forms of myelofibrosis (MF), a potentially deadly bone marrow disorder that frequently leads to leukemia according to researchers at the American Society of Clinical Oncology's 47th Annual Meeting. The trial - dubbed COMFORT II - and a companion Phase III study (COMFORT I) - are the first randomized drug trials for MF. In showing significant benefit compared to currently available therapies, the findings promise to change the standard of care for many patients with MF.

"There aren't really any therapies that work for a sustained period in myelofibrosis, and we've urgently needed new treatments for this condition," said study co-author Alessandro Vannucchi, M.D., associate professor of hematology at the University of Florence in Florence, Italy. "These patients responded very quickly to ruxolitinib - within two to four weeks. This therapy has the potential to significantly change the treatment landscape for these patients, and could greatly improve their outlook."

MF is a myeloproliferative disorder characterized by the progressive accumulation of scar tissue in the bone marrow, causing anemia and a variety of debilitating systemic symptoms, in addition to an enlarged spleen. Twenty-seven percent of patients eventually develop acute myeloid leukemia or bone marrow failure. While bone marrow transplantation is the only potentially curative therapy currently available, only 10 percent of patients are eligible; other therapies, including blood transfusion, anabolic steroids and thalidomide, are considered largely palliative because they do not alter the course of the disease and their activity usually is not sustained.

While the median overall survival for myelofibrosis can exceed five years, high-risk patients only live about two to four years after diagnosis. About half of all patients carry a mutation in the JAK 2 gene, though all have an activated JAK signaling pathway. Ruxolitinib is a JAK inhibitor and is active for patients regardless of whether or not they have a JAK2 mutation.

The COMFORT II trial studied the effectiveness, safety and tolerability of ruxolitinib compared to best available therapy (BAT) in adults with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF). In the study, 219 patients with intermediate or high-risk disease were randomized to either ruxolitinib (146) or BAT (73), with a response endpoint of a 35 percent or greater reduction in spleen size. After 48 weeks, 28.5 percent of patients receiving the drug achieved this reduction compared to 0 percent with BAT. At 24 weeks, the response rate was 31.9 percent for ruxolitinib versus 0 percent for BAT.

According to the authors, ruxolitinib had an adverse event profile similar to earlier studies. Adverse events including anemia and thrombocytopenia caused 8.2 percent of patients who received ruxolitinib to halt treatment, while 5.5 percent of those given BAT stopped therapy. There was one death that may have been related to ruxolitinib treatment.

Several research questions remain, including how ruxolitinib may be used with other treatments such as thalidomide, bone marrow transplantation or more novel agents, and whether ruxolitinib improves overall survival. Several such studies are in progress.

The trials were funded by Incyte.

ASCO2011特集

抗体製剤はALLに対し有効である（Abstract No. 6507）

Phase IIスタディにおいて難治性または再発性急性リンパ性白血病に対して61%の奏効率が認められた

Phase II study shows 61 percent response rate for patients with resistant or recurrent acute lymphoblastic leukemia

急性リンパ性白血病（ALL）細胞を選択的に破壊する化学療法薬となりうる薬剤と結合した抗体が、46人の患者の61%において疾患を根絶または著明に軽減させたとのPhase IIスタディの結果が2011年ASCOで発表された。CMC-544としても知られるこの薬剤は、90%以上のALL細胞の表面に認められた蛋白CD22を標的とする抗体および細胞毒性薬あるcalicheamicinと結合する。この薬剤がひとたびCD22に結合すると、ALL細胞はこれを内部に引き込み死滅する。今回のトライアルに組み入れられたのは、他の治療に抵抗性であるかまたは再発したALL患者であった。奏効性を評価された46人中9人が完全寛解し、14人は血小板数が完全に回復はしないが完全寛解し、5人は血球数の回復は認めないが骨髄中の芽球が5%未満となった。奏効が得られた患者のうち16人はその後、ドナーによる造血幹細胞移植を受けた。筆者らは、他の化学療法薬との併用に加え3週ごとの投与から毎週投与への移行に関して調査すべきであると提案している。

Full Text

An antibody packaged with a potent chemotherapy drug to selectively destroy acute lymphoblastic leukemia (ALL) cells eradicated or greatly reduced the disease for 61 percent of 46 patients in a phase II study. It was presented at the 47th annual meeting of the American Society of Clinical Oncology.

Patients enrolled in the trial led by investigators at The University of Texas MD Anderson Cancer Center had ALL that resisted other therapies or recurred after treatment.

"A response rate of more than 50 percent in this patient population probably makes inotuzumab ozogamicin the most active single-agent therapy ever for ALL," said Hagop Kantarjian, M.D., professor and chair of MD Anderson's Department of Leukemia and study senior investigator.

The drug, also known as CMC-544, links an antibody that targets CD22, a protein found on the surface of more than 90 percent of ALL cells, and the cytotoxic agent calicheamicin. Once the drug connects to CD22, the ALL cell draws it inside and dies.

Response rate for other second options is 20-30 percent

Kantarjian said second-line chemotherapy combinations used for ALL typically have a complete response rate of 20-30 percent. The monoclonal antibody-based drug developed by Pfizer, Inc., also is the first of its type for ALL.

The drug is safe, said Elias Jabbour, M.D., assistant professor in MD Anderson's Department of Leukemia, presented the study results at ASCO. Almost all side effects were of low grade (1-2) and manageable. Drug-induced fever was the most common side effect, reaching higher grades in nine of 48 patients.

Out of 46 patients evaluable for response, nine had a complete response, 14 had complete response without full recovery of platelets, and 5 had less than 5 percent blasts in their bone marrow without blood count recovery.

Sixteen responders subsequently received a donor blood stem cell transplant, Jabbour noted.

Combining inotuzumab with other chemotherapy might further improve ALL treatment, Jabbour said. MD Anderson has a phase II clinical trial under way following inotuzumab treatment with another monoclonal antibody drug, rituximab, currently used in some types of non-Hodgkin's lymphoma.

Rituximab targets the CD20 surface protein, which occurs in 50 percent of ALL cells.

In addition to combinations, the authors suggest that a shift from dosing every three weeks to weekly should be explored.

The clinical trial was funded by a grant from Pfizer.

Co-investigators with Jabbour and Kantarjian are Susan O'Brien, M.D., Deborah Thomas, M.D., Farhad Ravandi, M.D., Sergemne York, Monica Kwari, Stefan Faderl, M.D., Tapan Kadia, M.D., Guillermo Garcia-Manero, M.D., and Jorge Cortes, M.D., of MD Anderson's Department of Leukemia; Christopher Wilson and Robert Tarnai, of PPD, Inc.; and Anjali S. Advani, M.D., of the Cleveland Clinic Taussig Cancer Institute.

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