中年期のフィットネスはその後の人生におけるがんを予防する（Abstract＃1520）

中年男性の心肺フィットネスはその後の人生におけるがん発症およびがん死を予防する

Men's cardiopulmonary fitness in middle age protects against developing and dying from cancer later in life

第49回ASCO年次集会で、17,000人余りの男性を対象とした20年間の追跡調査の結果から、中年男性の心肺フィットネスはその後の人生における肺がんおよび大腸がんの発症やがん死亡を予防することが分かった。スタディでは、専門的な予防検診の一部として単回の心血管フィットネス評価を施行された男性17,049人（平均年齢50歳）を対象とした。参加者は彼らの心肺フィットネス度の成績に従って、5分位に分類された。追跡期間中央値20～25年の間に、2,332人が前立腺がん、276人が大腸がん、277人が肺がんと診断された。がんによる死亡は347例であり、心血管疾患死は159例であった。肺がんまたは大腸がんと診断されるリスクは、最もフィットネス度の高い男性において最もフィットネス度の低い男性に比べ、それぞれ68%および38%低いことが示された。フィットネス度は前立腺がんリスクには影響しなかった。フィットネス度が少し改善するだけでも生存率には有意な差があった－がんによる死亡および心血管疾患のリスクがそれぞれ14%および23%低下した。心肺フィットネス度が低いと、肥満がなくてもリスクが高かった。

Full Text

Findings from a large, prospective 20-year study to be presented on June 2 at ASCO's 49th Annual Meeting indicate that a high level of cardiovascular fitness in middle age reduces men's risk of developing and dying from lung and colorectal cancer, two of the most common cancers affecting men. Better fitness also reduces the risk of dying from, though not developing, prostate cancer.

"While poor fitness is already known to predict future cardiovascular disease, this is the first study to explore fitness as a marker of future cancer risk prognosis," said lead study author Susan Lakoski, M.D., assistant professor of medicine at the University of Vermont. "This finding makes it clear that patients should be advised that they need to achieve a certain fitness level, and not just be told that they need to exercise. And unlike exercise behavior, which relies on patient self-reporting, fitness can be objectively and accurately measured in a clinical setting."

The study included 17,049 men who had a single cardiovascular fitness assessment as part of a specialized preventive health check-up visit at a mean age of 50 years offered at the Cooper Institute. The fitness test, which is similar to a stress test for heart disease risk, entailed walking on treadmill under a regimen of changing speed and elevation. The men's performance was recorded in established units of fitness called metabolic equivalents or METs. Study participants were divided into five quintiles according to their fitness performance.

Researchers subsequently analyzed Medicare claims data to identify the participants of this study who had developed lung, colorectal, or prostate cancer – the three most common types of cancer among U.S. men. Over a median follow-up period of 20-25 years, 2,332 men were diagnosed with prostate cancer, 276 were diagnosed with colorectal cancer, and 277 were diagnosed with lung cancer. There were 347 deaths due to cancer and 159 men died of cardiovascular disease.

Researchers found that the risk of being diagnosed with lung or colorectal cancer was reduced by 68 and 38 percent, respectively, in men who were the most fit, relative to those who were the least fit. Fitness did not significantly impact prostate cancer risk. In the analysis, data were adjusted for smoking and other factors, such as body mass index and age.

Among the men who developed cancer, those who were more fit at middle age had a lower risk of dying from all the three cancers studied, as well as cardiovascular disease. Even a small improvement in fitness (by 1MET) made a significant difference in survival ─ reducing the risks of dying from cancer and cardiovascular disease by 14 and 23 percent, respectively.

Another interesting finding was that men who had low fitness had an increased risk of cancer and cardiovascular disease even if they were not obese. This suggests that patients should focus on improving their fitness, regardless of their body weight. Adequate fitness level depends on gender and age. In this study, men who fell in the lowest quintile for fitness achieved less than 13.5 minutes during the treadmill exercise test if they were 40-49 years old, less than 11 minutes if they were 50-59, and less than 7.5 minutes if they were 60 or older.

ASCO Perspective: "This important study establishes cardiorespiratory fitness as an independent and strong predictor of cancer risk and prognosis in men. While more research is needed to determine if similar trends are valid in relation to other cancers and among women, these results indicate that people can reduce their risk of cancer with relatively small lifestyle changes," said ASCO President Sandra M. Swain, M.D., FACP.

This research was supported by the National Cancer Institute

ASCO2013特集

新たな免疫療法は多くの進行がんにおいて有効である（Abstract＃3000）

進行したメラノーマ、肺、腎、大腸および胃がんに対する抗PD-L1抗体薬の抗がん作用は有望である

Anti-PD-L1 drug shows promising anti-cancer effects in advanced melanoma, lung, kidney, colorectal and stomach cancers

第49回ASCO年次集会で発表されるPD-L1標的抗体MPDL3280Aの第I相試験の結果、進行メラノーマおよび非小細胞肺がん、腎細胞がん、大腸がんおよび胃がんの患者の21%における腫瘍が縮小したことが分かった。全体で140人中29人（21%）の患者において腫瘍が有意に縮小し、また治療奏効数が最も高かったのは肺がんおよびメラノーマの患者であった。3～15か月の治療に参加中の29人中26人において、治療は現在も奏効を維持している。この新薬は安全であり効果は持続性で、ほぼ全てが奏効を維持している。何人かの患者では治療開始後数日以内に腫瘍の縮小を認めた。重要なことに、多くの患者が酸素吸入を必要としなくなったり疼痛コントロールのための麻薬性鎮痛薬の必要が減ったりという、がんに関連した症状の改善を報告した。このスタディはさらに広範囲の固形がんおよび血液がんに範囲を拡大し、現在275人を超える患者が組み入れられている。これらの早期データは有望であるが、この結果を確認するには無作為化試験が必要である。

Full Text

A phase I expansion study of the investigational drug MPDL3280A – an engineered PD-L1 targeted antibody – shows impressive tumor shrinkage rates in patients with several different cancers – including lung, melanoma, kidney, colorectal and gastric cancers – that had progressed despite several prior treatments. The research will be presented on June 3 at ASCO's 49th Annual Meeting.

The new drug was safe and produced durable responses, with nearly all responses still ongoing. Several patients experienced tumor shrinkage within days of starting treatment. Importantly, many patients reported improvement in their cancer-related symptoms, such as no longer requiring oxygen supplementation or decreased need for narcotics to control pain.

PD-L1 is a protein frequently overexpressed on the surface of cancer cells that acts as a disguise, allowing cancer cells to hide from the immune system. When MPDL3280A attaches to the PD-L1 protein, the cancer can no longer hide from the patient's immune system, allowing the body's T-cells to fight the cancer. MPDL3280A was specifically engineered for enhanced safety and efficacy compared to earlier PD-L1 or PD-1 targeted agents.

"We are impressed with the frequency and duration of the responses in these patients with very difficult-to-treat tumors. So far, almost none of the patients that have had tumor shrinkage have progressed," said Roy S. Herbst, M.D., Ph.D., Ensign professor of medicine at Yale Cancer Center and Chief of Medical Oncology at Smilow Cancer Hospital at Yale-New Haven. "This drug is part of an exciting new generation of drugs that unlock the power of the immune system to attack the cancer."

Efficacy was evaluated in 140 patients with locally advanced or metastatic solid tumors whose disease had progressed despite prior therapies. Tumor shrinkage was observed in patients with non-small cell lung cancer, melanoma, renal cell carcinoma, colorectal cancer, and gastric cancer.

Overall, 29 out of 140 (21 percent) patients experienced significant tumor shrinkage and the highest number of therapy responses occurred in patients with lung cancer and melanoma. Therapy responses are still ongoing, with 26 out of 29 responders continuing to respond (time on study of responders 3-15+ months).

It is not yet clear how PD-L1 expression affects response to MPDL3280A. Using an investigational diagnostic test, researchers analyzed archived tumor tissue from 103 patients and found that tumor shrinkage occurred in 36 percent of patients with PD-L1 positive tumors and, surprisingly, also in 13 percent of patients with PD-L1 negative tumors. The diagnostic test for PD-L1 is still evolving, so currently a negative result on the PD-L1 test could simply mean that tumors have less PD-L1 than the test currently detects.

This study has been expanded to include a larger range of solid tumors and blood cancers, with more than 275 patients currently enrolled. While these early data are encouraging, a randomized trial is needed to confirm the findings. A number of phase II and phase III studies are already planned to confirm the drug's anti-cancer activity and further validate the utility of the PD-L1 diagnostic test. Researchers are also looking at ways it could be combined with other anti-cancer therapies to further boost responses over current standard treatments.

ASCO Perspective: "The fact that this drug was active in such a variety of tumors suggests that PD-L1 is part of a universally or generally important immune mechanism. Over the next few years, drugs that target and help activate and direct the immune system will likely take on a growing role in patient care, and it's particularly exciting to see strong effects in patients whose cancer has progressed despite all other standard therapies," said ASCO President-Elect Clifford A. Hudis, MD.

This study was supported by Genentech, Inc.

Dr. Herbst is the recipient of a 1997 Conquer Cancer Foundation of ASCO Young Investigator Award and 1999 Career Development Award.

ASCO2013特集

進行肺がんに対して低線量放射線療法は高線量よりも優れている（Abstract＃7501）

Stage III非小細胞肺がん患者に対する標準線量の放射線療法は高線量よりもより安全で有効である

Standard-dose radiation is safer and more effective than high-dose for patients with stage III non-small cell lung cancer

第49回ASCO年次集会で発表された第III相試験の結果、stage III非小細胞肺がん患者に対する標準線量（SD:60 Gy）の放射線療法は高線量（HD:74 Gy）よりも治療の有効性および生存期間両者の観点から優れていることが示された。研究者らは464人の患者を標準的な化学療法（パクリタキセルとカルボプラチン）にSDまたはHDによる放射線治療を併用する群に無作為に割り付けた。生存期間中央値はSD放射線療法を施行された患者においてHD放射線療法群患者よりもはるかに長く（28.7か月対19.5か月）、推定18か月全生存率もたSD群で高かった（66.9%対53.9%）。18か月時点でのがん再発率はHD群においてSDと比較し高かった（局所再発率34.3%対25.1%、遠隔再発率44%対35.3%）。ほとんどの患者の主要死因は肺がんであったが、治療関連死数はHD群（10）でSD群（2）よりも著明に多かった。この患者集団におけるHD治療は第I相や第II相臨床試験では有望に思えたが、今回のスタディではそうではないことを明確に示している。

Full Text

A phase III trial in patients with stage III non-small cell lung cancer (NSCLC) concludes that standard dose (SD) radiotherapy (60 Gy) is safer and more effective than high-dose (HD) radiotherapy (74 Gy), extending survival by nine months and causing fewer treatment related deaths. While 60 Gy is already standard, many doctors use higher doses expecting better outcomes. These findings should put an end to higher-dose treatment, given better outcomes in the standard dose arm.

Although HD therapy in this patient population appeared promising in earlier phase I and phase II clinical trials, this study clearly shows that it is associated with dramatically shorter survival.

"We expected at the outset that high-dose radiation therapy would lead to better outcomes. We were surprised, though also pleased, to discover that less intense treatment led to better control of cancer progression and spread, and even improved overall survival," said lead author Jeffrey D. Bradley, M.D., a professor of radiation oncology at the Washington University School of Medicine in St. Louis, Missouri, USA. "The biological reasons for failure of the high dose with respect to overall survival and local-regional control are not readily apparent."

In the study, 464 patients were randomly assigned to treatment with SD or HD radiation therapy along with standard chemotherapy (paclitaxel and carboplatin). In each treatment arm, the patients were also randomly assigned to receive cetuximab or no additional therapy. Data on the effects of cetuximab on survival will be reported at a later date. The HD arm was closed after an interim analysis showed it was not superior to the SD arm.

The median survival for patients who received SD radiation therapy was much longer compared to that in patients who received HD radiation therapy (28.7 months vs. 19.5 months) and the estimated 18-month overall survival rates were also higher for the SD arm (66.9 percent vs. 53.9 percent). Cancer recurrence rates at 18 months were higher in the HD group of patients compared with the SD group (local recurrence rates were 34.3 percent vs. 25.1 percent, and distant recurrence rates were 44 percent vs. 35.3 percent). While the primary cause of death for most patients was lung cancer, there were a notably higher number of treatment-related deaths in the HD arm (10), compared to the SD arm (2).

"This is a critical study in the field of radiation oncology. After a decade of research, we can finally close the chapter on high-dose vs. standard-dose therapy debate in lung cancer therapy, using evidence-based data to improve care for our patients," said ASCO President Sandra M. Swain, M.D., FACP.

The study was presented at ASCO's 49th Annual Meeting.

This research was supported by the National Cancer Institute and Eli Lilly and Company.

ASCO2013特集

精巣摘出術後はサーベイランスで十分である（Abstract # 4502）

Stage Iセミノーマの男性に対する術後化学療法または放射線療法の追加は不要である

Additional chemotherapy or radiation therapy not needed following surgery for men with stage I seminoma

一般的な精巣がんであるセミノーマのstage I男性に関する長期スタディの結果、がんに対する手術が成功した男性のほとんどにおいては、化学療法または放射線療法の追加よりむしろがん再発のサーベイランスで十分であることが示唆された。サーベイランスには5年間の定期的な診察、胸部X線検査、CTスキャンおよび血液検査が課せられた。デンマークにおける国内臨床データベースを用いて研究者らは、5年間のサーベイランスプログラムで追跡されたstage Iセミノーマ患者1,822人を同定した。患者の記録と国内登録とを関連付けることにより、患者を期間中央値15.4年間追跡することができた。全ての患者が原発がんを治療するために初回手術を受けた。全体で1,822人中355人（19.5%）が再発し、放射線療法（216人）、化学療法（136人）または手術（3人）による治療を受けた。10年がん特異的生存率は99.6%であった。腫瘍サイズが1.5インチを超えていること、血液またはリンパ管への拡散、および血液マーカーであるヒト絨毛性ゴナドトロピン上昇が再発リスクを増加させた。これらの因子は過去の小規模スタディにおいて高リスク患者と関連していた。このスタディは第49回ASCO年次集会で発表された。

Full Text

A long-term study of men with stage I seminoma, a common form of testicular cancer, suggests that surveillance for cancer recurrence, rather than additional chemotherapy or radiation therapy, is sufficient for the vast majority of men who have undergone successful surgery for their cancer. Researchers found that 99.6 percent of patients who underwent surveillance only were alive 10 years after their initial diagnosis.

Surveillance entails five years of scheduled physical exams, chest X-ray exams, CT scans and blood tests. In Denmark, where this study was conducted, surveillance is the follow-up strategy of choice. Avoiding additional treatments spares patients of associated harmful side effects, such as a potential risk of secondary cancers, including gastrointestinal cancers and leukemia, following radiotherapy.

"To our knowledge, this study is the largest to address this issue in patients with stage I seminoma, and with the longest follow-up. Now we have solid proof that surveillance is safe and appropriate for most patients with this particular cancer," said Mette Saksø Mortensen, M.D., a Ph.D. student at the Department of oncology at the Copenhagen University Hospital in Copenhagen, Denmark. "We also characterized key prognostic factors for relapse, which can help us identify "high-risk" patients who may need adjuvant therapy instead of surveillance. However, in general, seminoma stage I patients can safely be followed on a surveillance program."

Using a nationwide clinical database, researchers identified 1,822 patients with stage I seminoma followed on a five-year surveillance program in Denmark. By linking the patient files with national registries they were able to follow the patients for a median period of 15.4 years. All patients had initial surgery to treat their primary cancer. Overall, 355 of 1,822 patients (19.5 percent) experienced a relapse, which was treated with radiotherapy (216 patients), chemotherapy (136 patients) or surgery (3 patients). The 10-year cancer-specific survival was 99.6 percent. This rate means that for every 1,000 men followed on a surveillance program, only four die within 10 years.

Researchers found that tumor size larger than 1.5 inches, spread to blood or lymphatic vessels, and elevated levels of a blood marker called human chorionic gonadotropin increased the risk of relapse. These factors had been associated with high-risk patients in prior, smaller studies.

Seminoma accounts for about half of testicular cancer cases. Testicular cancer is rare in the general population, but it is the most common solid tumor among young men. The typical initial treatment for the disease is orchiectomy.

"This important study is one of several recent reminders that sometimes "less is more" in patient care. Opting for surveillance spares patients, most of whom are young men, from the harmful side effects of chemotherapy and radiation without diminishing their chances for a long and healthy life," said ASCO President-Elect Clifford A. Hudis, M.D..

This research was supported in part by The Danish Cancer Society, The Danish Cancer Research Foundation and the Preben and Anna Simonsen Foundation.

ASCO2013特集

より長期のタモキシフェン療法により乳がん再発リスクが低下する（Abstract＃5）

aTTomスタディ: ER陽性乳がん再発および死亡に関して10年間のタモキシフェン療法は5年間の治療よりも優れている

aTTom study: Ten years of tamoxifen is superior to five in reducing ER-positive breast cancer recurrence and death

第49回American Society of Clinical Oncology年次集会で発表された英国aTTomスタディの結果、ER陽性（ER+）乳がん女性において10年間のタモキシフェンを用いた術後補助療法は、現在の標準的な5年のみのタモキシフェン治療に比べ乳がん遅発性再発および死亡の予防効果が高いことが報告された。タモキシフェンを5年間内服した英国女性（6,953人）がさらに5年間のタモキシフェン治療を継続する群または即中止する群に無作為に割り付けられた。無作為化後10年以上（一部の女性は20年もの長期間）追跡された女性5,000人において、乳がん再発は10年間療法群において5年間療法群よりも少なかった（16.7%対19.3%）。診断後5～9年間の再発率および死亡率は治療群間で差がほとんどなかった。しかしその後（つまり診断10年後以降）、タモキシフェン治療継続群は5年で治療を中止した群に比べ、再発率が25%低く乳がん死亡率が23%低かった。これらの結果は、最近雑誌に掲載された国際スタディATLASを補足し確証するものである。

Full Text

A randomized phase III study presented at the 49th Annual Meeting of the American Society of Clinical Oncology reports that ten years of adjuvant treatment with tamoxifen provides women with estrogen-receptor-positive (ER+) breast cancer greater protection against late recurrence and death from breast cancer than does the current standard of only five years of tamoxifen, according to the British aTTom study. While side effects are also increased with longer tamoxifen use, the researchers conclude that the overall benefits greatly outweigh the risk of continuing therapy. The findings from aTTom, a Phase III randomized study, complement and confirm the results of the recently published international study, ATLAS.

Hundreds of thousands of women worldwide take tamoxifen to prevent cancer recurrence after surgery for early-stage breast cancer. Tamoxifen is only effective in women with hormone-sensitive (ER-positive) tumors and most women start taking tamoxifen immediately after completing their initial surgery or chemotherapy.

Prior studies have shown that 5 years of tamoxifen reduces breast cancer death rates by about a third over a 15-year period following diagnosis. This study shows that 10 years of tamoxifen reduces breast cancer recurrence and death rates by an additional 25 percent, from year 10 onwards, compared to 5 years of tamoxifen therapy. The researchers estimate that, compared to taking no tamoxifen, 10 years of tamoxifen reduces breast cancer death rate by a third in the first 10 years after diagnosis and by half subsequently.

"Five years of adjuvant tamoxifen is already an excellent treatment but we thought that longer treatment might be even better because women with ER-positive breast cancer can have recurrences long after treatment is completed. Until now, though, there have been doubts whether continuing tamoxifen beyond five years is worthwhile," said lead study author Richard G. Gray, M.A., MSc., a professor of medical statistics at the University of Oxford in Oxford, United Kingdom. "This study and its international counterpart ATLAS confirm that there is definitely a survival benefit from longer tamoxifen treatment and many doctors will likely recommend continuing tamoxifen for an extra five years."

Between 1991 and 2005, 6,953 women in the United Kingdom who had been taking tamoxifen for 5 years were randomly assigned to continue treatment with tamoxifen for another 5 years or to stop immediately. The women were contacted yearly to assess treatment compliance, recurrence, hospital admissions and death rates. Compliance was good with about 75 percent of women in the 10-year group continuing to take tamoxifen.

With 5,000 women followed for more than 10 years after randomization, and some as long as 20 years, fewer breast cancer recurrences were seen in the 10-year tamoxifen group than in the 5-year group (16.7 percent vs. 19.3 percent). Longer treatment also reduced the risk of dying from breast cancer. The treatment allocation had little effect on either recurrence rates or death rates during the period 5-9 years after diagnosis. After that, however (i.e., during the second decade after diagnosis), the women who had been allocated to continue tamoxifen treatment had a 25 percent lower recurrence rate and a 23 percent lower breast cancer mortality rate than the women who had been allocated to stop after only 5 years.

"This landmark trial confirms recent findings of the ATLAS trial showing that extending therapy with tamoxifen to 10 years significantly lowers breast cancer recurrences and mortality. These results are therefore practice changing for premenopausal women with hormone receptor positive breast cancer and especially relevant for women who are at high risk of recurrence," said Sylvia Adams, M.D., ASCO spokesperson and breast cancer expert.

Women taking tamoxifen can experience side effects similar to menopausal symptoms, such as night sweats and hot flashes. Rare but serious side effects of tamoxifen include increased risk of endometrial cancer, blood clots and stroke. No excess incidence of stroke was observed with 10 years of tamoxifen therapy, though endometrial cancer risk was higher in this arm. Endometrial cancer is often detected early, when it is usually curable; the researchers estimated that for every endometrial cancer death that occurs as a side effect of long-term tamoxifen, there would be 30 deaths from breast cancer prevented. Therefore, the benefits of continuing tamoxifen to 10 years greatly outweigh the risks, said Professor Gray.

Researchers are planning to follow women in this and the ATLAS study for at least five more years to see if there is additional long-term benefit. A retrospective analysis of combined data from aTTom, ATLAS and three smaller trials will be conducted to determine if there are subgroups of women that benefit the most from longer tamoxifen treatment. Ongoing clinical trials are comparing 5-year and 10-year use of aromatase inhibitors to see if longer use leads to more benefit as has been seen with tamoxifen.

This research was supported in part by Cancer Research UK and the UK Medical Research Council.

ASCO2013特集

酢を用いた隔年の子宮頸がんスクリーニングは死亡率を低下させる（Abstract＃2）

有効で手軽な価格の子宮頸がんスクリーニング法が低所得国の何千人もの女性の命を救うことが期待される

Effective, affordable cervical cancer screening strategy promises to save thousands of women's lives in low-income countries

第49回American Society of Clinical Oncology年次集会で発表された大規模無作為化トライアルの結果、訓練されたプライマリヘルスケア職員が行う酢酸（VIA、つまり酢）を用いた目視検査による隔年スクリーニングが有効であり大規模な実施が可能であることが示された。がんの既往のないインドの女性（35～64歳）がVIAを用いた隔年スクリーニング（75,360人）またはスクリーニングなし（76,178人）に無作為に割り付けられた。コントロール群は組み入れ時に一通りのがん教育を受け、スタディ期間中に子宮頸がんの徴候や症状が何かあれば報告するように指示された。スクリーニング群は4回のVIAスクリーニングと24か月間隔のがん教育を受けた。浸潤性子宮頸がんの発生率は両群間で差はなく（スクリーニング群100,000人当たり26.7人、コントロール群100,000人当たり27.5人）、スクリーニングにより過剰診断に結びつくことはないことが示唆された。VIAを用いたスクリーニングにより、子宮頸がん特異的死亡率が31%低下した（100,000人当たりそれぞれ11.1人および16.2人）。このスクリーニング法により、インドにおいて毎年22,000件の子宮頸がん死を防ぐことができ、世界中の資源の乏しい国では73,000件近いであろう、と研究者らは推定している。

Full Text

A large, randomized study conducted among 150,000 women in India over a period of 15 years reports that biennial visual inspection with acetic acid (VIA), or vinegar, delivered by primary health workers, reduced cervical cancer mortality by nearly one-third (31 percent). The study was presented at a plenary session of the 49th Annual Meeting of the American Society of Clinical Oncology Cervical cancer is the leading cause of cancer death among women in many developing countries, where there is little or no access to Pap screening. The researchers estimate this strategy could prevent 22,000 cervical cancer deaths every year in India and close to 73,000 in resource-poor countries worldwide.

"We hope our results will have a profound effect in reducing the burden of cervical cancer in India and around the world," said lead study author Surendra Srinivas Shastri, M.D., a professor of preventive oncology at Tata Memorial Hospital in Mumbai, India. "This is the first trial to identify a cervical cancer screening strategy that reduces mortality and is feasible to implement on a broad scale throughout India and in other developing countries. Our trial used primary healthcare workers who can easily access women in the community, which is critical in India and other countries that lack sufficient nurses, physicians, and laboratory facilities. We are already working with state and national health authorities in India to make this screening strategy and health education available to women throughout the country."

In this study, women aged 35-64 years with no prior history of cancer were randomly assigned to biennial screening with VIA (75,360 women) or no screening (76,178 women), which is the current standard of care in India given that the infrastructure does not allow for country-wide Pap screening. According to the authors, in accordance with international standards for clinical research – including cancer screening trials – interventions are tested against the local standard of care. The control group received one round of cancer education, at enrollment. Women in the control group were asked to report to the primary health workers any signs or symptoms of cervical cancer that they noticed on the basis of what they had learnt during the initial cancer education sessions. The health workers then directed them to the Tata Memorial Hospital (where they received diagnosis and treatment at no cost) or to other nearby facilities of their choice. The screening group received four rounds of VIA screening and cancer education at 24-month intervals between 1998 and 2010. All trial participants were offered free cervical cancer treatment, if diagnosed.

The incidence of invasive cervical cancer was comparable in the two groups, (26.7 per 100,000 in the screening group and 27.5 per 100,000 in the control group), suggesting that screening did not lead to overdiagnosis. Screening with VIA resulted in a 31 percent reduction in cervical cancer-specific death rates (11.1 and 16.2 per 100,000, respectively). There was also a seven percent reduction in the overall death rate, because cancer was often diagnosed at an earlier stage in the screening group, although the difference in the overall death rate was not statistically significant.

According to the authors, based on the results of their study, Indian health officials in Maharashtra state, where the trial was conducted, are preparing to train primary health care workers to provide VIA screening to all women aged 35-64 years in the state – including women who participated in the study – at the same 24 month interval as was explored in the trial. In addition, the authors stated that the Indian government is working to implement VIA screening country-wide and has plans to reach out to other low to moderate income countries to inform them of these results and offer training resources.

In high income countries, screening for pre-cancerous and cancerous cells using Pap smears has reduced cervical cancer incidence and deaths by 80 percent. In India, however, large-scale Pap smear screening or HPV DNA testing is not currently possible due to lack of resources, laboratory infrastructure, and medical professionals. In this clinical trial, VIA was performed by primary health workers – community-based, non-medical personnel who received special training and provide basic health care services in areas where physicians and nurses are unavailable.

In 1996, around the time this study was initiated, the Indian Council of Medical Research estimated that, even if the number of existing Pap smear facilities in India were multiplied 12 times, they would only be able to provide a single round of screening to 25 percent of eligible women in 10 years. In 2006, the Government of India constituted a committee with assistance from World Health Organization to develop guidelines for population wide cervical cancer screening in India. This committee again observed that Pap smear based cervical screening was not feasible in India except at a few centers. Given that cervical cancer is the leading cause of cancer death in women in India, a strategy implementing early detection and treatment of the disease could have a profound impact on the state of women's health in the world's second largest country.

Previous studies have suggested VIA is a reasonable alternative to Pap smears or HPV DNA testing for its low cost and ease of use. The VIA test is performed by applying vinegar to the cervix using a cotton swab. After 60 seconds, the cervix is examined with the naked eye using a lamp. Pre-cancerous tissue turns white when vinegar is applied, whereas healthy tissue does not change color. The results are known immediately, a very important advantage in rural areas where women might otherwise have to travel for hours to see a doctor.

Two randomized population-based clinical trials of VIA screening were conducted in parallel with the present study in India but the strategies proposed in those studies are not implementable at the national level due to their requirement for trained nurses or sophisticated laboratory facilities. In the first study, a single round of VIA screening provided by trained nurses led to reduced cervical cancer mortality. The second study compared four cervical cancer prevention strategies: primary health workers delivering a single round of VIA screening, technicians delivering a single round of HPV DNA testing, technicians delivering a single round of Pap screening, and cancer education. That study found that a single round of HPV DNA testing reduced cervical cancer mortality, but a single round of VIA screening by primary health workers did not, nor did a single round of Pap testing.

The present study used primary health care workers, who are, according to Dr. Shastri, the only health professionals available to deliver VIA screening in remote and rural parts of India. The current trial thus addresses a critical gap in women's health in India and similar settings. The primary health workers that performed the screenings for this study were local women with at least 10th grade education and good communication skills. The workers received four weeks of intensive training at the beginning of the study, and one-week refresher courses every year.

The study was supported in part by the National Institutes of Health and Women's Cancer Initiative.

ASCO2013特集

進行子宮頸がんに対する初めての有効な生物学的治療（Abstract＃3）

化学療法にベバシズマブを併用することにより転移性または再発性子宮頸がんの女性の生存期間が改善する

Adding bevacizumab to chemotherapy improves survival for women with metastatic or relapsed cervical cancer

第49回American Society of Clinical Oncology年次集会で発表された第III相無作為化スタディの結果、標準的な化学療法にベバシズマブを併用することにより転移性または再発性子宮頸がんの女性の生存期間が改善したことが報告された。これらの患者集団において生物学的製剤が生存期間を有意に延長したのはこれが初めてである。今回の4群の臨床試験において、再発性転移性子宮頸がんの女性452人が従来通りの化学療法のみまたは化学療法にベバシズマブを併用する治療群に無作為に割り付けられた。検証された2つの化学療法レジメンは、シスプラチンとパクリタキセルの併用およびトポテカンとパクリタキセルの併用であった。これらの2つのレジメンを比較し、これらの患者群における標準的な化学療法であるシスプラチンよりもトポテカンがより有益であるかどうかを調べた。その結果、これら2つの化学療法群で生存期間に有意差はなかった。全体的に見て、ベバシズマブと化学療法を併用された患者の生存期間中央値は17.0か月であったのに対し化学療法のみを施行された患者では13.3か月であった。腫瘍縮小率はベバシズマブ投与群で高く（48%対36%）、奏効は長く持続した。さらに、ベバシズマブに関連した生存期間に関する有益性はQOL低下の代償として得られるものではなかった。

Full Text

A randomized phase III study presented at the 49th Annual Meeting of the American Society of Clinical Oncology reports that adding bevacizumab to standard chemotherapy improved survival for women with metastatic or relapsed cervical cancer. This is the first time a biologic drug has significantly prolonged survival in this setting. The study was performed by the Gynecologic Oncology Group.

Chemotherapy regimens are largely ineffective against advanced cervical cancer. Worldwide, cervical cancer takes 250,000 women's lives every year. This is the first study showing that a targeted drug that blocks blood vessel formation in the tumor can prolong survival for women with gynecologic cancers.

"Women with advanced cervical cancer don't have many options. We finally have a drug that helps women live longer," said lead study author Krishnansu Sujata Tewari, M.D., a professor of obstetrics and gynecology at the University of California Irvine in Orange, California. "This is also possibly a first step toward turning cervical cancer into a chronic disease, helping women live longer and allowing time for additional treatments that could further slow the cancer's progression and improve survival."

In this four-armed clinical trial, 452 women with recurrent of metastatic cervical cancer were randomly assigned to treatment with a chemotherapy regimen alone or a chemotherapy regimen plus bevacizumab. The two chemotherapy regimens tested were cisplatin plus paclitaxel and topotecan plus paclitaxel. Those two regimens were compared to determine if topotecan would be more beneficial than cisplatin, a standard chemotherapy option in this setting. There were no significant differences in survival between the two chemotherapy arms.

Overall, the median survival for patients who received bevacizumab plus chemotherapy was 17.0 months vs. 13.3 months for those who received only chemotherapy. Tumor shrinkage rates were higher in patients who received the bevacizumab (48 percent vs. 36 percent) and responses lasted longer. Analysis of quality of life data was also reported at the ASCO Annual Meeting. Generally, the results indicate that survival benefit associated with bevacizumab did not come at the cost of diminished quality of life.

"Treatment options for women with recurrent or advanced disease have been insufficient for far too long. This study clearly shows how our nation's investment in clinical cancer research pays off, offering the first ever treatment to extend the lives of women with aggressive cervical cancer," said Carol Aghajanian, M.D., ASCO spokesperson and gynecologic cancers expert.

Bevacizumab is currently approved by the FDA for use in several advanced cancers, but has not to date received approval in any gynecologic cancer.

This research was supported by the National Cancer Institute.

ASCO2013特集

血管新生阻害薬は卵巣がんの無病生存期間を延長する（Abstract # LBA5503）

進行卵巣がんを有する女性におけるパゾパニブを用いた維持療法は再発を遅延させる

Maintenance therapy with pazopanib delays relapse in women with advanced ovarian cancer

進行卵巣がん女性を対象とした第III相臨床試験の結果、初回の化学療法が奏効した後の経口分子標的薬パゾパニブによる治療はプラセボと比較し無病生存期間を平均5.6か月延長させたことが示された。パゾパニブは経口薬で、血管新生に関わるいくつかの標的を遮断する。今回のスタディにおいてstage III/IVの卵巣がん、卵管がん、および原発性腹膜がん患者をパゾパニブまたはプラセボを毎日24か月間内服する群に無作為に割り付けた。全ての患者はすでに手術を受け、5サイクル以上の化学療法が奏効し疾患の増悪が予防されていた。患者は平均24か月間追跡された。パゾパニブ群とプラセボ群における無増悪生存期間中央値は、それぞれ17.9か月および12.3か月であった。初回の手術および化学療法による治療が奏効したにもかかわらず、進行卵巣がん患者の70%が再発を経験し、半数は1年以内である。再発した際に、患者は強力な治療を受けなくてはならない。現時点で患者の再発リスクを予測する検査はなく、したがって今回のような維持療法が多くの患者において行われるであろう。このスタディ結果は第49回American Society of Clinical Oncology年次集会で発表された。

Full Text

A phase III clinical trial in women with advanced ovarian cancer finds that treatment with the oral targeted drug pazopanib following initial successful chemotherapy extends disease-free survival by an average of 5.6 months, compared to placebo. The study was presented at the American Society of Clinical Oncology's 2013 annual meeting.

Advanced ovarian cancer is an aggressive disease with a cure rate of only 20-25 percent. Despite successful initial treatment with surgery and chemotherapy, about 70 percent of patients with advanced ovarian cancer experience a relapse, half in the first year. Upon relapse, patients have to resume aggressive treatments. At this time, there is no test available to predict a patient's risk for relapse, so a maintenance therapy such as this one would be used for most patients.

"Our findings show that we finally have a drug that can maintain control over ovarian cancer growth achieved through initial treatments," said lead author Andreas du Bois, M.D., a professor of gynecologic oncology at Kliniken Essen Mitte in Essen, Germany. "If pazopanib is approved for ovarian cancer, many patients will experience longer disease-free and chemotherapy-free periods. During this time, the patient keeps control over the disease instead of the disease having control over patient's life."

Pazopanib is an oral drug that blocks several targets involved in angiogenesis. In the study, 940 patients with stage III/IV ovarian, fallopian tube, and primary peritoneal cancer were randomly assigned to receive pazopanib or placebo daily for 24 months. All patients had prior surgery and five or more rounds of chemotherapy that successfully prevented the disease from worsening. Patients were followed for 24 months, on average. The median progression-free survival time in the pazopanib and placebo group was 17.9 and 12.3 months, respectively.

"Relapses remain all too common for women with advanced ovarian cancer. This large trial shows us that targeting multiple molecular cancer drivers can have a substantial impact on this cancer's ability to grow, giving our patients significantly longer time before relapse. This study offers a real-world example of how the precision medicine era of cancer research is paying off in areas where no alternate approved drugs exist," said Carol Aghajanian, M.D., ASCO spokesperson and gynecologic cancers expert.

Ovarian cancer is the fifth leading cause of cancer death among women in developed countries. An immediate goal for this research is to combine pazopanib with other targeted drugs and personalize therapy according to patient and tumor characteristics.

This research was supported by GlaxoSmithKline.

ASCO2013特集

転移性メラノーマに対する有望な免疫療法の組み合わせ（Abstract＃CRA9007）

IpilimumabにGM-CSFを併用することにより転移性メラノーマ患者の生存率が改善する

Adding GM-CSF to ipilimumab significantly improves survival in patients with metastatic melanoma

第49回American Society of Clinical Oncology年次集会で発表された第Ⅱ相試験の結果、遺伝子組換え型顆粒球マクロファージコロニー刺激因子（GM-CSF, sargramostim）を高用量ipilimumabに併用することにより転移性メラノーマ患者の生存期間が延長することが示された。IpilimumabもGM-CSFも免疫系に働きかけることで作用する。Ipilimumabは免疫T細胞を不活化状態に維持する蛋白CTLA-4を標的とする。GM-CSFは一般的に化学療法または幹細胞移植後に白血球数を増加させるために使用される増殖因子である。今回のスタディでは過去に治療を多くて1回施行された転移性メラノーマ患者245人が、ipilimumabとGM-CSFの併用またはipilimumab（10mg/kgの用量）のみを投与される群に無作為に割り付けられた。腫瘍縮小率は両群で同等であった（11～14%）が、全生存期間は併用群で長かった：治療開始後1年の時点での生存率は併用群で68.9%であったのに対し、ipilimumab単独群では52.9%であった。死亡リスクは併用群でipilimumab単独群よりも35%低かった。さらに、併用療法の方がipilimumab単独治療よりも重篤な副作用が少なかった。

Full Text

A proof-of-principal phase II study shows that the recombinant granulocyte macrophage colony-stimulating factor (GM-CSF, sargramostim) added to an increased dose of the immunotherapy ipilimumab extends survival for patients with metastatic melanoma. More than two-thirds of patients were alive after one year of combination therapy vs. half of those treated with ipilimumab alone, a significant advance for metastatic melanoma. Interestingly, the combination also appears to be safer for patients than ipilimumab alone — GM-CSF decreased some of the serious side effects of ipilimumab.

Both ipilimumab and GM-CSF work by activating the immune system to fight cancer. Ipilimumab is a new treatment for advanced melanoma targeting CTLA-4, a protein that keeps immune T-cells in an inactive state. GM-CSF is a growth factor commonly used to boost white blood cell counts after chemotherapy or stem cell transplantation.

"This is the first randomized phase II study looking at the combination of ipilimumab and GM-CSF in any cancer," said lead author F. Stephen Hodi, M.D., an associate professor of medicine at Dana-Farber Cancer Institute in Boston, Massachusetts, USA and principal investigator for this ECOG-ACRIN clinical trial. "The results of the E1608 study provide another important sign that immunotherapy can have a big impact for patients with advanced melanoma. At the same time, we still need to clarify the best way to apply these findings in everyday practice."

In this study, 245 patients with metastatic melanoma who had undergone up to one prior treatment were assigned to receive ipilimumab plus GM-CSF or ipilimumab alone (at a dose of 10 mg/kg). The median follow up time was 13.3 months. Tumor shrinkage rates were comparable in both arms (11-14 percent) but the overall survival rate was longer in the combination treatment arm: one year after the start of therapy, 68.9 percent of patients who received the combination were alive, compared to 52.9 percent of patients who received ipilimumab alone. Patients who received the combination treatment had a 35 percent lower risk of dying compared with those that received ipilimumab alone.

In addition, the combination treatment was associated with fewer serious side effects compared to ipilimumab alone. The most significant differences were in lung and gastrointestinal toxicities. There were two possible treatment-related deaths in the combination arm vs. seven in the single-drug arm.

"This melanoma study builds upon the remarkable successes and advances we have seen for patients with advanced melanoma over the past two years," said Lynn Schuchter, M.D., ASCO spokesperson and melanoma expert.

The researchers noted that additional immune system boosters are being explored in early clinical trials, though the advantage of GM-CSF is that it improves both efficacy and safety of immunotherapy. The next step is to better define the role of GM-CSF in combination with other immune checkpoint targeting drugs, such as PD-1 and PD-L1.

This research was designed and conducted by the ECOG-ACRIN Cancer Research Group (formerly the Eastern Cooperative Oncology Group) and supported in part by the National Cancer Institute (Cancer Therapy Evaluation Program), Sanofi, and Bristol-Myers Squibb.

ASCO2013特集

2つの乳がん化学療法レジメンが比較された（Abstract # CRA1008）

2つの一般的な術後補助化学療法レジメンは有効性では同等であるが副作用では差があった

Two common adjuvant chemotherapy regimens have comparable efficacy but differ in side effects

第49回American Society of Clinical Oncology年次集会で発表された第III相試験の結果、外科手術を施行された高リスクの早期乳がんに対する週1回低用量パクリタキセル術後補助化学療法は、標準用量の2週間に1回のレジメンと有効性は同等であったが副作用はかなり少なかったことが報告された。リンパ節転移陽性またはリンパ節転移陰性高リスクで手術可能な患者が、まずドキソルビシンおよびシクロホスファミドの異なる3つのレジメンのうちの1つを受けその後にパクリタキセルを用いた2つの異なるレジメンのいずれかを無作為に施行された。パクリタキセルのレジメンは標準用量投与をpegfilgrastim（遺伝子組換え型顆粒球コロニー刺激因子）のサポートを用いながら12週間にわたり2週間に1回施行する群か、または毎週1回の低用量投与を12週間行う群のいずれかであった。推定5年無増悪生存期間は週1回と2週間に1回のパクリタキセル群とで同等であった（それぞれ82%および81%）。これらの2つの投与計画は副作用の種類および重症度の点で異なっていた：2週に1回の投与スケジュールでは週1回投与よりもアレルギー反応（1.4%対0.6%）、筋および骨痛（11%対3%）が多かった。神経毒性の頻度もまた2週に1回の群で多かった（17%対10%）。

Full Text

A phase III study presented at the American Society of Clinical Oncology 2013 annual meeting reports that a lower dose, weekly regimen of adjuvant paclitaxel chemotherapy for higher-risk, early-stage breast cancer who have undergone surgery was comparable to the standard dose, biweekly regimen, but caused substantially fewer side effects. These findings may lead to more doctors utilizing the weekly schedule and an improvement in patients' quality of life, and potentially, cost savings. These findings may lead to more doctors utilizing the weekly schedule, which could also result in cost savings, as the every two weeks regimen requires additional supportive care, including growth factors (e.g., pegfilgrastim) to boost white blood cell production.

Paclitaxel is a long-standing component of breast cancer treatment. The drug is typically given to patients either weekly or every two weeks, at a higher dose. Both approaches are widely used in practice but until this study, there has not been a formal comparison of their efficacies.

"Our results suggest that either regimen will give a good outcome, but the weekly schedule seems to result in better quality of life for patients, causing less muscle and bone pain and allergic reactions," said lead study author G. Thomas Budd, M.D., a medical oncologist at the Cleveland Clinic in Cleveland, Ohio. "The findings provide assurance that women can choose the lower-dose therapy without sacrificing their chances of survival."

In this trial, patients with node-positive or high-risk node-negative operable breast cancer first received treatment with one of three different regimens of doxorubicin and cyclophosphamide and then received one of two different regimens of paclitaxel, in a randomized fashion. The paclitaxel regimens studied were 1) a standard-dose treatment given every two weeks for 12 weeks with pegfilgrastim support, or 2) a low-dose weekly regimen for 12 weeks. The results of the doxorubicin and cyclophosphamide treatment were reported at ASCO in 2011, and the results of a comparison of the two ways of giving paclitaxel were reported at this year's meeting.

The estimated five-year progression-free survival rates for weekly and every two weeks paclitaxel were equivalent - 82 percent and 81 percent, respectively. The two schedules differed in the type and severity of side effects: the every two-week schedule was associated with higher frequency of allergic reactions (1.4 percent vs. 0.6 percent), and muscle and bone pain (11 percent vs. 3 percent), compared to the weekly schedule. The frequency of neurologic toxicity, a common side effect involving numbness, tingling and pain of the fingers and toes, was also higher in the every two week regimen (17 percent vs. 10 percent), but this difference may have been smaller had the patients received only four cycles of every two weeks therapy (as is current practice) rather than six. (Six cycles of every two weeks regimen was selected in this study so that patients in both arms would be on treatment for 12 weeks).

"The current trial demonstrates that weekly paclitaxel dosing and every two weeks dosing were equally effective in preventing breast cancer progression. However, weekly dosing caused less toxicity, and should ultimately be associated with lower cost due to less use of granulocyte colony stimulating factor. While some oncologists have already been using the weekly schedule for adjuvant therapy, these results will motivate many doctors, including myself, to use weekly dosing," said Andrew D. Seidman, M.D., ASCO spokesperson and breast cancer expert.

A longer follow-up of patients enrolled in this study is planned, in addition to several ancillary studies using participants' tumor samples. Those studies will explore genetic factors that predict the likelihood of toxic side effects in individual patients treated with paclitaxel and effects of diet and exercise on treatment efficacy and side effects.

This research was supported in part by the National Cancer Institute and Amgen, Inc.

ASCO2013特集

ソラフェニブは一部の進行の速い甲状腺がんの進行を抑制する（Abstract＃4）

DECISION:ソラフェニブはここ40年において治療抵抗性分化型甲状腺がんに対し有効であることが示された初めての薬剤である

DECISION: Sorafenib is first drug in four decades to be shown effective for treatment-resistant differentiated thyroid cancer

第49回American Society of Clinical Oncology年次集会で報告された第III相試験DECISIONの中間解析の結果、マルチターゲット阻害剤ソラフェニブは、標準的な放射性ヨード療法（RAI）に抵抗性の甲状腺分化がん患者の無増悪生存期間を延長することが示された。ソラフェニブは2つの別々の蛋白（Rafキナーゼおよび VEGF受容体キナーゼ）を阻害するマルチターゲット阻害剤である。このスタディにおいて、転移性、RAI抵抗性分化型甲状腺がん患者417人がソラフェニブまたはプラセボを投与される群に無作為に割り付けられた。患者は疾患が進行した際にはソラフェニブ群に切り替えることが許可されていた。無増悪生存期間中央値はソラフェニブ群で10.8か月であり、プラセボ群では5.8か月であった。30%以上の腫瘍縮小が認められたのはソラフェニブ群で12.2%、プラセボ群で0.5%であった。ソラフェニブ群ではさらに42%が6か月以上の病勢安定、病勢コントロール率は54%であったのに対し、プラセボ群の病勢コントロール率は34%であった。全生存期間のデータは完成していない。もし承認されれば、ソラフェニブは分化型甲状腺がんに対しこの40年で初めての新たな有効な薬剤となるであろう。

Full Text

A randomized phase III study, DECISION, finds that the targeted drug sorafenib stalls disease progression by five months in patients with metastatic differentiated thyroid cancer that has progressed despite standard radioactive iodine (RAI) therapy. If approved, sorafenib would become the first new active drug for this form of thyroid cancer in 40 years.

Differentiated thyroid cancer is the most common subtype of thyroid cancer, accounting for about 85 percent of the 60,000 thyroid cancer cases diagnosed each year in the United States. Although differentiated thyroid cancer generally has high cure rates following standard treatment – surgery and RAI– roughly 5-15 percent of patients develop RAI resistance. The only approved treatment for those patients, doxorubicin, is rarely used due to its low efficacy and high toxicity. This is the first time a kinase inhibitor has been assessed for this indication in a large clinical trial.

"After having no effective drugs for these patients for so many years, it is very exciting to find an oral drug that stops growth of the cancer for several months," said lead study author Marcia Brose, M.D., Ph.D., an assistant professor of otolaryngology and head and neck surgery in the Abramson Cancer Center and the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, Pa. "For these patients, a longer progression-free survival means more months without hospitalization and invasive procedures to control pain and other symptoms. This is the first time we have had a systemic treatment that can help."

In this study, 417 patients with metastatic, RAI-resistant differentiated thyroid cancer were randomly assigned to receive sorafenib or placebo. Patients were allowed to cross over to the sorafenib arm upon disease progression. The median progression-free survival was 10.8 months in the sorafenib group vs. 5.8 months in the placebo arm. Tumor shrinkage of 30 percent or more was observed in12.2 percent and 0.5 percent of patients in the sorafenib and placebo arms, respectively. An additional 42 percent of patients in the sorafenib arm had stable disease for 6 months or longer for a disease control rate of 54 percent, compared with a disease control rate of 34 percent in the placebo arm. Overall survival data are not yet mature.

"Few good options exist for patients with these more aggressive thyroid cancers, so these findings offer renewed hope and momentum for patients and researchers alike. Sorafenib provides meaningful activity for these patients, nearly doubling progression-free survival. Future studies will help identify which patients can benefit most from this therapy, and how other targeted therapies may further improve the outcome for these patients," said Gregory Masters, M.D., ASCO spokesperson and head and neck cancers expert.

Further analysis of data from this clinical trial is planned to find markers that would help identify patients that respond well to sorafenib and those that may need additional therapy. Unfortunately, the disease will eventually progress after sorafenib treatment in most patients. Additional treatment options still need to be developed for use as second-line agents and beyond.

Sorafenib is a multi-targeted drug that blocks two distinct proteins – Raf kinase and VEGF receptor kinase –which control tumor cell division and growth of tumor blood vessels, respectively. The drug is already approved in the U.S. for the treatment of advanced kidney cancer and inoperable liver cancer.

This research was supported in part by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals.

ASCO2013特集

大腸がんトライアルにおいてにセツキシマブはベバシズマブより優れていた（Abstract # LBA3506）

FIRE-3:転移性大腸がんに対するファーストライン治療としてセツキシマブはベバシズマブよりも優れている

FIRE-3: Cetuximab is superior to bevacizumab as first-line treatment for metastatic colorectal cancer

第49回American Society of Clinical Oncology年次集会で発表された第III相臨床試験FIRE-3の結果、セツキシマブとFOLFIRI化学療法（葉酸、フルオロウラシル、イリノテカン）併用によるファーストライン治療はベバシズマブとFOLFIRIの併用療法よりも生存期間を約4か月延長することが示された。これらの併用療法はいずれも、*KRAS*野生型の進行大腸がんに対し現在使用されているが、今回の新たな結果から、ファーストラインとしてFOLFIRIとの併用はセツキシマブの方が選択肢として優れていることが示唆された。今回のスタディにおいて、変異のない*KRAS*野生型の転移性大腸がん患者592人がファーストライン治療として、FOLFIRIとセツキシマブ併用またはFOLFIRIとベバシズマブ併用群に無作為に割り付けられた。全奏効率はFOLFIRIとセツキシマブ併用群で良好であったが、有意なレベルに到達したのは評価可能な患者においてのみであった。これらの患者（526人）は、ベースライン後に少なくとも1回は画像検査を施行されている必要があった。無増悪生存期間は2群間でほぼ同等であった（10.0対10.3か月）が、全生存期間はセツキシマブ群（28.7か月）においてベバシズマブ群（25.0か月）よりも明らかに長かった。FOLFOX（葉酸、5フルオロウラシル、オキサリプラチン）とベバシズマブ併用またはセツキシマブ併用の直接比較試験が現在行われている。

Full Text

The German phase III clinical trial FIRE-3 reports that first-line cetuximab plus FOLFIRI chemotherapy (folinic acid, fluorouracil, irinotecan) offers a roughly four-month survival advantage for patients with metastatic colorectal cancer, compared with bevacizumab plus FOLFIRI. The targeted drugs cetuximab and bevacizumab, both in combination with chemotherapy, are approved and commonly used as initial therapy but, until this study, it has been unclear which approach is better for patients with non-mutated forms of the KRAS gene. Findings from FIRE-3 were presented during the plenary session at the 49th Annual Meeting of the American Society of Clinical Oncology.

These findings suggest that first-line treatment with cetuximab in combination with FOLFIRI is superior, whereas bevacizumab could be reserved for second-line therapy.

"This degree of survival benefit was equivalent to the survival benefit seen in clinical trials that led to the approval of cetuximab and bevacizumab in this setting," said Volker Heinemann, M.D., Ph.D., a professor of medical oncology at the University of Munich in Munich, Germany. "We suspected that cetuximab would produce a better response, but we didn't know this would translate into better survival."

In the study, 592 patients with non-mutated (wild-type) KRAS metastatic colorectal cancer were randomly assigned to first-line therapy with FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab. Overall response rate favored FOLFIRI plus cetuximab, but reached the level of significance only in assessable patients. These patients (n=526) were required to have at least one imaging procedure after baseline. The median time to disease progression (progression-free survival) was nearly identical in the two arms (10.0 vs. 10.3 months), but the overall survival was markedly longer in the cetuximab arm (28.7 months) compared to the bevacizumab arm (25.0 months).

While FOLFIRI is standard chemotherapy for patients with metastatic colorectal cancer in Germany, in the United States, patients more commonly receive FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin). Both chemotherapy regimens have been found to be very effective in combination with cetuximab and bevacizumab in prior studies. A head-to-head comparison study of bevacizumab plus FOLFOX vs. cetuximab plus FOLFOX is ongoing.

"Patients confronting advanced colorectal cancer and their doctors are striving to extend lives. In the FIRE-3 trial initial therapy with FOLFIRI and cetuximab helped achieve that goal," said Richard M. Goldberg, M.D., ASCO spokesperson and gastrointestinal cancers expert. "The study prescribed the initial chemotherapy and in both groups tumors eventually grew at a similar pace. More research is needed to explain the overall survival benefit observed in this study, given the lack of improvement in progression- free survival."

Cetuximab targets the epidermal growth factor receptor (EGFR), blocking tumor growth. Prior studies have shown that mutations in KRAS undermine the activity of anti-EGFR treatments. Bevacizumab targets VEGF, which is involved in the growth of tumor blood vessels. It appears that KRAS mutation status does not affect responsiveness to bevacizumab. Researchers are also working on identifying molecular markers that predict response to bevacizumab vs. cetuximab.

This research was supported by Merck KGaA.

ASCO2013特集

新薬により肺がん生存期間が改善する（Abstract # CRA8007）

GALAXY-1:新たな画期的標的治療薬は進行肺腺がん患者の生存期間を改善する

GALAXY-1: First in class targeted drug improves survival for patients with advanced lung adenocarcinoma

第49回American Society of Clinical Oncology年次集会で発表された大規模第II相試験GALAXY-1の結果、初回治療後に進行した進行肺腺がん患者のセカンドライン治療において、新たな熱ショック蛋白質90（Hsp90）阻害薬ganetespibとドセタキセルの併用は、標準的なセカンドラインドセタキセル単独療法と比較し、全生存期間が延長することが示された。EGFRやALKなどの肺がんの増殖を促進する多くの蛋白質の形成にはHsp90を必要とする。今年のASCOで報告された252人の患者は、ドセタキセルとganetespib併用またはドセタキセル単独療法を行う群に無作為に割り付けられた。Ganetespib併用群ではドセタキセル単独群と比較し、全生存期間が長かった（9.8か月対7.4か月）。この併用療法は特に進行肺がんの初回診断から6か月以上経過した患者において興味深く、これらの患者群ではganetespibとドセタキセル併用で全生存期間が67%改善した（全生存期間中央値10.7か月対6.4か月）。最近開始された第III相試験GALAXY-2においてこれらの患者群のスタディが現在施行されている。これらの結果が確認されればganetespibはこの条件の患者の予後を改善するここ10年間で初めての治療法となるであろう。

Full Text

Findings from GALAXY-1, a large phase II study presented at ASCO's 2013 annual meeting, finds that a novel heat shock protein 90 inhibitor (Hsp90), ganetespib, when combined with docetaxel in second-line therapy, leads to longer overall survival compared to standard second-line docetaxel alone in patients with advanced lung adenocarcinoma that progresses after initial therapy. If confirmed in an ongoing phase III trial, this would be the first treatment to improve patient outcomes in this setting in a decade.

Hsp90 belongs to a class of proteins known as molecular "chaperones." Chaperones help newly formed proteins assume the proper shape needed to perform their specific biologic function. Formation of many proteins that drive lung cancer growth, such as EGFR and ALK, requires Hsp90. Blocking such chaperones is a completely new strategy in cancer therapy, and is promising because it can disable many different cancer-fueling proteins at the same time. In addition, this strategy may still work in patients who develop mutations that make them resistant to traditional targeted drugs, because blocking the chaperone will inhibit the function of the mutated proteins, too.

"This is the first randomized study to demonstrate therapeutic benefit with a heat shock protein inhibitor in patients with cancer," said lead study author Suresh S. Ramalingam, M.D., a professor of medical oncology at the Winship Cancer Institute of Emory University in Atlanta, Georgia, USA. "We hope that the ongoing phase III study will confirm our findings, as patients with this common form and stage of lung cancer urgently need more effective treatments."

All patients in this clinical trial had disease that progressed despite standard treatment with platinum-based chemotherapy. The current study reports on the primary enrollment stage of the trial, which completed in November 2012. The 252 patients were randomly assigned to treatment with docetaxel plus ganetespib or docetaxel alone. Those in the ganetespib arm had longer overall survival (9.8 vs. 7.4 months) compared to docetaxel alone.

The combination was particularly interesting in patients who were at least six months from initial diagnosis of advanced lung cancer as that group of patients experienced a 67 percent improvement in overall survival with the combination of ganetespib and docetaxel (median overall survival 10.7 months vs. 6.4 months). This group of patients is being studied in a recently launched phase III trial, GALAXY-2, that is comparing docetaxel plus ganetespib to docetaxel alone.

"Ganetespib, in combination with docetaxel, shows promising early results in lung adenocarcinoma. We're hopeful about the outcome of an ongoing phase III study, which could help more patients with this form of advanced lung cancer access this promising drug," said Marjorie Zauderer, M.D., ASCO spokesperson and lung cancer expert.

Early Hsp90 drugs did not succeed in clinical trials due to liver toxicity and insufficient efficacy. This is the first randomized clinical trial of a second-generation Hsp90 inhibitor and the first time an agent in this class has been shown to be both safe and effective. This study was limited to patients with stage IV lung adenocarcinoma. Adenocarcinoma is the most common type of lung cancer overall. Progress in second-line therapy for NSCLC has plateaued in the past decade, so the survival improvement seen with the addition of ganetespib is significant.

Researchers are planning to separately assess outcomes in subsets of patients defined by genetic markers in the tumor or markers in blood. In the present study to date, the observed improvements in progression-free survival and overall survival did not appear to be associated with EGFR mutations status, KRAS mutations status, or baseline level of LDH in blood.

This research was supported by Synta Pharmaceuticals.

ASCO2013特集

眼のメラノーマに対する新たなMEK阻害剤（Abstract＃CRA9003）

早期スタディの結果、selumetinibは進行ぶどう膜メラノーマに対する初めての有効な治療薬となる可能性があることが示唆された

Early study suggests selumetinib may be the first active drug for treating advanced uveal melanoma

第49回American Society of Clinical Oncology年次集会で報告された第II相試験の結果、標的治療薬selumetinibが一般的な*Gnaq/Gna11*遺伝子変異を有する眼の進行メラノーマの患者において臨床的に強力な有効性を示すことが明らかにされた。*Gnaq*および*Gna11*の変異はがん細胞増殖を促進するMAPKパスウェイを活性化する。これらの変異はこの疾患患者の85%以上において発現する。Selumetinib はMAPKパスウェイの重要な構成要素であるMEK蛋白質を阻害する。今回のスタディにおいて、転移性ぶどう膜メラノーマ患者98人がselumetinib（48人）またはテモゾロミド（50人）投与群に無作為に割り付けられた。テモゾロミド治療で悪化した患者はselumetinibに切り替えることが許可された。Selumetinib群では50%の患者において腫瘍が縮小し、15%で腫瘍が著明に縮小した。テモゾロミド群では有意な縮小に達した者はいなかった。無増悪期間中央値はselumetinib群において15.9週であったのに対し、テモゾロミド群では7週であった。全生存期間に関してselumetinibの有害作用はなく、生存期間中央値はselumetinib群で10.8か月、テモゾロミド群では9.4か月であった。この臨床試験は、転移性ぶどう膜メラノーマ患者の治療成績が薬物により改善することを認めた初めてのものである。

Full Text

Final analysis of data from a phase II cross-over study in patients with metastatic uveal melanoma finds that selumetinib resulted in tumor shrinkage in half of all patients treated and a duration of disease control more than twice that achieved with temozolomide. While temozolomide is a long-time standard therapy for skin melanoma, it has little effect in most patients with skin or eye melanoma, and alternate treatment options are urgently needed. There is no known effective systemic therapy for metastatic uveal melanoma. Indeed, of the 157 patients treated on eight different clinical trials testing potential new therapies for this cancer, including chemotherapy, targeted therapy and immunotherapy, over the past decade, only two patients experienced major tumor shrinkage.

This clinical trial is the first to identify a drug that improves clinical outcome in patients with advanced melanoma of the eye. Results were reported at ASCO's 2013 annual meeting.

"Ours is the largest randomized study of patients with melanoma of the eye. It proves that inhibiting the MAPK pathway in this unique molecular subset of melanoma, which is commonly characterized by mutations in Gnaq and Gna11, is effective, more than doubling progression-free survival," said lead author Richard D. Carvajal, M.D., a medical oncologist at Memorial Sloan-Kettering Cancer Center in New York, NY. "While we are hopeful an agent like selumetinib will be commercially available in the near future, in the meantime we must continue to steer patients towards clinical trials."

Uveal melanoma is a rare cancer, with only 2,000 new cases diagnosed in the United States every year. While most patients are diagnosed with early-stage disease, about half eventually develop metastatic disease, with survival ranging from nine to 12 months. Gnaq and Gna11 alterations activate the MAPK pathway, which fuels cancer cell growth. These alterations occur in greater than 85 percent of patients with this disease. Selumetinib blocks the MEK protein, a key component of the MAPK pathway. The drug is being investigated for the treatment of various cancers, including cancers of the thyroid and lung.

In this study, 98 patients with metastatic melanoma of the eye were randomly assigned to receive selumetinib or temozolomide, with 48 receiving selumetinib and 50 receiving temozolomide. Patients whose disease worsened on temozolomide were permitted to cross over to selumetinib. Fifty percent of patients experienced tumor shrinkage, with 15 percent achieving major tumor shrinkage in the selumetinib group. None achieved significant shrinkage in the temozolomide group.
The median progression-free survival time was 15.9 weeks in the selumetinib arm vs. seven weeks in the temozolomide arm. No detrimental effects of selumetinib were observed in terms of overall survival, with a median survival of 10.8 months in the selumetinib arm and 9.4 months in the temozolomide arm.

"Uveal melanoma is one the most difficult cancers to treat. This represents the first real advance for these patients," said Lynn Schuchter, M.D., ASCO spokesperson and melanoma expert.

This study was supported in part by a Conquer Cancer Foundation of ASCO Career Development Award, the National Institutes of Health, Cycle for Survival, and the Fund for Ophthalmic Knowledge.

ASCO2013特集

新たに診断された神経膠芽腫においてベバシズマブの有益性は認められなかった（Abstract＃1）

RTOG 0825:新たに診断された神経膠芽腫に対する標準的な化学療法にベバシズマブを併用しても延命効果は認められなかった

RTOG 0825: No survival benefit to adding bevacizumab to standard chemoradiation for newly diagnosed glioblastoma

神経膠芽腫患者における第III相試験の結果、ベバシズマブはファーストライン治療として使用されるべきではないことが示唆された。ベバシズマブとテモゾロミド併用で治療された患者はテモゾロミド単独で治療された患者よりも副作用が多く、全生存期間は改善しなかった。この多施設臨床試験において、新たに診断された神経膠芽腫患者637人が化学放射線療法（テモゾロミドと放射線療法）にプラセボを追加する群または化学放射線療法にベバシズマブを追加する群に無作為に割り付けられた。全ての患者が化学放射線療法を開始する前に手術を施行された。全生存期間中央値は、両群間で統計的な差はなかった（プラセボ群16.1か月対ベバシズマブ群15.7か月）。無増悪生存期間中央値はプラセボ群と比較しベバシズマブ群で長かった（10.7か月対7.3か月）が、この差はこのスタディで規定された事前設定レベルには達しなかった。分子マーカー（MGMTメチル化状況および9つの遺伝子発現様式）に基づくサブグループ解析の結果、ベバシズマブを用いることにより生存期間が延長するサブグループは認められなかった。第49回American Society of Clinical Oncology年次集会プレナリーセッションで発表されたこの結果から、ベバシズマブはこれらの神経膠芽腫患者に対するファーストライン治療の一部としては使用すべきでないことが示唆された。

Full Text

A randomized phase III study finds no overall survival improvement from the addition of bevacizumab to standard first-line chemoradiation for glioblastoma. Patients who received bevacizumab also experienced more side effects compared to those treated with chemoradiation alone. The findings suggest that it should not be a part of first-line therapy for these patients with glioblastoma.

This study was presented during the plenary session of the 49th Annual Meeting of the American Society of Clinical Oncology.

Glioblastoma is the most common and most aggressive form of primary brain tumor. Bevacizumab, an antibody that blocks the growth of tumor blood vessels, is currently used for patients with recurrent glioblastoma. Despite a lack of clear evidence, bevacizumab has been used off-label as first-line therapy in certain patients, in hopes of increasing the benefit to the patient.

"Unless we can identify a group of patients that clearly benefits from early use of bevacizumab, it appears that it should not be used in the first-line setting," said Mark R. Gilbert, M.D., a professor of neuro-oncology at the University of Texas M.D. Anderson Cancer Center in Houston, Texas. "Bevacizumab remains an important part of our armory against glioblastoma, but in most situations it should be reserved as a salvage regimen."

In this multi-institutional clinical trial, 637 patients with newly diagnosed glioblastoma were randomly assigned to treatment with chemoradiation (temozolomide and radiation) plus placebo or chemoradiation plus bevacizumab. All patients had undergone surgery before starting chemoradiation. Patients were allowed to cross over to the placebo group or continue bevacizumab at the time of progression.

The median overall survival was not statistically different between the two groups (16.1 months with placebo vs. 15.7 months with bevacizumab). The median progression-free survival was longer in the bevacizumab group relative to the placebo group (10.7 months vs. 7.3 months), but the difference did not reach the pre-set level of significance prescribed for this study. A subgroup analysis based on molecular markers (MGMT methylation status and a nine-gene expression signature) found no subgroup with improved survival using bevacizumab.

Overall, there were more side effects in the bevacizumab group, particularly low platelet counts, blood clots and high blood pressure. However, Dr. Gilbert said that toxicity differences alone would not have precluded the decision to use bevacizumab had the trial found a survival benefit.

"Bevacizumab received FDA approval for recurrent glioblastoma based on dramatic radiographic activity in several phase II trials. Now, two separate multinational randomized phase III trials demonstrate that bevacizumab modestly increases progression-free survival but not overall survival for newly diagnosed patients. Although bevacizumab will clearly continue to have an important role in the treatment of patients with glioblastoma, the timing of its use, the specific subpopulation of patients that benefit the most, and the biological and clinical consequences of chronic VEGF inhibition on glioma and normal cells within the central nervous system need to be clarified," said Howard Fine, M.D., ASCO spokesperson and CNS tumors expert.

Researchers also assessed patients' quality of life, symptom burden and neurocognitive function, which also favored the group of patients who received chemoradiation alone; the findings from those analyses were presented in separate oral presentations at ASCO's 2013 Annual Meeting. This study component revealed that patients in the bevacizumab arm had a greater increase of symptom burden and more decline of neurocognitive function over time compared to patients in the placebo arm. Molecular profiles of tumor samples collected on this study, as well as imaging scans, are being examined to determine if there is any group of patients that could still benefit from bevacizumab in the first-line setting.

This research was supported in part by the National Cancer Institute and Genentech.

ASCO2013特集

進行メラノーマに対する有望な免疫療法（Abstract # CRA9006）

治験薬の抗PD-1抗体薬nivolumabは進行メラノーマ患者において強力な抗がん作用を有することが示された

Investigational anti-PD-1 antibody nivolumab shows strong anti-cancer activity in patients with advanced melanoma

Nivolumabの長期拡大第I相試験の結果から、この新たな免疫療法は標準的な全身療法にもかかわらず進行した進行メラノーマ患者において単剤使用薬として非常に有効であることが示された。腫瘍縮小率および全生存期間中央値は、この条件下における過去の免疫療法薬のデータと比較し著明に改善した。今回のスタディにおいて、107人の患者が5つの異なる用量の nivolumabで治療された。全ての患者が過去の標準全身治療にもかかわらず疾患が悪化していた−25%は過去に 3回以上の治療歴があり、63%は 2回以上の治療歴があった。全体で、107人中 33人（31%）において腫瘍が 30%以上縮小し、いずれの用量でも奏効が認められた。推定 2年生存率は 43%であった。全ての用量での全生存期間中央値は 16.8か月であった；その後の臨床試験で選択された用量では20.3か月であった。今回は初期臨床データであるが、結果は顕著であり、全生存期間中央値はごく最近承認されたメラノーマ治療薬で認められたよりも長かった。これらの結果を確認する第III相試験が現在進行中である。この研究結果は第 49回 American Society of Clinical Oncology年次集会で発表された。

Full Text

Long-term follow-up results from an expanded phase I study indicate that nivolumab produces long-lasting responses in patients with stage IV melanoma. Historical response rates to immunotherapy drugs in advanced melanoma are five to 10 percent, but 30 percent of patients experienced tumor shrinkage in this study.

This research was presented at the 49th Annual Meeting of the American Society of Clinical Oncology.

Nivolumab targets the PD-1 receptor, an immune system gatekeeper or "checkpoint" on the surface of T-cells, releasing the brakes on the immune system and boosting its ability to fight off cancer. This study affirms immunotherapy as an important treatment approach for melanoma.

"I think nivolumab is a real breakthrough drug for patients with metastatic melanoma, and probably for other diseases, too," said lead author Mario Sznol, M.D., a professor of medical oncology at the Yale Cancer Center in New Haven, Connecticut, USA. "The high level of activity observed with this drug opens up a number of avenues for future research to understand and challenge the ways tumors evade the immune system. We're very excited that there is potential for even more activity in combination with other drugs."

In this study, 107 patients were treated with five different doses of nivolumab. All patients had disease that worsened despite prior standard systemic therapies — 25 percent had three or more prior therapies and 63 percent had two or more. Overall, 33 out of 107 (31 percent) of patients experienced tumor shrinkage of at least 30 percent and responses were seen at all doses. The estimate for survival at two years was 43 percent. The median overall survival across all doses was 16.8 months; 20.3 months for the dose chosen for study in subsequent clinical trials. While this is an early-phase study, and the results cannot be directly compared to those with other drugs, the results are striking, with median overall survival exceeding that seen with the most recently approved melanoma drugs.

"Results confirm that 'revving' up the immune system is a powerful approach in shrinking melanoma. Melanoma patients are living longer and better with these new treatments. Truly remarkable," said Lynn Schuchter, M.D., ASCO spokesperson and melanoma expert.

"While this was not a randomized clinical trial, it had a considerable number of patients and the durability of responses is a sign of very promising clinical activity," said Dr. Sznol. Another reassuring point, according to Dr. Sznol, is that patients in this clinical trial are representative of typical patients with advanced melanoma – the investigators did not select for the very best patients. Randomized phase III trials have been initiated to confirm these findings.

More research is needed to identify molecular markers that can help predict which patients are most likely to benefit from nivolumab. One potential marker is the protein PD-L1 on the surface of tumor cells, which is being studied in several other clinical trials.

This research was supported by Bristol-Myers Squibb.

ASCO2013特集