PSAに基づき再発とされた前立腺がん患者においてホルモン療法延期は安全なようである（Abstract: 5003）

PSA検査により再発が発見された前立腺がん患者においてアンドロゲン除去療法を症状発現まで遅らせても安全なようである

Delaying androgen deprivation therapy until onset of symptoms may be safe for men with prostate cancer relapse detected by PSA testing

前立腺手術または放射線療法後にPSAのみで再発とされた前立腺がん患者において、症状発現または画像上がんが出現するまでアンドロゲン除去療法（ADT）を遅らせても長期生存率は実質的に悪化しない、と第50回American Society of Clinical Oncology学会で発表された。スタディでは14,000人超の患者を解析し、うち2,012人は治癒目的の前立腺全摘術または放射線療法後にPSAに基づき再発が認められた。PSA再発後3か月以内にADTを開始した患者は"迅速"療法群とされた。PSA再発後2年以上経過してから、または転移、症状発現、またはPSA倍化時間が短い場合にADTを開始した患者は"遅延"療法群とされた。初回治療からPSA再発までの時間中央値は27か月であった。再発後、患者は中央値41か月追跡された。推定5年全生存率は2つのADT開始群で同等であった：遅延ADT群87.2%に対し迅速ADT群85.1%であり、迅速なADT開始は遅れて開始する場合と比較し生存率に関する有益性はほとんどないか、または全くないことが示唆された。この結果から、ADTを延期することは安全であり、治療に関連した副作用や医療費を軽減したり遅らせたりできると考えられる。

Full Text

According to a large, population-based observational study of men who had a PSA-only based relapse after prostate surgery or radiation therapy, delaying androgen deprivation therapy (ADT) until the onset of symptoms or appearance of cancer on a scan does not substantially compromise long-term survival. The findings suggest that it may be safe to postpone ADT, reducing and/or delaying treatment-related side effects and costs.

"Rising PSA levels trigger a lot of anxiety, and many men want to start treatment as soon as possible," said lead study author Xabier Garcia-Albeniz, M.D., a research associate at Harvard University School of Public Health in Boston, MA. "These findings suggest that there may be no need to rush to ADT. If our results are confirmed in randomized trials, patients could feel more comfortable waiting until they develop symptoms or signs of cancer that are seen on a scan, before initiating ADT."

The current study provides novel data on patients with so-called "PSA relapse," where PSA levels are increased but patients have no symptoms, and there is no evidence of a tumor on a CT or bone scan. There are no standard guidelines for timing of ADT initiation in such patients.

The study analyzed national prospective registry data (CaPSURE: Cancer of the Prostate Strategic Urologic Research Endeavor, based at the University of California, San Francisco) on over 14,000 patients, 2,012 of whom had a PSA relapse after radical prostatectomy or radiation therapy with curative intention. Patients were assigned to the "immediate" strategy if they received ADT within three months of PSA relapse. They were assigned to the "deferred" strategy if they started ADT at least two years after the PSA relapse, or when they presented with metastasis, symptoms, or a short PSA doubling time.

In the current observational study, the median time from primary treatment to PSA relapse was 27 months. After a relapse, patients were followed for a median period of 41 months. The estimated five-year overall survival was similar between the two ADT timing strategies: 87.2 percent for deferred ADT vs. 85.1 percent for immediate ADT, suggesting that there was little or no survival benefit of immediate ADT initiation compared with deferred initiation. As this was an observational study, the authors cannot exclude the possibility that some unmeasured characteristics affecting survival (e.g., healthy behavior, diet, blood pressure) were different among compared groups and, despite the best possible statistical adjustment, the true difference between the compared strategies might differ from the one reported.

In practice, deferred initiation could help delay ADT by two or more years for some men, according to the authors, offering men substantially better quality of life by avoiding common and often debilitating side effects — sexual dysfunction, osteoporosis and risk of bone fracture, hot flashes, decreased mental sharpness, fatigue, loss of muscle mass, increased cholesterol, weight gain, and depression. Some of those side effects may become more severe the longer a patient is on ADT.

"Hormone therapy is one of the oldest, most common and most effective treatment approaches in prostate cancer, and these findings will influence the treatment of thousands of patients worldwide," said Peter P. Yu, M.D., FASCO, ASCO President-Elect. "This study is also a great example of how less aggressive treatment can sometimes offer patients optimal outcomes while sparing them from side effects that impair their quality of life."

This research was supported in part by the National Institutes of Health (P01-CA134294), ASISA, SEOM (Sociedad Española de Oncología Médica) and an independent educational grant from Abbott.

ASCO2014特集

新薬は肺がん治療薬として有望である（Abstract: 8009）

新たなEGFR阻害薬は難治性非小細胞肺がんにおいて有望な作用を示す

New EGFR inhibitor shows promising activity in treatment-resistant non-small cell lung cancer

新規変異型選択的EGFRチロシンキナーゼ阻害薬（TKI）、AZD9291の第1相試験の結果は、EGFR変異を有する進行非小細胞肺がん（NSCLC）を有し標準的なEGFR阻害薬に対して不応の患者に対して新たな治療選択肢として有望であることを示した、との研究結果が第50回American Society of Clinical Oncology学会で発表された。このスタディにおいて、EGFR変異を有し1回以上の標準的なEGFR療法後に疾患が悪化した進行NSCLC患者199人が異なる用量のAZD9291を投与された。全ての用量および全てのサブグループ（脳転移患者を含む）において奏効が認められた。全体で、51%の患者に腫瘍の縮小を認めた。T790M変異が確認されている患者89人のうち64%においてAZD9291が奏効したのに対し、T790M陰性患者では23%であった。データカットオフの時点で、ほぼ全ての患者において奏効は持続して認められ、最長で8か月間以上持続した。この治療法が全生存期間を延長するかを究明するためには、さらに長期の経過観察が必要である。重要なことに、AZD9291は腫瘍内EGFRを選択的に標的とし、承認済みのEGFR TKIsよりも皮膚毒性が少ないようである。

Full Text

Findings from a phase I study of a new mutant selective EGFR tyrosine kinase inhibitor (TKI), AZD9291, point to a promising new treatment option for patients with advanced, EGFR mutant, non-small cell lung cancer (NSCLC) that is resistant to standard EGFR inhibitors according to researcher presented at the American Society of Clinical Oncology's 50th Annual Meeting. Roughly 50 percent of patients experienced tumor shrinkage, and the drug worked particularly well in patients with the T790M mutation (detected in 60 percent of patients), which causes the most common form of EGFR therapy resistance.

"There is currently no standard treatment for patients with lung cancer who experience disease progression after initial therapy with an EGFR kinase inhibitor," said lead study author Pasi A. Jänne, M.D., Ph.D., a professor of medicine at Dana-Farber Cancer Institute and Harvard Medical School in Boston, MA. "Although it is still a bit early, our study suggests that AZD9291 may offer an effective new therapy option for these patients, without the skin side effects we typically see with existing EGFR inhibitors."

EGFR mutations are found in 10-15 percent of Caucasian patients and about 40 percent of Asian patients with NSCLC. Many of these patients initially respond well to approved EGFR inhibitors erlotinib and afatinib, but all ultimately become resistant to this therapy – generally within 10 to 14 months. Many patients become resistant to EGFR inhibitors through the development of another mutation, the T790M mutation. The only therapy that is somewhat effective in patients with the T790M mutation is a combination of two EGFR inhibitors (afatinib and cetuximab), but it is very toxic.

In this study, 199 patients with advanced NSCLC harboring EGFR mutations, whose disease progressed after one or more standard EGFR therapies, received different doses of AZD9291. Responses were observed at all dose levels and in all subgroups of patients, including those with brain metastasis.

Overall, 51 percent of patients experienced tumor shrinkage. Among the 89 patients with a confirmed T790M mutation, 64 percent responded to AZD9291, vs. 23 percent of T790M-negative patients. The responses were still ongoing in nearly all patients at data cut-off, with the longest response lasting more than eight months.

Longer follow up is needed to determine if this therapy prolongs overall survival. Given that these data show that AZD9291 is working more effectively for patients with the T790M mutation, future studies of this drug will be limited to this subgroup of patients, according to the researchers.

Importantly, AZD9291 selectively targets EGFR in tumors and appears to cause fewer skin toxicities than approved EGFR TKIs. While existing drugs block both the mutant EGFR in the tumor and the normal EGFR in the skin (and other organs), which often leads to debilitating skin rash or acne, AZD9291 acts mostly on the mutant EGFR in a tumor.

"The reduced skin toxicity seen with AZD9291 heralds greater precision in targeting cancer mutations and sparing healthy tissues which retain normal germ line EGFR status," said Peter P. Yu, M.D., FASCO, ASCO President-Elect.

This research was supported by Astra Zeneca.

ASCO2014特集

まれな腫瘍性関節疾患の治療に対する有望な結果（Abstract: 10503）

色素性絨毛結節性滑膜炎再発患者に対する新たな治療選択肢

New treatment option for patients with recurrent pigmented villonodular synovitis

2014年ASCO年次総会で発表された第1相試験の初期結果によると、新たな標的治療薬PLX3397は、まれな腫瘍性関節疾患である色素性絨毛結節性滑膜炎（PVNS）に対し有効なようである。今回のスタディは、他の可能な治療を行ったにもかかわらず疾患が進行した患者を評価した。単群第1相のこのスタディで、最初に治療された23人の患者の結果が報告されている。患者は進行PVNSで膝、足関節、足、または肘に腫瘍を有していた。ほとんどの患者が複数回の手術を受け、前治療として放射線治療および/またはイマチニブやニロチニブなどの他の分子標的治療薬による全身治療を受けた患者もいた。患者は疾患の増悪または薬剤への忍容性がなくなるまでスタディ参加を継続した。評価可能な患者14人中11人（79%）は治療が奏効したと見なすのに十分な腫瘍縮小を示し、残りの3人は疾患が安定していた。患者の腫瘍容積は平均61%減少し、全体的な関節機能、疼痛やこわばりの軽減などの症状改善を含む迅速で実質的な改善が認められた。この薬剤の忍容性は良好であった。最も多い治療関連副作用は髪色変化、倦怠感、嘔気、眼周囲浮腫、味覚異常、下痢、嘔吐、および食欲低下であった。

Full Text

According to early results from a phase I study presented at ASCO's 2014 Annual Meeting, a new targeted drug, PLX3397, appears remarkably active against pigmented villonodular synovitis (PVNS), a rare neoplastic joint disorder. The study evaluated patients whose disease had progressed despite all other available therapies. More than three-quarters (79 percent) of the evaluable patients responded to the treatment, having a mean 61 percent reduction in tumor volume and rapid and substantial improvements in symptoms.

"These results are a shining example of how patients can experience a meaningful clinical benefit when we are able to match the right treatment with the right target," said lead author William D. Tap, M.D., Chief of the Sarcoma Medical Oncology Service at Memorial Sloan-Kettering Cancer Center in New York, NY. "PLX3397 seemed to have a tremendous impact on the joint-destructive disease process as patients often reported a marked decrease in swelling and pain even very early in their treatment course."

PVNS is a type of rare, often locally aggressive, musculoskeletal neoplasm that arises from the soft tissues of joints and tendons. In these patients, tumors form in the joint cavity, leading to gradual destruction of the joint and debilitating symptoms. Although it is characterized by an overgrowth of abnormal cells, PVNS is not referred to as a cancer per se, because it usually does not spread to other parts of the body. PVNS typically affects the hip or knee, and tends to occur in younger persons. Symptoms include joint swelling, pain, and reduced mobility.

While most patients are well managed with surgery, in some patients the disease comes back, necessitating additional surgery often requiring a joint replacement, and eventually advances to the point where it is no longer operable. PLX3397 may be an effective new therapy option for such patients.

PLX3397 is a novel oral tyrosine kinase inhibitor that blocks several molecular targets including the colony stimulating factor 1 (CSF1) receptor. In PVNS, a genetic abnormality causes the neoplastic cells to overproduce CSF1. This recruits CSF1 receptor-bearing immune cells that fill and destroy the joint. Therefore, PLX3397 blocks molecular pathways of the genetic abnormality that drives PVNS. This may slow the destruction of the joint and also reduce the inflammation that accompanies the disease process.

Results from the first 23 patients treated on this single-arm, phase I study are being reported. The patients had advanced PVNS with tumors in the knees, ankles, feet, or elbows. Most of the patients have undergone multiple surgeries and some have received prior treatment with radiation and/or with other systemic targeted treatments such as imatinib or nilotinib. The patients remained on the study until disease progression or inability to tolerate the drug.

Eleven out of 14 (79 percent) evaluable patients had tumor shrinkage sufficient to qualify as responders, and the disease was stable in the other three patients. Patients had substantial improvements in overall joint functionality, as well as decreased pain and stiffness. The drug was well tolerated. The most common treatment-related side effects were hair color changes, fatigue, nausea, swelling around the eyes, abnormal taste, diarrhea, vomiting, and decreased appetite.

"While it's still early, this study offers an exciting glimpse of the payoff of the precision medicine era, even for rare diseases like PVNS," said Clifford A. Hudis, M.D., FACP, ASCO President. "The research shows what's possible when we unravel the molecular drivers of a disease and identify a drug that directly targets these defects."

This research was supported by Plexxikon Inc.

ASCO2014特集

肥満および乳がんに関連した死亡率(Abstract: 503)

肥満は閉経前ER陽性乳がん患者においてのみ実質的に乳がん死亡率を上昇させる

Obesity substantially increases breast cancer mortality only in women with pre-menopausal ER+ disease

70の臨床試験における早期乳がん患者80,000人のスタディにおいて、肥満は閉経前エストロゲン受容体(ER)陽性患者においてのみ乳がん関連死リスクを34%上昇させることが示された。このEarly Breast Cancer Trialists' Collaborative Groupスタディでは、同じ臨床試験で同じ治療を受けた女性の記録を比較した。標準体重、過剰体重、および肥満(20-25、25-30、≧30 kg/m^2)は、ボディーマスインデックス(BMI)を用いて定義した。予後に対するBMIの独立した影響を評価するために研究者らは、腫瘍の特徴を腫瘍の大きさやリンパ節への拡がり、および治療に関するあらゆる相違などの結果で補正した。ER陽性閉経前女性患者20,000人において、肥満女性は標準体重の女性よりも乳がん死亡率が3分の1高かった。これは例えるなら、乳がん10年死亡リスクを15%から20%に引き上げることになる。これとは対照的に、ER陽性閉経後女性40,000人またはER陰性女性20,000人いずれにおいても、肥満は乳がんの予後にはほとんど影響しなかった。この研究結果は第50回American Society of Clinical Oncology学会で発表された。

Full Text

A new study of 80,000 women with early breast cancer in 70 clinical trials finds that obesity is associated with a 34 percent higher risk of breast cancer-related death only among the 20,000 pre-menopausal women with estrogen receptor (ER)-positive disease. Obesity had little effect in post-menopausal ER-positive disease or in ER-negative disease.

"Obesity substantially increases blood estrogen levels only in post-menopausal women, so we were surprised to find that obesity adversely impacted outcomes only in pre-menopausal women," said Hongchao Pan, Ph.D., a researcher at the University of Oxford in the United Kingdom. Dr. Pan continued: "This means we don't understand the main biological mechanisms by which obesity affects prognosis."

This Early Breast Cancer Trialists' Collaborative Group (EBCTCG) study compared records from women who received the same treatment in the same clinical trial. Body-mass index (BMI) was used to define normal weight, overweight, and obesity (20-25, 25-30 and ≥30 kg/m^2). To assess the independent effects of BMI on prognosis, the researchers adjusted the findings for tumor characteristics such as size and nodal spread, and for any differences in treatment.

Among the 20,000 pre-menopausal patients with ER-positive disease, the breast cancer mortality rate was one-third higher in obese women than in women of normal weight. This would, for example, change a 10-year breast cancer mortality risk of 15 percent into a 10-year risk of 20 percent.

In contrast, obesity had little effect on breast cancer outcome either among the 40,000 post-menopausal women with ER-positive disease or among the 20,000 with ER-negative disease.

"This study is part of the growing body of evidence showing that patients who are obese generally fare worse with cancer— in this case, younger women with breast cancer," explained Clifford A. Hudis, M.D., FACP, ASCO President. "With some two-thirds of our nation's adult population now obese or overweight, there's simply no avoiding obesity as a complicating factor in cancer care. ASCO is working to support physicians and patients in addressing this challenge, and we urge researchers to examine new strategies for reducing obesity's cancer-related toll."

The study was funded by Cancer Research UK, the MRC and the British Heart Foundation.

ASCO2014特集

メラノーマに対する併用療法による過去最長の生存期間（Abstract: LBA9003）

Ipilimumabとnivolumabの併用免疫療法は進行メラノーマの長期生存を達成する

Combination immunotherapy with ipilimumab and nivolumab achieves long-term survival for patients with advanced melanoma

拡大第I相試験の長期追跡結果から、進行メラノーマ患者に対するipilimumabとnivolumabの同時併用療法が約3年半（40か月）という前例のない生存期間中央値を生み出した、と第50回American Society of Clinical Oncology学会のLate Breaking Clinical Trial sessionで発表された。この併用療法により、どちらかの薬剤を用いた単剤療法の過去のスタディで認められた全生存期間中央値が、ほぼ2倍になった。全体で、切除不能stage IIIまたはIVのメラノーマ患者53人中22人（41%）に奏効を認め、9人（17%）は完全寛解した。腫瘍縮小は迅速かつ広範囲であった—42%の患者が第36週までに80%超の腫瘍縮小を示した—持続的な奏効は、解析時点で22人中18人（82%）に認められた。全ての用量で、1年および2年全生存率中央値は、それぞれ85%および79%であり、生存期間中央値は39.7か月であった。臨床的奏効は*BRAF*変異やPD-L1発現の有無に関係なく認められた。副作用はほぼ全ての患者で、対処可能かつ可逆性であった。

Full Text

Long-term follow-up results from an expanded phase I study show that concurrent treatment with ipilimumab and nivolumab produces an unprecedented median survival of roughly three and a half years (40 months) for patients with advanced melanoma. In the study, the combination treatment nearly doubled the median overall survival found in previous studies of either agent alone.

"Just a few years ago, median survival for patients diagnosed with advanced melanoma was as little as a year or less, and only approximately 20-25 percent survived two years, so it's truly remarkable that we're seeing a median survival over three years in this trial. Even in the latest era of targeted and immunotherapy agents, the median survival is on average only about 16-18 months with any new treatment alone," said lead study author Mario Sznol, M.D., a professor of medical oncology at Yale School of Medicine in New Haven, CT. "While we're encouraged by what we're seeing with the use of these two drugs together, this trial was small, so a randomized phase III trial will be important to validate our initial results."

Nivolumab and ipilimumab are antibody drugs that target and block two different "gatekeepers" or checkpoints (PD-1 and CTLA-4, respectively) on T cells, disarming the tumor's defense against the immune system and boosting the immune system's ability to fight melanoma. Ipilimumab is FDA-approved for the treatment of metastatic melanoma. Lasting antitumor effects have been observed with nivolumab as a single-agent therapy.

In the study, 94 patients with inoperable stage III or IV melanoma who had undergone up to three prior systemic therapies received concurrent treatment with ipilimumab and nivolumab. Approximately 53 percent of patients had very advanced disease (stage M1c), and 55 percent had no prior systemic treatments.

Long-term follow-up data on the 53 patients enrolled in the initial four concurrent dosing cohorts are being reported. Those patients received ipilimumab and nivolumab every three weeks for four cycles, followed by nivolumab alone every three weeks for four cycles. At week 24, patients who did not have disease progression or severe side effects could continue nivolumab plus ipilimumab every 12 weeks for eight cycles.

Overall, 22 out of 53 patients (41 percent) responded to the treatment, and nine (17 percent) had complete remissions. Tumor shrinkage was rapid and extensive — 42 percent of the patients had a greater than 80 percent tumor reduction by week 36 — and the responses were durable, with 18 of 22 responses (82 percent) ongoing at time of analysis. Across doses, the one-year and two-year median overall survival rates were 85 percent and 79 percent, respectively, and the median survival duration was 39.7 months. (At the nivolumab 1 mg/kg and ipilimumab 3 mg/kg dose being tested in an ongoing phase II/III trial, one- and two-year overall survival rates were 94 and 88 percent, respectively). The rate of side effects related to induction of immune reactivity against normal tissues was higher than previously observed for either single agent, but side effects were manageable and reversible in almost all patients.

Clinical responses were seen regardless of tumor *BRAF* mutation status or PD-L1 status, and across all dose levels. According to the authors, the activity of the combination in the PD-L1 negative subgroup was higher than observed in prior trials of nivolumab alone, and therefore supports the observation that the combination is more effective than nivolumab by itself. In addition, the authors stated, if the activity is validated in the phase III trial, patients with melanomas that test positive for a *BRAF* mutation would have an even more effective immunotherapy option in addition to targeted therapy for treatment of their disease.

Researchers will continue following patients in all cohorts of this study, including a separate cohort of 41 patients who received the combination treatment every three weeks for four cycles, followed by nivolumab alone every two weeks for up to two years. A separate, ongoing phase III study comparing nivolumab plus ipilimumab versus nivolumab or ipilimumab alone, and a phase II randomized study comparing nivolumab plus ipilimumab to ipilimumab alone, completed accrual; findings have not yet been reported.

"Anti CTLA-4 and anti PD1 single-agent therapies for metastatic melanoma have made significant contributions in recent years. This study combines the two checkpoint inhibitors concurrently in efforts to improve clinical outcomes further," said Steven O'Day, M.D., ASCO Expert. "This update on the initial group of 53 patients treated with ipilimumab and nivolumab confirm continued excitement, with remarkable clinical benefit and longer survival than we've typically seen. Phase III trials will be necessary to determine the benefit of combination checkpoint therapy versus sequential single-agent therapy and delineate the price of additional toxicities."

This research was supported by Bristol-Myers Squibb and Ono Pharmaceutical.

ASCO2014特集

アロマターゼ阻害薬は閉経前乳がん患者において有効である（Abstract: LBA1）

ホルモン感受性早期乳がんにおいて術後補助療法にエキセメスタンと卵巣機能抑制とを組み合わせるとタモキシフェンよりも有効である

Adjuvant exemestane beats tamoxifen when combined with ovarian function suppression in hormone-sensitive, early-stage breast cancer

アロマターゼ阻害薬エキセメスタンは、閉経前ホルモン受容体陽性早期乳がん患者において卵巣機能抑制（OFS）と併用することによりタモキシフェンより乳がん再発予防効果が高い、と2014年American Society of Clinical Oncology学会で発表された。TEXTおよびSOFTトライアルの共同解析では、4,690人の女性（平均年齢43歳）をエキセメスタンとOFSの併用またはタモキシフェンとOFSの併用を5年間施行する群にランダムに割り付けた。OFSは薬剤triptorelin、卵巣摘出術、または卵巣放射線照射により行った。一部の患者はまた、主治医の判断で術後化学療法も施行された。5年無がん生存率はエキセメスタンとOFS併用群の91.1%に対し、タモキシフェンとOFS併用群では87.3%であった（28%の相対リスク低下）。エキセメスタンとOFS併用群におけるタモキシフェンとOFS併用群に対する相対リスク低下は、乳がん再発に関しては34%であり、転移リスクに関しては22%であった。5年全生存率は両群ともに高かった—エキセメスタンとOFS併用群95.9%、タモキシフェンとOFS併用群96.9%。このスタディの結果は、*New England Journal of Medicine* オンライン版に同時に掲載された。

Full Text

The aromatase inhibitor exemestane more effectively prevents breast cancer recurrences than tamoxifen, when given with ovarian function suppression (OFS), in premenopausal women with hormone receptor-positive, early breast cancer according a Late Breaking Clinical Trial presentation session at the 50th Annual Meeting of the American Society of Clinical Oncology.

The landmark study was a joint analysis of two-phase III trials, TEXT and SOFT. In the study, exemestane plus OFS reduced the relative risk of women developing a subsequent invasive cancer by 28 percent, and specifically reduced the relative risk of breast cancer recurrence by 34 percent, compared with tamoxifen plus OFS.

"For years, tamoxifen has been the standard hormone therapy for preventing breast cancer recurrences in young women with hormone-sensitive disease. These results confirm that exemestane with ovarian function suppression constitutes a valid alternative," said lead study author Olivia Pagani, M.D., clinical director of the Breast Unit at the Oncology Institute of Southern Switzerland in Bellinzona, Switzerland. "Our findings indicate that exemestane is better than tamoxifen, when given with ovarian function suppression, but longer follow up of these young women will be important to assess survival, and any long-term side effects and fertility."

The TEXT and SOFT trials were led by the International Breast Cancer Study Group (IBCSG) in collaboration with the Breast International Group (BIG) and the North American Breast Cancer Group (NABCG) as a successful, worldwide collaboration spanning 27 countries and six continents.

The joint analysis of TEXT and SOFT is the largest study worldwide evaluating adjuvant aromatase inhibitor therapy with OFS in young women with breast cancer, and the first to demonstrate the value of such therapy in women with hormone receptor-positive cancer. Aromatase inhibitors have primarily been used in postmenopausal women, because their use requires that women have a low level of estrogen. In the TEXT and SOFT trials, ovarian function suppression was used in premenopausal women to emulate the low estrogen levels that naturally occur in menopause.

The standard adjuvant endocrine therapy for premenopausal women is currently five years of tamoxifen. In some countries, physicians recommend adding OFS to tamoxifen in high-risk younger women. The SOFT trial also addresses the impact of adding OFS to tamoxifen, and the results will be available in late 2014. The joint analysis of the TEXT and SOFT trials studied the outcomes of 4,690 women, whose average age was 43 years, who were randomized to receive exemestane plus OFS or tamoxifen plus OFS for five years. OFS was achieved through treatment with the drug triptorelin, surgical oophorectomy, or ovarian irradiation. Some women also received adjuvant chemotherapy, as decided with their physician.

The cancer-free survival at five years was 91.1 percent in the exemestane plus OFS group, versus 87.3 percent in the tamoxifen plus OFS group, which was a 28 percent relative reduction in risk. There was a 34 percent relative reduction in breast cancer recurrence risk in the exemestane plus OFS group compared to the tamoxifen plus OFS group and a 22 percent relative reduction in metastasis risk. The five-year overall survival rates were high in both groups — 95.9 percent in the exemestane plus OFS group and 96.9 percent in the tamoxifen plus OFS group. Longer follow-up is needed to accurately assess the impact of the two treatments on long-term survival.

The side effects were similar to those reported in previous studies comparing adjuvant aromatase inhibitors and tamoxifen in postmenopausal women, and differed depending on the agent. Despite the side effects, only 14 percent of TEXT and SOFT participants completely stopped the protocol-assigned treatments early – an adherence rate that is higher than what is seen in everyday practice. Dr. Pagani stated that this high compliance rate is important information for doctors who wish to propose this treatment to their patients.

The TEXT and SOFT trials were conducted at the same time and in the same general population – premenopausal women with hormone receptor-positive early breast cancer. The original plan was to analyze each trial separately as well as jointly, given the common treatment groups of exemestane plus OFS and tamoxifen plus OFS in both trials. However, by combining the trials in a joint analysis, the results could be presented earlier, giving physicians and patients the possible benefit of acting on the results sooner.

ASCO Perspective: "Young women with breast cancer have long needed additional treatment options after surgery, and now they may have one," said ASCO president Clifford A. Hudis, M.D., FACP. "Tamoxifen has been a gold standard for decades and has significant benefits. Now, with ovarian suppression, aromatase inhibitors are an option offering a further reduction in the risk of recurrence."

This research was supported in part by Pfizer, Ipsen, the International Breast Cancer Study Group, and the National Cancer Institute, National Institutes of Health.

ASCO2014特集

転移性前立腺がんにおける生存の劇的な有益性（Abstract: LBA2）

初回ホルモン療法にドセタキセルを併用することで転移性ホルモン感受性前立腺がん患者の生存期間が大幅に改善する

Addition of docetaxel to initial hormone therapy substantially improves survival in men with metastatic, hormone-sensitive prostate cancer

第50回American Society of Clinical Oncology学会のLate Breaking sessionで発表された研究の結果、新たにホルモン感受性前立腺がんと診断された患者において、標準的なホルモン療法に化学療法薬ドセタキセルを併用することにより生存期間が約10か月延長することが示された。今回の第III相試験において、新たに転移性前立腺がんと診断された患者790人がアンドロゲン除去療法（ADT）単独またはADTとドセタキセルの併用を18週間投与する群にランダムに割り付けられた。約3分の2の患者において病変は広範であった。ADTとドセタキセル併用群の患者45人は疾患が悪化したため、ドセタキセルの追加投与が行われた。ADT単独群患者123人は、疾患が増悪した時点でドセタキセルの投与を受けた。追跡期間中央値29か月の時点で、ADT単独群で死亡は136人であったのに対し、ADTとドセタキセル併用群では101人であった。全生存期間中央値はADT群で44か月でありADTとドセタキセル併用群では57.6か月であった。総生存期間中央値の相対的な改善は、疾患が広範に及ぶ患者520人においてより大であった（32.2か月対49.2か月）。ECOG E3805 CHAARTEDトライアルの研究者らは、これらの結果は"日常診療を変化させる"そして"変化させる力がある"と述べている。

Full Text

Findings from a phase III study, E3805, indicate that adding the chemotherapy drug docetaxel to standard hormone therapy extends survival for men with newly diagnosed hormone-sensitive prostate cancer by roughly 10 months. The survival benefit is even greater for the subset of men with high-extent disease.

"Hormone therapy has been a standard treatment for prostate cancer since the 1950s," said lead study author Christopher Sweeney, MBBS, medical oncologist at the Lank Center of Genitourinary Oncology at the Dana-Farber Cancer Institute in Boston, MA. "This is the first study to identify a strategy that prolongs survival in newly diagnosed metastatic prostate cancer. The benefit is substantial and warrants this being a new standard treatment for men who have high-extent disease and are fit for chemotherapy."

Androgen hormones fuel prostate cancer growth. Hormonal therapy – also called androgen deprivation therapy (ADT) – alone is the standard first-line treatment for hormone-sensitive prostate cancer. Although ADT is effective, the disease eventually becomes resistant to the therapy in most patients. Chemotherapy is typically initiated only after the disease progresses despite ADT.

In this National Cancer Institute-led study, 790 men with newly diagnosed metastatic prostate cancer were randomly assigned to receive either ADT alone or ADT with docetaxel over a period of 18 weeks. Approximately two-thirds of patients had high-extent disease, meaning that the cancer had spread to major organs and/or the patient had bone metastases. When the disease worsened, 45 patients in the ADT plus docetaxel group received additional docetaxel. In the ADT only group, 123 patients received docetaxel at disease progression.

At a median follow-up of 29 months, there were 136 deaths in the ADT-alone group vs. 101 in the ADT plus docetaxel group. The median overall survival was 44 months in the ADT group and 57.6 months in the ADT plus docetaxel group. The relative improvement in median overall survival was even larger among the 520 patients with high-extent disease (32.2 months vs. 49.2 months). The median overall survival for the subset with low-extent disease takes longer to reach as these patients respond better to ADT, and the median survival has not yet been reached.

Docetaxel also delayed disease progression, assessed by either PSA rise or appearance of new metastases or symptom worsening. At one year, the proportion of patients with PSA levels less than 0.2 ng/mL was 11.7 percent in the ADT group vs. 22.7 percent in the ADT plus docetaxel group. The median time to clinical progression was 19.8 months in the ADT group vs. 32.7 months in the ADT plus docetaxel group.

This new treatment paradigm will entail earlier, multidisciplinary care involving the collaboration of both urologists and oncologists, who both commonly treat men with prostate cancer, Dr. Sweeney said. Follow-up of patients will continue to assess survival benefits for patients with low-extent disease. Quality-of-life data from this study will be analyzed and reported at a later time.

"These results demonstrate how we can use 'old tools' in new, more powerful ways to improve and extend patients' lives," said ASCO president Clifford A. Hudis, MD, FACP. "This study is also a powerful testimony to the importance of National Cancer Institute-led research, as both of these drugs are available in generic form today and this research might have otherwise not been pursued."

This research was supported by the National Cancer Institute, National Institutes of Health.

ASCO2014特集

大腸がんの治療成績は同等である（Abstract: LBA3）

転移性大腸がんにおけるベバシズマブ併用化学療法とセツキシマブ併用化学療法の生存期間への有益性は同等である

Bevacizumab plus chemotherapy and cetuximab plus chemotherapy provide similar survival benefits in metastatic colorectal cancer

*KRAS*変異を有さない転移性大腸がん患者に対する4つの一般的なファーストライン治療―ベバシズマブ併用化学療法およびセツキシマブ併用化学療法―の有効性は同等であるとの大規模第III相試験の結果が第50回American Society of Clinical Oncology学会Late Breaking sessionで発表された。このスタディにおいて、未治療の転移性大腸がん患者1,137人は、ベバシズマブ併用化学療法またはセツキシマブ併用化学療法のいずれかを施行される群にランダムに割り付けられた。化学療法は担当医が選択した（26.6%がFOLFIRI、73.4%がFOLFOXを施行された）。追跡期間中央値は24か月であった。全生存期間および無増悪生存期間は、治療群間で有意差はなかった。ベバシズマブ併用化学療法群では全生存期間および無増悪生存期間はそれぞれ29か月および10.8か月であり、セツキシマブ併用化学療法群ではそれぞれ29.9か月および10.4か月であった。データから、FOLFOX（オキサリプラチン/5-フルオロウラシル/ロイコボリン）またはFOLFIRI（イリノテカン/5-フルオロウラシル/ロイコボリン）療法と今回のいずれかの分子標的薬との組み合わせは許容できることも示唆された。治療による新たな副作用は検出されず、患者の全体的なQOLは2つの抗体で同等であった。

Full Text

Results from a large phase III study demonstrate that four common first-line treatment regimens – bevacizumab plus chemotherapy and cetuximab plus chemotherapy – are equally effective for patients with metastatic colorectal cancer and no *KRAS* mutations. In the study, the median overall survival was roughly 29 months with either approach. The data also suggest that either FOLFOX (oxaliplatin/5-fluorouracil/leucovorin) or FOLFIRI (irinotecan/5-fluorouracil/leucovorin) chemotherapy regimens are acceptable in combination with either of the two targeted drugs.

"About 75 percent of patients with metastatic colorectal cancer in the United States initially receive bevacizumab-based therapy, although we know that cetuximab-based therapy is also a good option for a subset of patients," said lead author Alan P. Venook, M.D., the Madden Family Distinguished Professor of Medical Oncology and Translational Research at the University of California in San Francisco, CA. "Our findings clearly show that the two antibodies – with either FOLFOX or FOLFIRI – are both acceptable, and similarly effective. This should reassure doctors and patients facing decisions about treatment selection."

Each year, about 50,000 Americans are diagnosed with metastatic colorectal cancer. Targeted therapies have played a key part in extending survival for patients with metastatic colorectal cancer, from 10 months 20 years ago to the nearly 2.5 years seen in this study. Bevacizumab targets VEGF, blocking the development of blood vessels that tumors need to grow, while cetuximab targets EGFR, a protein involved in cancer growth and spread. Bevacizumab with FOLFOX is widely used in the United States, while cetuximab-based regimens tend to be used more frequently in Europe.

In the study, 1,137 patients with untreated metastatic colorectal cancer were randomly assigned to receive bevacizumab plus chemotherapy or cetuximab plus chemotherapy. The selection of chemotherapy was based on physician preference (26.6 percent received FOLFIRI, 73.4 percent FOLFOX). The median follow-up was 24 months.

There were no significant differences in either overall or progression-free survival between the treatment groups. In the bevacizumab plus chemotherapy group, the overall and progression-free survival were 29 months and 10.8 months, respectively, and 29.9 months and 10.4 months respectively in the cetuximab plus chemotherapy group.

No new treatment side effects were detected in this study. Common side effects of bevacizumab are high blood pressure, headache, mouth sores, nosebleed, diarrhea, bleeding from the rectum, loss of appetite, fatigue, and weakness, and the most common side effects of cetuximab are acne-like rash, itching, changes in fingernails and toenails, infections, fatigue, and low blood electrolyte levels. Costs of bevacizumab and cetuximab are comparable but side effects are slightly different. FOLFIRI and FOLFOX also differ in side effects – FOLIFIRI causes more hair loss and diarrhea but FOLFOX causes neuropathy that often necessitates stopping treatment. Updated analyses show that the overall quality of life for patients on either of the antibodies is similar.

Dr. Venook remarked that this kind of head-to-head comparative clinical trial comparing two agents from different companies with similar indications probably would not have been possible without the nation's investment in clinical trials led by the National Cancer Institute. "This study shows that we are still doing good, important work, even in the era of reduced funding for cooperative groups," he said.Forthcoming analyses from this study will explore benefits of these approaches in different subsets of patients. Genomic profiling will be conducted to identify potential prognostic markers, which might be helpful in selecting optimal treatments for individual patients in the future.

ASCO Perspective: "With this finding, oncologists and patients have more ways to personalize cancer treatment," said ASCO president Clifford A. Hudis, M.D., FACP. "They can be reassured that two widely used regimens offer good and equivalent survival."

This research was supported in part by the National Cancer Institute, National Institutes of Health; Imclone; Roche; Genentech; BMS; and Eli Lilly.

ASCO2014特集

進行非小細胞肺がんにおいて生存に関する有益性が軽度認められた（Abstract: LBA8006）

進行非小細胞肺がんにおいて標準的なドセタキセルにramucirumab併用によるセカンドライン治療は生存期間を延期させる

Second-line treatment with ramucirumab plus standard docetaxel extends survival in advanced non-small cell lung cancer

新たな抗血管新生薬ramucirumabと標準的なドセタキセルによる化学療法の併用により、ドセタキセルとプラセボの併用と比較し、初回治療後再発したstage IV非小細胞肺がん（NSCLC）患者の全生存期間が延長する。第III相REVELスタディにおいて、標準的なプラチナ製剤ベースの治療を受けたにもかかわらず進行したstage IV NSCLC患者1,253人（26%は扁平上皮がん）が、ramucirumabとドセタキセルまたはプラセボとドセタキセル併用群にランダムに割り付けられた。Ramucirumabを併用することによりセカンドラインとしてのドセタキセル治療の有効性が改善した：ramucirumab群患者の22.9%に腫瘍縮小を認め、プラセボ群では13.6%であった。全生存および無増悪生存期間中央値はそれぞれ、ramucirumabとドセタキセル併用群で10.5か月および4.5か月であり、プラセボとドセタキセル併用群では9.1か月および3か月であった。生存に関する有益性は、扁平上皮がんおよび非扁平上皮がんなどの主なサブグループで同等であり、この治療法はNSCLCの主なサブタイプにおいて適切であることが示唆された。これにより、NSCLC患者のセカンドライン治療において生存に関する有益性が過去10年で初めてもたらされた。この発表は、2014年American Society of Clinical Oncology学会で行われた。

Full Text

Findings from the REVEL phase III study of patients with stage IV non-small cell lung cancer (NSCLC) indicate that a combination of a new anti-angiogenesis drug, ramucirumab, and standard docetaxel chemotherapy extends overall survival for patients who have a relapse after initial treatment compared to docetaxel plus placebo. The median overall survival was 10.5 months in the ramucirumab arm compared to 9.1 months in the placebo arm. The late breaking study was presented at ASCO's 2014 Annual Meeting.

This phase III clinical trial marks the first time in a decade that a survival benefit has been achieved in second-line therapy for patients with advanced non-small cell lung cancer.

"This is the first treatment in approximately a decade to improve the outcome of patients in the second-line setting," said lead study author Maurice Pérol, M.D., Head of Thoracic Oncology at Cancer Research Center of Lyon in France. "The survival improvement is significant because patients with advanced NSCLC typically have a very short survival time following second-line therapy."

Ramucirumab is a monoclonal antibody that specifically targets VEGF receptor 2, blocking growth of new blood vessels in the tumor. No other approved anti-angiogenesis drugs are available in the second-line setting for advanced NSCLC, and currently ramucirumab is approved only for advanced gastric cancer treatment.There is a large unmet medical need in the second-line treatment of advanced NSCLC, as all patients eventually experience a relapse following initial therapy. Approved second-line therapies for advanced NSCLC include docetaxel, erlotinib, and pemetrexed (for non-squamous NSCLC only), though clinical outcomes remain poor, with tumor shrinkage rates around 10 percent and median overall survival ranging between seven and nine months.

In the study, 1,253 patients with stage IV NSCLC (26 percent had the squamous subtype) that had progressed despite standard platinum-based therapy were randomly assigned to treatment with ramucirumab plus docetaxel or placebo plus docetaxel.

The addition of ramucirumab improved the efficacy of second-line docetaxel therapy – 22.9 percent of patients experienced tumor shrinkage in the ramucirumab arm compared to 13.6 percent in the placebo arm. The median overall and progression-free survival periods were 10.5 and 4.5 months in the ramucirumab plus docetaxel arm vs. 9.1 and 3 months in the placebo plus docetaxel arm, respectively. The survival benefits were consistent in the major subgroups of patients, including squamous and non-squamous subtypes, suggesting that this therapy could be suitable for all major subtypes of NSCLC. The safety profile was as expected for an anti-VEGFR agent in combination with docetaxel, with no increase in the rate of pulmonary hemorrhage.

"This study expands the treatment options for patients with recurrent or refractory non-small cell lung cancer," said Gregory A. Masters, M.D., ASCO Expert. "Ramucirumab is an effective targeted agent when added to chemotherapy, with low toxicity. This will be a significant benefit to those patients whose cancer progresses following initial chemotherapy."

This research was supported by ImClone, a wholly owned subsidiary of Eli Lilly.

ASCO2014特集

CLLにおいて経口薬が生存に関する有益性を示した（Abstract: LBA7008）

難治性または再発性慢性リンパ性白血病においてibrutinibは疾患の増悪を遅延させる

Ibrutinib delays disease progression and extends survival for patients with resistant or relapsed chronic lymphocytic leukemia

第III相RESONATEスタディの早期結果により、再発した慢性リンパ性白血病（CLL）においてibrutinibは標準的なオファツムマブより腫瘍への奏効性を継続させ生存期間が著明に改善したことが示された。2014年ASCO年次総会で発表されたLate Breaking trialにおいて、過去に2回以上の治療歴があり再発または難治性CLLあるいは小リンパ球性リンパ腫患者391人がオファツムマブまたはibrutinib治療群にランダムに割り付けられた。患者の年齢中央値は67歳であり、40%は70歳超であった。追跡期間中央値9.4か月時点の奏効率は、オファツムマブ群に比べibrutinib群で劇的に高かった（42%対4%）。Ibrutinib治療を受けたさらに20%の患者が、持続するリンパ球増多を伴う部分寛解を認めた。Ibrutinibはオファツムマブに比べ、疾患増悪リスクを80%、死亡リスクを57%、それぞれ減少させた。無増悪生存および全生存期間中央値は未到達だった。Ibrutinibは非常にハイリスクの2つのグループの患者（17p欠失およびプリン類似体抵抗性）において同等に活動性が高かった。この結果は、再発したCLLにおいて、経口治療薬が標準治療よりも生存期間を改善させることを示した初めてのものである。

Full Text

Early findings from the phase III RESONATE study indicate that ibrutinib yields lasting tumor responses and marked improvement in survival over standard ofatumumab for patients with relapsed chronic lymphocytic leukemia (CLL). This is the first time an oral drug has demonstrated a survival improvement over standard therapy in relapsed CLL. Just as important, the therapy was well tolerated by patients, causing few serious side effects.

CLL is the most common form of leukemia in adults. The standard treatment for CLL is chemo-immunotherapy, a combination of intensive chemotherapy and an antibody such as rituximab. However, elderly patients, who account for the majority of patients with CLL, often cannot tolerate intensive chemotherapy. Ofatumumab is an alternative option for such patients, but studies have shown it is much less effective than intensive chemotherapy.

"With ibrutinib, about 80 percent of patients were still in remission at one year, twice as many as we would expect with standard therapy," said lead study author John Byrd, MD, a professor of medicine at The Ohio State University Comprehensive Cancer Center in Columbus, Ohio. "Although the follow-up was short in this study, the data definitely support the use of ibrutinib before anything else in this setting."

In the study, 391 patients with relapsed or refractory CLL or small lymphocytic lymphoma that had progressed after two or more prior therapies were randomly assigned to treatment with ofatumumab or ibrutinib. The median patient age was 67 years, and 40 percent were older than 70 years.

At a median follow-up of 9.4 months, the response rates were dramatically higher in the ibrutinib arm compared to the ofatumumab arm (42 percent vs. 4 percent). An additional 20 percent of patients treated with ibrutinib had a partial response with persistent lymphocytosis. Ibrutinib was associated with an 80 percent lower risk of disease progression and a 57 percent lower risk of dying compared to ofatumumab; the median progression-free and overall survival have not been reached. Ibrutinib had similarly high activity in two very high-risk groups of patients (17p deletions and purine analog refractory).

Based on these striking early results, patients in the ofatumumab arm were offered the opportunity to cross over to the ibrutinib arm, and patient follow-up continues. According to the researchers, the median overall survival is expected to be in the range of several years.

Overall, both ibrutinib and ofatumumab were well tolerated. Diarrhea, minor bleeding, and atrial fibrillation were more common in the ibrutinib arm, whereas peripheral neuropathy was more common in the ofatumumab arm. This study alleviated concerns about kidney problems that were raised in the phase II ibrutinib study.

"This phase III study in relapsed refractory chronic lymphocytic leukemia confirms that ibrutinib, administered orally, has significant efficacy and is well-tolerated," said Olatoyosi Odenike, MD, ASCO Expert. "These results provide a compelling new treatment option for patients with chronic lymphocytic leukemia, including older adults with this disease, and will significantly change practice."

This research was supported by Pharmacyclics.

ASCO2014特集

ホルモン抑制剤は乳がん患者の妊孕性を温存する（Abstract: LBA505）

標準的な化学療法にゴセレリンを併用することにより乳がんに対し化学療法を施行される女性の妊孕性が温存される

Adding goserelin to standard chemotherapy helps preserve fertility among women undergoing chemotherapy for breast cancer

ゴセレリン併用ホルモン療法は、ホルモン受容体陰性早期乳がん患者の化学療法による早期卵巣不全（OF）リスクを劇的に減少させるとの第III相研究の結果が、第50回American Society of Clinical OncologyのLate Breaking Clinical Trial sessionで発表された。このスタディにおいて、ホルモン受容体陰性閉経前stage I-IIIA乳がん患者257人が、シクロホスファミドを含む化学療法単独（標準療法群）または化学療法とゴセレリン併用群にランダムに割り付けられた。2年後、OFを来していたのはゴセレリン併用群の8%に対し、標準治療群では22%であった。妊娠を試みたと報告した女性の数は、2群間で同等であった。ゴセレリン併用群の21%（22人）が妊娠したが、化学療法単独群で妊娠したのはわずか11%（12人）であった。ゴセレリンは流産や妊娠中絶のリスクを上昇させることはなかった。ゴセレリンは無病生存期間および全生存期間にも影響したことに研究者らは驚いた。病期で補正後、治療後4年生存率はゴセレリン併用群において標準治療群に比べ50%高かった。

Full Text

New phase III study presented in a Late Breaking Clinical Trial session at the 50th Annual Meeting of the American Society of Clinical Oncology demonstrates that hormone therapy with goserelin dramatically reduces the risk of chemotherapy-associated premature ovarian failure among women with early-stage hormone receptor-negative breast cancer. Women who received the additional therapy were more likely to conceive following cancer treatment, and even had improved survival.

New findings from a federally funded phase III clinical trial, S0230/POEMS, indicate that adding a hormone suppressing drug called goserelin to standard chemotherapy may be an effective method of preserving fertility among women with early-stage hormone receptor-negative breast cancer. In the study, women who received goserelin along with chemotherapy were 64 percent less likely to develop premature ovarian failure compared to women who received chemotherapy alone, and they were more likely to have successful pregnancies. Survival was also improved among women in the goserelin arm: women were 50 percent more likely to be alive four years after starting chemotherapy compared to those in the standard arm.

"Preserving fertility is a common and important concern among younger women diagnosed with cancer, and these findings offer a simple, new option for women with breast cancer, or possibly other cancers," said lead study author Halle Moore, MD, a staff physician at Cleveland Clinic in Cleveland, OH. "Goserelin appears to be not only highly safe but also effective, as it increased the odds of becoming pregnant and delivering a healthy baby following chemotherapy."

Ovarian failure (OF) – defined in this study as cessation of menstrual periods and postmenopausal levels of follicle-stimulating hormone (FSH) – is a common side effect of chemotherapy. OF risk depends on the type and dose of chemotherapy as well as patient age and perhaps ovarian cycling at the time of chemotherapy.

Goserelin and similar luteinizing hormone-releasing hormone (LHRH) analogs temporarily shut down ovarian function, essentially putting the patient into a postmenopausal state. It is speculated that this protects follicles from chemotherapy damage. These medications are widely used to control ovulation timing for infertility procedures, such as *in vitro* fertilization. LHRH drugs are also widely used as hormonal therapies to treat advanced prostate and breast cancer.

In this study, 257 premenopausal women with stage I-IIIA hormone receptor-negative breast cancer were randomized to treatment with cyclophosphamide-containing chemotherapy alone (standard arm) or chemotherapy plus goserelin. Goserelin was given as monthly injections starting one week before the first dose of chemotherapy.

Two years after starting chemotherapy, 8 percent of women in the goserelin arm had OF vs. 22 percent of women in the standard arm. There was not a statistically significant difference in the number of women who reported attempting to conceive in the two arms. Twenty-one percent of women (22 individuals) assigned to goserelin plus chemotherapy became pregnant, and only 11 percent (12 women) among those assigned to chemotherapy alone became pregnant. These pregnancies resulted in 16 patients (15 percent of the group) delivering at least one baby on the goserelin arm compared with eight patients (7 percent) on the control arm. An additional three patients on the goserelin arm and two on the standard arm had not had a documented delivery but were still pregnant at the time of data submission. The study also found goserelin was safe – it was not associated with an increased risk of either miscarriage or pregnancy termination.

Researchers were surprised to find that goserelin also affected disease-free and overall survival. After adjusting for disease stage, women in the goserelin arm were 50 percent more likely to be alive four years after starting treatment compared to those in the standard arm. While these early results are very encouraging, Dr. Moore cautioned that more research is needed to understand any role of goserelin in the treatment of ER-negative breast cancer. On the other hand, the POEMS findings do establish a role for LHRH analogs in preserving ovarian function and fertility prospects for women treated with curative intent chemotherapy for breast cancer.

"Preserving fertility is an important component of quality survivorship care," said Patricia Ganz, MD, ASCO Expert. "This study provides strong evidence for a safe and effective strategy for younger women with breast cancer to preserve ovarian function and the possibility of pregnancy."

This research was supported by the National Institutes of Health.

ASCO2014特集

PD-1標的抗体はメラノーマ患者の生存率を上昇させる（Abstract: LBA9500）

PD-1標的免疫療法MK-3475は転移性メラノーマに対し持続性で高い活性作用を有する

PD-1 targeting immunotherapy MK-3475 has high and long-lasting activity against metastatic melanoma

第50回American Society of Clinical Oncology学会で発表された大規模第I相研究の新たな結果から、PD-1標的抗体MK-3475は転移性メラノーマ患者において高率に長期の奏効性を有することが示された。スタディには、ipilimumabによる前治療歴のある患者221人およびipilimumabによる前治療歴のない患者190人が組み入れられた。全ての患者が皮膚、肺、または他の主要臓器に拡散した進行メラノーマを有していた。3つの異なる用量のMK-3475単剤使用が計画された。Ipilimumabによる前治療歴のない患者の40%およびipilimumabによる前治療歴で増悪を認めた28%の患者を含む、全体で34%の患者に奏効が認められた。奏効は持続性であり、解析の時点で88%の患者において持続していた。全ての用量および患者サブグループにわたって活性が認められ、ipilimumab前治療歴の有無、パフォーマンスステータス、LDH値、*BRAF*変異の有無、病期、および前治療の数やタイプとは関係がなかった。推定1年生存率は69%であり、全生存期間中央値には到達しなかった。推定1年生存率はipilimumabによる前治療歴のない患者で74%であり、ipilimumabによる前治療歴のある患者では65%であった。

Full Text

New findings from a large phase I study of 411 patients with advanced melanoma show that the PD-1 targeting antibody MK-3475 yields long-term responses in a high percentage of patients. In the study, the one-year overall survival was 69 percent across all patient subgroups, and responses were ongoing in 88 percent of patients at analysis, after ent options.

"This is probably the biggest phase I trial ever conducted in oncology. We were excited to see that MK-3475 was effective in previously untreated patients as well as in those who had multiple prior therapies, including ipilimumab," said lead study author Antoni Ribas, M.D., Ph.D., a professor of medicine at the David Geffen School of Medicine at the University of California in Los Angeles, CA. "These are early data, but they tell us we are on to something really important."

The study enrolled 221 patients with prior ipilimumab treatment and 190 patients who had not previously received ipilimumab. All patients had advanced melanoma that had spread to the skin, lungs, or other major organs. Three different MK-3475 dose schedules as a single agent were tested.

Overall, 34 percent of patients experienced tumor response, as assessed by Independent Review, including 40 percent of patients not previously treated with ipilimumab and 28 percent of patients whose disease progressed on prior ipilimumab. Responses were durable with 88 percent ongoing at the time of analysis. Activity was observed across all dose levels and patient subgroups, irrespective of prior ipilimumab therapy, performance status, LDH levels, *BRAF* mutation status, tumor stage, and number and type of prior therapies. The estimated one-year survival rate was 69 percent, and median overall survival duration was not reached. The estimated one-year survival rate was 74 percent in patients not previously treated with ipilimumab and 65 percent in patients who received prior ipilimumab therapy. Overall, eight percent of patients experienced serious treatment-related side effects, but only four percent discontinued treatment due to a drug-related side effect.

Ongoing randomized controlled studies are assessing the efficacy and safety of MK-3475 in advanced melanoma patients not previously treated with ipilimumab and those who progressed on or after ipilimumab. Studies in an adjuvant setting are planned.

An expanded access program for MK-3475 is now available for eligible patients with advanced melanoma who have been previously treated with ipilimumab and, if indicated, a *BRAF* inhibitor.

"This large phase I clinical trial demonstrates continued excitement for anti PD-1 therapy. We're seeing that MK-3475 results in long-lasting clinical responses in the majority of patients, and impressive overall survival with low toxicity," said Steven O'Day, M.D., ASCO Expert. "Importantly, it's effective regardless of prior ipilimumab treatment. Anti PD-1 as a single agent is a major breakthrough and improves on the initial success of ipilimumab in metastatic melanoma."

This research was supported by Merck.

ASCO2014特集

乳がん患者においてゾレドロン酸の投与頻度を減少させても安全である（Abstract: LBA9003）

骨転移を有する乳がん女性においてゾレドロン酸の投与頻度を減らしても安全であり有効性は通常頻度の場合と同等である

Less frequent zoledronic acid is safe and has comparable efficacy for women with breast cancer and bone metastases

2014年ASCO年次総会で発表された第III相ランダム化スタディの結果、骨転移を有する乳がん女性において毎月のゾレドロン酸治療を1年間施行した後に、治療を3か月毎のスケジュールに変更しても安全であることが示唆された。OPTIMIZE-2スタディにおいて、乳がんの骨転移を有する患者で約1か月毎のゾレドロン酸治療を終了した女性403人が、次の1年間、ゾレドロン酸3か月毎投与群と毎月投与群にランダムに割り付けられた。研究者らは骨イベント（長骨や椎骨骨折、脊髄圧迫、および骨転移により行われた治療）率を評価した。骨イベントは2つの投与群で同等であり（毎月投与群22%対3か月毎投与群23.2%）、毎月毎の治療に対する治療頻度の減少の非劣性が示唆された。初回骨イベントまでの時間や骨代謝マーカーなどの他の有効性評価項目もまた、2群間で同等であった。疼痛レベルや鎮痛薬の使用も2つの投与群で差はなかった。全体的な安全性プロファイルや腎の副作用に関して、2つのゾレドロン酸投与群間で明らかな差は認められなかった。

Full Text

New findings from a phase III randomized study, OPTIMIZE-2, suggest that after a year of monthly treatment with zoledronic acid, women with breast cancer and bone metastasis can safely scale back treatment to an every-three-month schedule. Lower-frequency dosing appeared to have comparable efficacy in reducing complications from bone metastases as monthly dosing, and may decrease the risk of rare, serious side effects associated with zoledronic acid.

"The addition of bisphosphonate drugs like zoledronic acid has dramatically improved the care of patients with bone metastases. But long-term treatment carries the risk of serious side effects, such as osteonecrosis of the jaw and kidney problems," said lead study author Gabriel N. Hortobagyi, M.D., a professor of medicine at the M.D. Anderson Cancer Center in Houston, TX. "We found that less frequent treatment may reduce the risk of serious side effects, with added benefits in reduced patient inconvenience and cost."

Zoledronic acid is commonly used to reduce complications from bone metastases, such as bone fractures and spinal cord compression. Most doctors give zoledronic acid every four weeks for the first year, starting at diagnosis of bone metastases. It is thought that the treatment should continue indefinitely, but doctors have been concerned about the risk of side effects. To date, there has been limited research, and there are no evidence-based guidelines for the optimal treatment schedule after the first year.

In the OPTIMIZE-2 study, 403 women with bone metastases from breast cancer who had completed roughly one year of monthly zoledronic acid therapy were randomly assigned to receive zoledronic acid every month vs. every three months for an additional year. Researchers assessed the skeletal event rate (fractures of long bones and vertebrae, spinal cord compressions, and interventions precipitated by bone metastases).

The skeletal event rates were comparable between the two arms (22 percent in the monthly arm vs. 23.2 percent in the every-three-months arm) indicating that less frequent treatment was not inferior to monthly treatment. Other efficacy measures, such as time to first skeletal event and bone turnover markers, were also similar between the two arms. There were no differences in pain levels and use of pain medications between the two treatment schedules. However, due to design limitations and statistical concerns, the efficacy data of OPTIMIZE-2 should be interpreted with caution.

No obvious differences in overall safety profile and in kidney side effects were noted between the two zoledronic acid treatment regimens. Two cases of osteonecrosis of the jaw were reported in the monthly arm, whereas none in the every-three-months treatment arm.

"Women with metastatic breast cancer who require long-term protection against bone fractures now have the option of receiving maintenance bisphosphonate therapy at less frequent intervals without compromising benefit or safety," said Patricia Ganz, M.D., FASCO, ASCO Expert.

This research was supported by Novartis Pharmaceuticals.

ASCO2014特集

子宮頸がんにおけるT細胞免疫療法（Abstract: LBA3008）

HPV標的養子T細胞療法は進行子宮頸がんに対する個別化医療となる可能性がある

HPV-targeted adoptive T-cell therapy may provide a personalized strategy for advanced cervical cancer

第50回American Society of Clinical Oncology学会で発表された第II相研究から、進行子宮頸がんに対し養子T細胞療法として知られる新たな個別化免疫療法を施行された複数の女性において、注目すべき結果が得られたことが示された。HPV標的養子T細胞療法は、腫瘍内のHPVに対する自然免疫応答を本質的に増幅させる。今回のスタディにおいて、9人の患者が養子T細胞療法を受け、うち3人が治療に奏効を示した。1人の患者は部分寛解し、腫瘍体積が39%減少し、2人の患者は完全寛解した。これら2人の患者は広範な転移を有しており、以前の治療にもかかわらず子宮頸がんが増悪していた。解析の時点で、これら2人の患者は治療後11か月および18か月寛解状態が持続していた。この治療には重篤な副作用があり、最も多かったのが血球数減少、感染症、および代謝障害であった。養子T細胞療法が子宮頸がんに対し検証されたのは今回が初めてである；過去にはメラノーマ、白血病、およびサルコーマにおいて有望であることはすでに示されている。研究者らは今回のスタディを拡大しさらに患者を組み入れることを計画している。このスタディではまた、咽喉がんや肛門がんなど他のHPV関連がんの治療としての養子T細胞療法に関しても調査している。

Full Text

A small phase II study shows striking results in several women with advanced cervical cancer, using a new type of personalized immunotherapy, known as adoptive T-cell therapy. In the study, two patients with widespread metastases had complete remissions after a single treatment with the HPV-targeted T-cells, and have been cancer free for nearly a year or longer.

"This proof-of-principal study shows that adoptive transfer of HPV-targeted T-cells can cause complete remission of metastatic cervical cancer and that this remission can be long-lasting," said lead study author Christian Hinrichs, M.D., an assistant clinical investigator at the National Cancer Institute in Bethesda, M.D.. "One implication of the study is that cellular therapy might have application to a broader range of tumor types than previously recognized. This treatment is still considered experimental and is associated with significant side effects. We also need to explore why this therapy worked so well in certain women, and not in others."

Women with metastatic cervical cancer – caused by the human papillomavirus (HPV) – have limited treatment options. The median survival with the two standard first-line therapies, chemotherapy and a combination of chemotherapy and bevacizumab, is 13 and 17 months, respectively. No second-line treatments that improve survival are available.

HPV-targeted adoptive T-cell therapy essentially augments the natural immune response to HPV in the tumor. To develop the therapy, HPV-targeted T-cells are grown from a patient's tumor in the laboratory. Those cells are subsequently infused back into the patient to fight the cancer. This is the first time adoptive T-cell therapy has been tested in cervical cancer; it has previously shown promise in melanoma, leukemia, and sarcoma.

In the study, nine patients received adoptive T-cell therapy, and three responded to the treatment. One patient had a partial response, with a 39-percent reduction in tumor volume, and two patients had complete remissions. Those two patients had widespread metastases, and the disease had progressed despite prior therapy. At the time of analysis, those patients remained in remission for 11 and 18 months after treatment. The treatment was associated with serious side effects, the most common being low blood counts, infections, and metabolic disorders.

Researchers are planning to expand this study to enroll additional patients. The same study is also exploring adoptive T-cell therapy for treatment of other HPV-related cancers, such as throat cancer and anal cancer.

Adoptive T-cell therapy is being offered at an increasing number of major medical centers in the United States and other countries. Along with screening and preventative vaccines, better treatments are needed to reduce cervical cancer deaths in the future.

"Novel treatments are needed for women with recurrent or metastatic cervical cancer. Because of the association between cervical cancer and the HPV virus, adoptive immunotherapy is a promising approach for these patients," said Don S. Dizon, M.D., FACP, ASCO Expert. "These preliminary data demonstrate, not only the viability of this approach, but that gains in survival can be realized in a cancer where patients have little to no effective treatment options and where median survival is usually less than two years."

This research was supported by the National Cancer Institute, National Institutes of Health.

ASCO2014特集

分子標的薬の併用により卵巣がんの予後が改善する（Abstract: LBA5500）

新規分子標的薬の併用は再発卵巣がん患者の無増悪生存期間を有意に延長させる

New targeted drug combination significantly increases progression-free survival in women with recurrent ovarian cancer

2つの経口治験薬、PARP阻害薬olaparibおよび抗血管新生薬cediranibの併用は、再発プラチナ製剤感受性卵巣がんまたは*BRCA*遺伝子変異のある卵巣がんに対し、olaparib単剤よりも有意に有効である。再発プラチナ製剤感受性高悪性度漿液性卵巣がんまたはBRCA変異陽性卵巣がん患者90人がolaparib単剤群またはolaparibとcediranib併用群にランダムに割り付けられた。患者には再発卵巣がんに対する抗血管新生薬やPARP阻害薬による前治療歴はなかった。腫瘍縮小率はolaparib単剤群に比べ併用群において著明に高かった（80%対48%）。併用群患者5人およびolaparib単剤群患者2人が完全寛解した。併用療法は疾患の増悪を実質的に遅延させ、無増悪生存期間はolaparib単剤群の9か月に対し、併用群では17.7か月であった。プラチナ製剤感受性患者における標準的な化学療法の過去のトライアルでは、無増悪生存期間は8～13か月であった。この第II相研究の結果は、第50回American Society of Clinical OncologyのLate Breaking sessionで発表された。

Full Text

Findings from a federally funded, NCI-sponsored phase II study suggest that the combination of two investigational oral drugs, the PARP inhibitor olaparib and the anti-angiogenesis drug cediranib, is significantly more active against recurrent, platinum chemotherapy-sensitive disease or ovarian cancer related to mutations in *BRCA* genes than olaparib alone. The progression-free survival was 17.7 months with the combination treatment vs. nine months with olaparib alone.

"The significant activity that we saw with the combination suggests that this could potentially be an effective alternative to standard chemotherapy," said lead study author Joyce Liu, M.D., M.P.H., an instructor in medical oncology at Dana-Farber Cancer Institute in Boston, MA. "At the same time, this approach is not yet ready for clinical practice as neither of these drugs is currently FDA approved for ovarian or any other cancer. We also need additional clinical trials to confirm the findings of this study to see how this combination compares to standard treatment."

This study is the first time a combination of a PARP inhibitor and an anti-angiogenic drug has ever been explored in a clinical trial for ovarian cancer. It confirms preclinical research that suggested that olaparib and cediranib synergize. Dr. Liu and her colleagues designed this trial to confirm, in a clinical setting, that the combination of these two drugs was more active than the single drug olaparib alone.

As many as 80 percent of women with high-grade serous ovarian cancer experience a relapse after initially responding to chemotherapy. When the cancer comes back, it is more difficult to treat, because it will have metastasized to the pelvis and abdomen, or even the lungs. The current standard treatment for recurrent ovarian cancer is chemotherapy, which often causes significant side effects. Even in the setting of initial response, resistance to chemotherapy eventually develops. Therefore, researchers have been exploring alternate regimens using targeted drugs, with the goal of overcoming such treatment resistance.

Ninety women with recurrent, platinum-sensitive, high-grade serous or BRCA mutation-related ovarian cancer were randomly assigned to treatment with olaparib alone or olaparib plus cediranib. The women had no prior treatment with anti-angiogenic drugs in the setting of recurrent ovarian cancer or PARP inhibitors.

Tumor shrinkage rates were markedly higher in the combination arm than in the olaparib arm (80 vs. 48 percent). Five patients in the combination arm and two patients in the olaparib alone arm had a complete remission. The combination treatment substantially delayed disease progression, with a progression-free survival of 17.7 months compared to nine months for olaparib alone. Past trials of standard chemotherapy in the platinum-sensitive setting have demonstrated progression-free survival times between eight and 13 months.

Although certain side effects — high blood pressure, fatigue, and diarrhea — occurred more frequently in the combination arm, they were usually controllable by symptom management and dose reductions as needed.

Prior trials have suggested that PARP inhibitors tend to have the most activity in women who have either platinum-sensitive ovarian cancer or BRCA mutations in their tumors. An exploratory analysis from this study suggests that the combination treatment appears to also be active in patients without a known BRCA-mutation. Dr. Liu remarked that it is reasonable to explore whether the combination treatment would be effective in women with platinum-resistant disease as well.

"The combination of cediranib plus olaparib resulted in a significantly higher response rate, though at the expense of higher toxicity. Whether this response translates into gains in survival needs further follow-up," said Don S. Dizon M.D., FACP, ASCO Expert. "However, this combination represents an oral, non-chemotherapy-based combination treatment option for women with high-grade serous or BRCA-mutation related ovarian cancers and definitely warrants further study."

This study was supported by the National Cancer Institute, National Institutes of Health.

ASCO2014特集

進行性甲状腺がんにおいて新規分子標的薬は有効性が高い（Abstract: LBA6008）

Lenvatinibは進行性放射性ヨウ素治療抵抗性分化型甲状腺がん患者において高い奏効率を示す

Lenvatinib yields high response rates in patients with radioiodine-resistant, advanced differentiated thyroid cancer

SELECTスタディの結果、lenvatinibは標準的な放射性ヨウ素（RAI）療法に抵抗性の分化型甲状腺がんに対し有効性が高いことが示された。Lenvatinibは、VEGFR1-3、FGFR 1-4、PDGFR-β、KIT、およびRETなどのがん細胞内のいくつかの標的をブロックする経口チロシンキナーゼ阻害薬である。この薬剤は今、肝がん、肺がん、および腎がんや他のタイプの固形がんの治療に対する可能性を第II相および第III相試験において検証されている。今回のスタディにおいて、1年以内に増悪した進行性RAI治療抵抗性分化型甲状腺がんの患者392人が、lenvatinibまたはプラセボ群にランダムに割り付けられた。プラセボ群患者は疾患が増悪した時点でlenvatinib群へクロスオーバーすることが許可された。Lenvatinib群では約65%の患者に腫瘍縮小が認められたのに対し、プラセボ群ではわずか3%であった。奏効は多くが治療開始後2か月以内に認められた。無増悪生存期間中央値はプラセボ群よりもlenvatinib群において有意に長かった（18.3か月対3.6か月、p<0.001）。全生存期間中央値には到達しなかった。この第III相スタディは第50回American Society of Clinical OncologyのLate Breaking sessionで発表された。

Full Text

Findings from the SELECT phase III study show that lenvatinib is highly effective against differentiated thyroid cancer that is resistant to standard radioiodine (RAI) therapy. The new oral targeted drug delayed disease progression by 14.7 months, and nearly two thirds of patients experienced tumor shrinkage. The median overall survival has not been reached.

"We are confident that, based on our findings, lenvatinib will eventually become a standard treatment for radioiodine-resistant thyroid cancer," said lead study author Martin Schlumberger, M.D., a professor of oncology at the University Paris Sud in Paris, France. "As little as a year ago, this group of patients had no effective treatment options. It's remarkable that we now have two active drugs in this setting, both of them tyrosine kinase inhibitors."

Differentiated thyroid cancer is the most common subtype of thyroid cancer. Although differentiated thyroid cancer is generally curable with standard treatment – surgery and RAI – roughly 5-15 percent of patients develop RAI resistance.

Lenvatinib is an oral tyrosine kinase inhibitor that blocks several targets in a cancer cell, including VEGFR1-3, FGFR 1-4, PDGFR-β, KIT, and RET. It is being explored in phase II and phase III clinical trials as a potential treatment for liver, lung, and kidney cancers and other types of solid tumors.

In this study, 392 patients with advanced, RAI-resistant, differentiated thyroid cancer that had progressed within a year were randomly assigned to treatment with either lenvatinib or placebo. Patients on the placebo arm were allowed to cross over to the lenvatinib arm upon disease progression.

Approximately 65 percent of patients experienced tumor shrinkage in the lenvatinib arm, compared to only 3 percent in the placebo arm. The majority of responses occurred within two months of starting treatment. The median progression-free survival was 18.3 months in the lenvatinib arm vs. 3.6 months in the placebo arm. The median overall survival has not been reached.

The five most common side effects of lenvatinib were high blood pressure, diarrhea, decreased appetite, decreased weight, and nausea. Although the side effects necessitated dose reductions in 78.5 percent of patients, the benefit of lenvatinib persisted with decreased dose, Dr. Schlumberger noted.

"The progress we're seeing with targeted agents for uncommon cancers is encouraging," said Gregory A. Masters, M.D., ASCO Expert. "Patients with differentiated thyroid cancer have historically had limited options when the disease progresses despite radioactive iodine therapy. Now this new drug, lenvatinib, offers an effective option with reasonable side effects and can help patients live longer before the disease worsens."

This research was supported by Eisai Inc.

ASCO2014特集