進行性腎細胞がん治療の進歩

RECORD-1トライアルの結果、everolimusは標準治療が無効だった進行した転移性腎細胞がん患者の無増悪生存期間を有意に延長させることが示された

RECORD-1 trial shows that everolimus significantly lengthens time to progression in patients with advanced kidney cancer who failed standard therapies

Everolimusは標準治療が無効だった進行した転移性腎細胞がん患者に有意に有益である、とAmerican Society of Clinical Oncology学会で発表された。RECORD-1トライアルは、ソラフェニブ、スニチニブまたはその両者を含む治療を行ったにもかかわらず悪化した患者400人以上を無作為化した。無増悪生存期間はeverolimusにおいてプラセボと比較し有意に改善した（中央値はそれぞれ4ヵ月対1.9ヵ月）。標的病変における最大腫瘍変化率は、評価可能な患者（everolimusとプラセボでそれぞれ223人および107人）の判定結果から、初回の二重盲検試験期間中にeverolimusを投与された患者の50%に腫瘍の縮小が認められたのに対し、プラセボ群におけるその割合は8%であった。この試験では疾患の進行が確認された時点で非盲検化され、プラセボ群の患者は実薬治療に切り換えられた。中間解析結果が完了した後、試験の二重盲検部分は中止された。

Full Text

Everolimus (RAD001) significantly lengthens progression-free survival in patients with metastatic renal cell carcinoma who have failed standard therapies, according to trial results presented at the annual meeting of the American Society of Clinical Oncology.

"This is the first study to show clinical benefit in patients with advanced kidney cancer who have experienced treatment failure with the most commonly used first-line therapies," said Robert J. Motzer, MD, attending physician, Memorial Sloan-Kettering Cancer Center, New York, and principal investigator of the RECORD-1 trial. "The results show RAD001 extended progression-free survival in patients regardless of their prior treatments, risk status, age, or gender."

The RECORD-1 trial (REnal Cell cancer treatment with Oral RAD001 given Daily) is the largest Phase III trial to evaluate an oral mTOR inhibitor in the setting of metastatic renal cell carcinoma, randomizing more than 400 patients with disease that worsened despite prior treatment, including sorafenib, or sunitinib, or both. In addition, eligible patients were allowed to have had prior therapy with bevacizumab, interferon, or interleukin-2.

Primary endpoint was progression-free survival assessed via a blinded, independent central review and defined as the time between randomization and first documented disease progression or death due to any cause. There was a statistically significant improvement for RAD001 compared with placebo (median progression-free survival 4 months versus 1.9 months, respectively).

Secondary endpoints included comparison of overall survival, objective response rate, quality of life, safety, and pharmacokinetics. There was no significant difference in overall survival between groups. Study design allowed patients to be unblinded at the time of radiological disease progression; patients receiving placebo were allowed to cross over to receive active treatment. There was no significant difference in objective response rate between the RAD001 and placebo groups (1 percent versus 0 percent).

However, in a central review among patients evaluable for best percentage change in target lesions (223 and 107 patients in RAD001 and placebo arms, respectively), tumor shrinkage was observed in 50 percent of patients receiving RAD001 during the double-blind portion of the study versus 8 percent of patients receiving placebo. Quality of life measurements taken throughout the study showed no significant difference between groups.

Safety findings were consistent with those in prior Phase II studies. The most frequent adverse events in patients who took RAD001 included mouth sores (40 percent), feelings of weakness (37 percent), and rash (25 percent). The trial had a low rate of adverse drug reactions leading to discontinuation among patients who took RAD001 (6 percent).

The interim study findings demonstrated that RAD001 significantly extended progression-free survival from 1.9 to 4 months and reduced the risk of cancer progression by 70 percent. Earlier this year, an independent data monitoring committee stopped the RECORD-1 trial after interim results showed that patients receiving RAD001 had significantly longer progression-free survival compared with patients receiving placebo.

RAD001 is a once-daily oral therapy that may offer a new approach to cancer treatment by continuously inhibiting the mTOR protein, a central regulator of tumor cell division and blood vessel growth in malignant cells.

ASCO2008 特集

ビタミンDと乳がん

乳がん診断時にビタミンDが欠乏していた女性は転移および死亡のリスクが有意に高いようである

Women with vitamin D deficiency at the time of diagnosis with breast cancer appear to be at significantly higher risk for metastases and death

乳がん診断時にビタミンDが欠乏していた女性は転移および死亡のリスクが有意に高いようである、とAmerican Society of Clinical Oncology学会で発表された。研究者らは512人の女性において血中のビタミンDレベル、乳がん転移の発現および全生存期間を調査した。患者は2006年まで前向きに追跡された（追跡期間中央値11.6年）。診断時のビタミンDレベルが十分であったのは患者のうちわずか24%であった。ビタミンDが欠乏（< 50nmol/L）している女性は、より高悪性度のがんを有する傾向にあった。10年後ビタミンDレベルが十分（> 72nmol/L）であった女性の83%に転移はなく85%が生存していたのに対し、ビタミンD欠乏症の女性におけるそれぞれの割合は69%および74%であった。ビタミン欠乏症の女性における最も多い死因は乳がんであった。この相関関係を確認するスタディが始まっている。

Full Text

Women with vitamin D deficiency when their breast cancer is diagnosed appear to be at significantly higher risk for metastases and death compared with women who have adequate blood levels, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

Specifically, women with vitamin D deficiency were 94 percent more likely to develop metastatic disease and 73 percent more likely to die. The significance of low vitamin D levels was compounded by the finding that more than a third (37.5 percent) of women with breast cancer had vitamin D levels that were classified as deficient and another 38.5 percent were classified as having insufficient levels of vitamin D).

"We were concerned to find that vitamin D deficiency was so common in women diagnosed with breast cancer and that very low vitamin D levels adversely affected patient outcome. Our results need to be replicated in other clinical studies," explained lead author Pamela Goodwin, MD, professor of medicine at the University of Toronto and holder of the Marvelle Koffler Chair in Breast Research at the Samuel Lunenfeld Research Institute, Mount Sinai Hospital.

"These data indicate an association between vitamin D and breast cancer outcome, but we can't say at this time if it is causal."

In the current study, Goodwin and her Canadian colleagues examined the relationship between vitamin D levels in the blood, incidence of breast cancer metastases and overall survival in 512 women diagnosed with breast cancer between 1989 and 1995. Women were prospectively followed until 2006, for a median follow-up of 11.6 years.

Researchers found that only 24 percent of patients had adequate levels of vitamin D when diagnosed with cancer. Women deficient in vitamin D (less than 50 nmol/L) were more likely to have high-grade cancers. After 10 years, 83 percent of women with adequate levels (more than 72 nmol/L) remained free of metastases and 85 percent were still alive, compared with only 69 percent and 74 percent, respectively, of women with vitamin D deficiency. Most of these deaths were attributed to breast cancer.

If these observations are confirmed in a second, similar study including other women with breast cancer, which is already ongoing, Goodwin recommends a new randomized clinical trial examining the effects of raising blood levels of vitamin D on outcomes in women with breast cancer.

ASCO2008 特集

進行肺がんの治療の進歩（Abstract #: 3）

プラチナ製剤ベースの化学療法にcetuximabを追加することにより進行肺がんと診断された患者の生存期間が改善する

Adding cetuximab to platinum-based chemotherapy improves survival for patients diagnosed with advanced-stage lung cancer

プラチナ製剤ベースの化学療法にcetuximabを追加することにより、進行非小細胞肺がんと診断された患者の生存期間が改善する、とAmerican Society of Clinical Oncology学会で発表された。この国際スタディでは1,125人の患者をシスプラチンおよびビノレルビンのみの化学療法（568人）またはそれにcetuximabを組み合わせた化学療法（557人）に無作為に割り付けた。94%の患者がステージIVであった。全生存期間は、cetuximabを追加した化学療法群（11.3ヵ月）においてシスプラチンおよびビノレルビンのみの化学療法（10.1ヵ月）群よりも長く、奏効率は追加療法群（36.3%）においてシスプラチンおよびビノレルビンのみの化学療法群（29.2%）よりも高かった。Cetuximabは腺がんおよび扁平上皮がんを含む全ての組織学的サブタイプにおいて有効であり、この結果から今回のトライアルは、分子標的薬をファーストライン治療の一部として使用すると全てのサブタイプの非小細胞肺がんに対して有効であることを示した初めてのものといえる。

Full Text

Adding cetuximab to platinum-based chemotherapy improves survival for patients diagnosed with advanced non-small cell lung cancer of any subtype, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

The large phase III study was the first to document that a targeted drug has a survival benefit as first-line treatment for all subtypes of non-small cell lung cancer. The study evaluated addition of cetuximab to the platinum-based chemotherapy regimen of cisplatin and vinorelbine.

"Patients with advanced non-small cell lung cancer [NSCLC] have limited treatment options and life expectancy is short, so the survival increase shown in this study is an important step for these patients" said Robert Pirker, MD, an associate professor of medicine at Medical University of Vienna in Austria and the study's lead author.

"These results clearly establish cetuximab in combination with chemotherapy as a new standard in first-line treatment of NSCLC."

The current standard of care for patients newly diagnosed with advanced disease is cisplatin or carboplatin combined with a "third-generation drug," namely, vinorelbine, gemcitabine, paclitaxel or docetaxel. Earlier studies of gefitinib and erlotinib did not show an additional benefit as part of first-line standard chemotherapy. These agents are currently approved for patients whose initial chemotherapy has failed.

In the current study, 1,125 patients in 30 countries were randomized to chemotherapy with cisplatin and vinorelbine alone (568) or chemotherapy plus cetuximab (557); 94 percent of patients had stage IV disease.

Overall survival was longer for patients who received cetuximab plus chemotherapy (11.3 months) compared with those receiving chemotherapy alone (10.1 months). Additionally, the response rate was better in combination arm (36.3 percent) than in the arm with chemotherapy alone (29.2 percent).

The benefit of cetuximab was seen in patients with all histological subtypes, including adenocarcinoma and squamous cell carcinoma, the two most common subtypes. Other targeted therapies for lung cancer have only proven effective against certain subtypes.

As expected, the most frequent side effect was an acne-like rash, which was manageable with medication. Moderate rashes were seen more frequently in patients receiving cetuximab (10.4 percent) than in patients receiving chemotherapy alone (0.2 percent).

The authors noted more studies will evaluate cetuximab for patients with earlier stages of the disease based on the positive findings of the current trial. Cetuximab may be tried in combination with chemotherapy or chemoradiotherapy for patients with locally advanced disease or as an additional treatment after surgery in patients with early-stage disease.

ASCO2008 特集

精巣がんに対する単回投与化学療法（Abstract #: 1）

早期精巣がん患者に対する単回投与の化学療法は放射線療法と同等に有効であり毒性は少ない

A single dose of chemotherapy is equally effective and less toxic than radiation therapy for patients with early-stage testicular cancer

早期精巣がん患者に対する単回投与の化学療法は放射線療法と同等に有効であり毒性は少ない、とAmerican Society of Clinical Oncology学会で発表された。これまでで最大規模の今回の精巣がんトライアルでは、stage Iのセミノーマを、術後カルボプラチン単回投与療法（患者573人、腎機能に基づき用量を決定）または2～3週間の放射線療法（患者904人、毎日照射）に無作為に割り付けた。5年後の再発率は両群間で同等であった（カルボプラチン群5%、放射線療法群4%）。追跡期間中央値6.5年後にカルボプラチン群の患者は残存している方の精巣に腫瘍が発症する確率が78%低かった（放射線療法群15例、カルボプラチン群2例）。死亡例は1例であった（放射線療法群）。経過観察は今後も継続される。前立腺がん領域では多方面で有効な治療があることにより医師や患者らがファーストライン治療を決定する際に選択の余地があることから、発表者は精巣がんと前立腺がんを比較した。

Full Text

A single dose of chemotherapy is equally effective and less toxic than radiation therapy for early-state testicular cancer, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

The study was the first randomized trial to evaluate long-term outcome after a single dose of chemotherapy compared with radiation therapy, the current standard of care. The study, the largest ever in testicular cancer, also showed that after five years, patients receiving chemotherapy had a decreased risk of developing a second tumor in the other testicle, although longer follow-up is needed.

All patients in the study had stage I seminomas. After surgical resection of the affected testicle, patients were randomized to a single dose of carboplatin given over one hour on an outpatient basis (573 patients) or a course of daily radiation therapy given for two or three weeks (904 patients).

The dose of carboplatin varied because it was based on each patient's kidney function. After five years, the rate of cancer recurrence was comparable in both arms - 5 percent of patients in the chemotherapy group and 4 percent of patients in the radiation therapy group. With a median follow-up of 6.5 years, patients who received carboplatin were 78 percent less likely to develop a tumor in the remaining testicle (15 patients in the radiation therapy arm versus 2 patients in the carboplatin arm).

One patient in the radiation therapy arm died of seminoma versus none in the chemotherapy arm. Side effects for both treatments were few, although those in the radiation therapy group reported higher levels of moderate or severe lethargy (24 percent versus 7 percent for patients receiving carboplatin) four weeks after starting treatment.

"Personal preference is becoming a more important factor in determining the best treatment for patients with testicular cancer. We've also seen this in prostate cancer, where there are a number of equally strong treatment options," said Tim Oliver, MD, professor emeritus of medical oncology at St. Bartholomew's Hospital in London and the study's lead author. "This study establishes surgery followed by carboplatin chemotherapy as a safe new alternative for patients who have early-stage seminoma and would prefer a treatment that lasts a shorter period of time."

The researchers said that future studies will investigate the option of lumpectomy and single-dose carboplatin for men who present early enough with small tumors, allowing them to avoid losing the diseased testicle.

ASCO2008 特集

転移性大腸がんの遺伝子（Abstract #: 2）

KRAS遺伝子に変異のない転移性大腸がん患者はファーストラインの一部としてcetuximabを用いた治療がより有効である

Patients who have no mutations in the KRAS gene are more likely to respond to cetuximab as part of their first-line therapy for metastatic colorectal cancer

腫瘍細胞のKRAS遺伝子に変異のない転移性大腸がん患者は変異のある患者よりも、ファーストラインの一部としてcetuximabを用いた治療がより有効であるとAmerican Society of Clinical Oncology学会で発表された。今回のスタディでは、CRYSTALトライアルの患者1,198人中587人の組織検体を用いて、このサブグループの患者がcetuximabにより有益性がより多く得られるかを評価した。変異は35.6%の患者の腫瘍において認められた。KRAS遺伝子が正常であった患者のうち治療が有効であったのはcetuximabを追加した化学療法群で59.3%（約半分の腫瘍縮小）であったのに対し、従来の化学療法のみの群では43.2%であった。変異のある患者においては、これらの治療群間で奏効率に差はなかった。全ての患者のデータを解析したオリジナルのスタディでは、FOLFIRIとcetuximabの併用により進行リスクが15%低下した。

Full Text

Patients whose tumor cells have no mutations in the KRAS gene are more likely to respond to cetuximab as part of their first-line therapy for metastatic colorectal cancer, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

"While our initial study indicated that cetuximab has the potential to become part of the standard treatment for patients with newly diagnosed metastatic colorectal cancer, this study helps us to identify which patients are most likely to benefit from adding the drug to treatment," said Eric Van Cutsem, MD, PhD, professor at the University Hospital Gasthuisberg in Leuven, Belgium, and the study's first author.

"KRAS testing should be routinely conducted in all colorectal cancer patients immediately after diagnosis to ensure the best treatment strategies for the individual patient."

KRAS mutations, which are found in 30 to 45 percent of all colorectal tumors, have previously been shown to predict whether patients will benefit from agents that block epidermal growth factor receptors in the second-line or later setting.

The CRYSTAL trial was the first randomized study to compare patients who received chemotherapy alone to those who received chemotherapy plus cetuximab as part of initial therapy. Researchers presented data last year that showed addition of cetuximab to FOLFIRI chemotherapy resulted in longer progression-free survival than treatment with the combination chemotherapy alone.

The current study is an extension of the CRYSTAL trial that sought to determine whether certain subsets of patients benefited more from the addition of cetuximab than others.
Researchers had access to tumor material from 587 of the 1,198 patients in the original trial and used these samples to determine each patient tumor's KRAS status.

KRAS mutations were detected in 35.6 percent of patients' tumors. Investigators found that among patients with normal KRAS, 59.3 percent responded to treatment with chemotherapy and cetuximab (their tumors shrank by more than half), compared with 43.2 percent who responded to chemotherapy alone. Among patients with mutated KRAS in their tumors, there was no difference in response rates between those who received chemotherapy alone and those who received chemotherapy and cetuximab.

In the overall study, which analyzed data for all patients, the addition of cetuximab to FOLFIRI resulted in a 15-percent decreased risk for progression. When KRAS was evaluated, the normal KRAS gene group was shown to have a 32-percent decreased risk for progression with the addition of cetuximab. Patients with a mutation in KRAS did not get an additional benefit from addition of cetuximab to chemotherapy.

ASCO2008 特集

乳がん再発リスクの低下（Abstract #: LBA4）

ゾレドロン酸は術後ホルモン療法を受けている早期乳がん患者の再発リスクを軽減する

Zoledronic acid reduces risk for recurrence when given to patients with early-stage breast cancer who are receiving postoperative hormone therapy

ゾレドロン酸は、術後卵巣機能抑制およびホルモン療法を受けている閉経前早期乳がん患者の再発リスクを軽減する、とAmerican Society of Clinical Oncology学会で発表された。このphase IIIトライアルでは、ゴセレリンを用いた術後卵巣抑制療法を受けているstage IまたはIIの患者を、タモキシフェンまたはアナストロゾールのいずれかにゾレドロン酸を追加または追加なしの4群のいずれかに無作為に割り付けた。一次エンドポイントは無増悪生存期間であった。追跡期間中央値の60ヵ月後、ホルモン療法とゾレドロン酸の併用によりホルモン療法単独と比較し再発リスクが35%低下した2つのホルモン療法群の間に有意な差はなかった。4つの治療群全てにおいて忍容性は良好であり予想外の副作用は認められなかった。

Full Text

Zoledronic acid reduces risk for recurrent breast cancer in premenopausal patients with early-stage disease who have undergone surgery and are receiving ovarian suppression and hormone therapy, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

All women in the multicenter phase III trial had cancer that was positive for estrogen receptors, progesterone receptors, or both.

"It's very exciting to find that in addition to preventing bone loss in women undergoing adjuvant endocrine therapy for breast cancer, zoledronic acid can also reduce the likelihood that breast cancer will return in some women," said Michael Gnant, MD, a professor of surgery at the Medical University of Vienna, the president of the Austrian Breast and Colorectal Cancer study group, and the study's lead author.

"Future research will focus on optimizing the administration schedule and the dose, and determining which patients will benefit the most from treatment with zoledronic acid."

The study randomized 1,803 patients with stage I or II disease who were receiving postoperative ovarian suppression using goserelin to one of four arms: treatment with tamoxifen or anastrozole with or without zoledronic acid.

The study's primary endpoint was disease-free survival. After a median follow-up of 60 months, hormone therapy plus zoledronic acid reduced the risk of relapse by 35 percent compared with hormone therapy alone. There was not a significant difference between the two hormone therapies. Treatment was well tolerated in all four groups and there were no unexpected side effects.

ASCO2008 特集

子宮内膜がんに対する膣内小線源放射線療法（Abstract #: LBA5503）

高リスクの子宮内膜がん再発予防目的の膣内小線源放射線療法は外照射療法と比較し有効性は同等で毒性は少ない

Vaginal brachytherapy is equally effective and less toxic than external beam radiation in preventing recurrence of higher-risk endometrial cancer

高リスクの子宮内膜がん再発予防目的の膣内小線源放射線療法は外照射療法と比較し有効性は同等で毒性は少ない、とAmerican Society of Clinical Oncology学会で発表された。PORTEC-2 phase IIIトライアルでは、中等度～高リスクの子宮内膜がん患者427人のうち214人を骨盤外照射療法に、213人を膣内シリンダーを用いた小線源放射線療法に無作為に割り付けた。全ての患者は両側卵管卵巣摘出術を含む子宮摘出術を施行された。3年間の追跡調査後、膣、骨盤内、および遠隔転移は小線源療法でそれぞれ0%、1.3%、および6.4%であり、外照射療法ではそれぞれ1.6%、0.7%、および6.0%であった。全生存期間（90.4%対90.8%）または無増悪生存期間（89.5%対89.1%）には有意差はなかったが、小線源療法を受けた患者の方が外照射を受けた患者よりも訴える副作用のレベルが低かった。

Full Text

The first phase III study of its kind has found that vaginal brachytherapy is as effective at preventing recurrence of higher-risk endometrial cancer as external beam radiation therapy with fewer side effects and a better quality of life, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

"Based on this study, we expect that vaginal brachytherapy will be adopted as the new standard of care for patients with this type of endometrial cancer," said Remi A. Nout, MD, a resident in radiation oncology in the department of clinical oncology at Leiden University Medical Center and the study's lead author.

"This treatment is simpler and just as effective as external beam radiation, and it allows patients to have a better quality of life both during and after treatment. This new strategy will make treatment and recovery for many patients much more manageable moving forward."

For intermediate-to-high risk disease, determined by tumor grade, disease stage, and patient age, the standard treatment has been surgery followed by external beam radiation therapy. Brachytherapy is currently used in combination with external beam radiation for more advanced disease. Patients with low-risk disease are treated with surgery alone.

The PORTEC-2 study, a multicenter Dutch trial, randomized 427 patients with intermediate-to-high risk endometrial cancer into one of two arms: 214 patients received external beam pelvic radiotherapy and 213 received vaginal brachytherapy with a cylinder placed into the vagina.

All patients had previously undergone hysterectomy with bilateral oophorectomy. At three years of follow-up, rates of vaginal, pelvic, and distant relapse were 0 percent, 1.3 percent, and 6.4 percent for brachytherapy and 1.6 percent, 0.7 percent, and 6.0 percent for external beam radiotherapy.

There were no significant differences in overall survival (90.4 percent vs. 90.8 percent) or progression-free survival (89.5 percent vs. 89.1 percent).

Patients who received brachytherapy, however, reported a lower level of side effects than patients who received external beam radiotherapy. The most common side effect was diarrhea. After completion of radiotherapy, 22 percent of external beam radiotherapy patients reported moderate to severe diarrhea compared with 6 percent in the vaginal brachytherapy group. As a result, 13 percent of external beam radiotherapy patients reported moderate to severe limitation in their daily activities due to intestinal problems compared with 5 percent in the vaginal brachytherapy group.

Although these side effects gradually decreased over time, two years after treatment 6 percent of external beam radiotherapy patients still reported moderate to severe diarrhea compared with 1 percent in the vaginal brachytherapy group, which resulted in 5 percent and 2 percent moderate to severe limitation in daily activities due to intestinal problems, respectively.

Physicians reported significantly higher rates of gastrointestinal toxicity during external beam radiotherapy: 35 percent of patients had mild diarrhea or cramping and 19 percent had moderate diarrhea greater than five times a day during external beam radiation therapy, compared with 12 percent and 1 percent for brachytherapy.

膵臓がんに対する有効な化学療法（Abstract #: LBA4504）

ゲムシタビンは早期膵臓がん患者の全生存率を改善する

Gemcitabine improves overall survival for patients with early-stage pancreatic cancer

早期膵臓がん患者に対し、ゲムシタビンは全生存率を改善し利益をもたらした初めての化学療法薬であるとAmerican Society of Clinical Oncology学会で発表された。CONKO-001トライアルでは外科的切除術（すなわち肉眼的腫瘍摘出術）の成功した患者368人をゲムシタビン投与群または特別な抗がん療法を施行せず経過観察する群に無作為に割り付けた。過去に公表されたデータではゲムシタビンは無病生存率を改善した。最終のデータを用いた今回の解析では、3年後および5年後の無病生存率はゲムシタビンでそれぞれ23.5%および16.5%であり、経過観察ではそれぞれ7.5%および5.5%であった。3年後および5年後の全生存率はゲムシタビンでそれぞれ36.5%および21%であり、経過観察ではそれぞれ19.5%および9.0%であった。現在進行中のスタディでは、ゲムシタビンと分子標的薬erlotinibまたはsorafenibの併用を評価している。

Full Text

Gemcitabine improves overall survival for patients with early-stage pancreatic cancer, the first chemotherapeutic drug to provide a benefit for these patients, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

The large, multicenter study showed that gemcitabine more than doubled overall survival in patients who have undergone surgery for pancreatic cancer. Gemcitabine is the standard treatment for pancreatic cancer that is too advanced for surgery.

The CONKO-001 study examined whether gemcitabine is beneficial earlier in the course of the disease. Previous results from this study, presented at in 2005, showed that adjuvant gemcitabine improved disease-free survival; investigators continued to follow these patients in order to determine whether the drug also improves overall survival.

"The ultimate goal of adjuvant therapy is improving the cure rate, and we have shown that this treatment more than doubles the overall survival five years after treatment," said Hanno Riess, MD, PhD, a professor at Charite University Medical School in Berlin and the leader of the CONKO study group.

"Based on the earlier results of this study, this regimen is already more widely used in both Europe and the United States. These findings can reassure physicians that the drug is also extending lives."

The trial randomized 368 patients to postoperative gemcitabine or observation with no specific anticancer treatment. All patients had already undergone complete surgical resection of their tumor. Only about 15 to 20 percent of patients are diagnosed at an earlier stage that makes surgery possible.

Estimated disease-free survival at three and five years, respectively, was 23.5 percent and 16.5 percent for gemcitabine versus 7.5 percent and 5.5 percent for the observation group. Overall survival at three and five years was 36.5 percent and 21.0 percent for gemcitabine versus 19.5 percent and 9.0 percent for observation.

Gemcitabine was well-tolerated among patients and there were no differences in toxicity between groups except for white blood cell and platelet counts, which were lower in the gemcitabine group.

Additional studies are already underway comparing treatment with gemcitabine alone to treatment with gemcitabine plus the targeted therapies erlotinib or sorafenib in patients who have undergone successful surgical resection.

ASCO2008 特集

AVADOトライアルでドセタキセルとベバシズマブの併用効果が評価された（Abstract #: LBA1011）

ベバシズマブをドセタキセルに追加しファーストライン化学療法とすることにより局所進行乳がんまたは転移性乳がん患者の病勢進行が抑制された

Adding bevacizumab to docetaxel slows disease progression as first-line chemotherapy for patients with locally advanced or metastatic breast cancer

ベバシズマブをドセタキセルに追加しファーストライン化学療法とすることにより局所進行乳がんまたは転移性乳がん患者の病勢進行が抑制された、とAmerican Society of Clinical Oncology学会で発表された。AVADOトライアルにおいては736人の患者をドセタキセルとプラセボ併用、ベバシズマブ15mg/kgとドセタキセル併用、またはベバシズマブ7.5mg/kgとドセタキセル併用する群に無作為に割り付けた。追跡期間中央値11ヵ月ののち、低用量群の患者はドセタキセル／プラセボ群患者と比較し進行した者が21%少なかった。高用量の患者はドセタキセル／プラセボ群患者と比較し進行した者が28%少なかった。腫瘍が縮小した者はドセタキセル／プラセボ群で44.4%、低用量ベバシツマブ群で55.2%、高用量ベバシツマブ群で63.1%であった。患者数が少なかったため、2用量を統計学的に比較することはできなかった。

Full Text

Adding bevacizumab to docetaxel slows disease progression when used as first-line chemotherapy for patients with locally advanced or metastatic breast cancer, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

Previous studies had shown that adding bevacizumab to paclitaxel doubled progression-free survival in patients with metastatic breast cancer. The current trial was the first phase III study to evaluate bevacizumab in combination with docetaxel, the taxane used more often in Europe, Asia, and Australia.

"This study shows the antiangiogenic approach to treating breast cancer is effective, regardless of which taxane drug it is combined with," said David Miles, MD, a professor and medical oncologist at the Mount Vernon Cancer Centre and the study's lead author.

"We found it does not add a great deal to the toxicity of chemotherapy, which should be reassuring to physicians recommending this course of treatment."

In the current study, the AVADO trial, 736 patients were randomized among three arms: placebo plus docetaxel, 15 mg/kg bevacizumab plus docetaxel, and 7.5 mg/kg bevacizumab plus docetaxel. The higher dose was the standard established in earlier breast cancer studies; however, the lower dose was the standard used to treat colorectal cancer.

After a median follow-up of 11 months, patients in the low-dose group were 21 percent less likely to have disease progression compared with patients who received docetaxel alone. High-dose patients were 28 percent less likely to have disease progression than patients who received docetaxel only.

The percentage of patients with tumor shrinkage was 44.4 percent in the placebo plus docetaxel group, 55.2 percent in the low-dose bevacizumab group, and 63.1 percent in the high-dose group. Because of the number of patients in the trial, it was not possible to statistically compare the two doses with each other.

Patients in the two bevacizumab groups had a slightly higher rate of severe side effects: 74.8 percent in the low-dose group and 74.1 percent in the high-dose group compared with 67.0 percent in the docetaxel plus placebo group.

The most common side effect attributed to bevacizumab was high blood pressure, which was treatable with medication. Severe bowel perforation, a toxicity seen in some other bevacizumab trials, occurred in two patients in the placebo arm and one patient in each of the experimental arms.

ASCO2008 特集

肺がんの維持療法としてのペメトレキセド（Abstract #: 8011）

ペメトレキセドをプラチナ製剤ベースの導入化学療法後の維持療法として使用することにより進行非小細胞肺がんの進行が遅延する

Pemetrexed delays progression of advanced non-small cell lung cancer when used as maintenance therapy after platinum-based induction chemotherapy

プラチナ製剤ベースの導入化学療法完了3～6週後に維持療法としてペメトレキセドを開始することにより進行非小細胞がんの進行が遅延する、とAmerican Society of Clinical Oncology学会で発表された。研究者らはシスプラチンまたはカルボプラチンを含む化学療法を4クール施行後に安定しているstage III BまたはIVの患者441人をペメトレキセドで維持療法を施行する群に無作為に割り付けた。222人の患者はプラセボでの維持療法群に割り付けた。無増悪生存期間はペメトレキセド群においてプラセボ群よりも有意に長かった（4.3ヵ月対2.6ヵ月）。全生存期間はペメトレキセド群で13ヵ月でありプラセボ群では10.2ヵ月であった。筆者らは、ペメトレキセド維持療法の全生存期間に対する効果に関して結論付けるには、最終データの解析が必要であると注意を喚起している。

Full Text

Pemetrexed delays progression of advanced non-small cell lung cancer by 50 percent when started as maintenance therapy three to six weeks after completing four cycles of platinum-based induction chemotherapy, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

"This is the first study to show that lung cancer patients can benefit from maintenance therapy. The fact that this approach significantly increases the amount of time that patients have before their cancer progresses, without increasing additional side effects, is particularly significant," said lead author Tudor Eliade Ciuleanu, MD, PhD, associate professor at the University of Medicine and Pharmacy Iuliu Hatieganu in Romania.

"We recommend giving pemetrexed after a patient completes initial induction therapy, but before cancer progression occurs. This approach affords the greatest chance of killing stray cancer cells before they have a chance to contribute to tumor growth."

Until the current trial, maintenance chemotherapy had not been proven to be of value for patients with lung cancer and is not a part of the standard of care. Pemetrexed is currently approved by the U.S. Food and Drug Administration for treating disease that has progressed despite previous chemotherapy.

In the current study, researchers analyzed progression-free survival and overall survival among 663 patients with stage IIIB or IV disease that was stable following treatment with a platinum-containing drug such as cisplatin or carboplatin. A total of 441 patients were randomized to pemetrexed; 222 patients received a placebo.

Progression-free survival was significantly longer for pemetrexed (4.3 months) than for placebo (2.6 months). Overall survival was 13 months for pemetrexed compared with 10.2 months for placebo.

However, Ciuleanu cautioned that the findings on overall survival are preliminary, noting that final results will be necessary before researchers are able to draw conclusions about the impact of pemetrexed maintenance therapy on overall survival.

The incidence and severity of side effects were generally similar between the two groups. The most significant side effect was moderate to severe anemia, which occurred in 4.5 percent of the pemetrexed group and 1.4 percent of the placebo group.

ASCO2008 特集

化学療法の成功する患者の予測（Abstract #: 7510）

15の遺伝子の発現プロファイルから術後化学療法の最も有益な早期非小細胞肺がん患者が予測できる可能性がある

Expression profile of 15 genes may predict which patients with early-stage non-small cell lung cancer are most likely to benefit from postoperative chemotherapy

15の主要遺伝子の発現プロファイルから早期非小細胞肺がんの進行の速さを予測でき術後化学療法が最も有効と考えられる患者を見極めることができる可能性がある、とAmerican Society of Clinical Oncology学会で発表された。研究者らは、ビノレルビンとシスプラチンによる術後療法が生存期間に有益性をもたらしたことを示したあるスタディの参加者133人の腫瘍検体を解析した。まず、研究者らは化学療法を受けていない患者における生物学的悪性度と遺伝子発現プロファイルの相互関係を示すために、再発リスクの高さと発現レベルに相関する15の遺伝子を同定した。次に、化学療法を受けた患者71人の腫瘍検体を評価した。悪性度の高い進行の速い腫瘍と予測された患者は、化学療法の最大の恩恵を被ることが示された（死亡リスクが67%低下）。一方、再発および死亡のリスクが低いと予測された患者において化学療法は死亡のリスクを低下させなかった。

Full Text

The expression profile of 15 key genes may predict aggressiveness of early-stage non-small cell lung cancer and identify the patients most likely to benefit from postoperative chemotherapy, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

"Not all patients benefit from chemotherapy and not all patients require chemotherapy after surgery," said lead author Ming Tsao, MD, professor of laboratory medicine and pathobiology at the University of Toronto. "Knowing that a patient has a genetic signature for a more aggressive cancer and that their chance of cure may be improved with chemotherapy gives patients and their doctors a clearer picture of the need for post-operative treatment."

The current study is a follow-up analysis of data from a trial conducted by the National Cancer Institute of Canada Clinical Trials Group (JBR.10, conducted in collaboration with the US National Cancer Institute), which showed a significant survival benefit from postoperative vinorelbine and cisplatin in patients with stage I and II non-small cell lung cancer.

In the current analysis, Researchers performed a genetic analysis of tumor tissue from the 133 (28 percent) of the 482 patients from the JBR.10 study who had banked frozen tumor samples available. They identified a group of 15 genes that together predicted patient outcome. Some of these genes are known to play important roles in cell growth and death or regulate other genes involved in cancer.

The investigators first identified the 15-gene expression profile in 62 patients who did not receive adjuvant chemotherapy and used it to predict which patients had aggressive cancers with a high risk of recurrence and death (31 patients) and which had less aggressive disease and a low risk of recurrence (31 patients).

Finally, researchers checked the gene profile in 71 patients who were randomized to chemotherapy in the JBR.10 trial. Patients predicted to have aggressive disease were found to obtain the greatest benefit from chemotherapy -a 67 percent reduction in the risk of death - while chemotherapy did not reduce the risk of death in patients designated as low risk.

While a previous JBR.10 analysis showed that overall, only patients with stage II disease benefited from chemotherapy after surgery, this study has demonstrated that the 15-gene signature may identify patients with both stage I and II cancers who may benefit from post-operative chemotherapy, further supporting its use in the selection of appropriate treatment.

ASCO2008 特集

乳房切除術施行の傾向（Abstract #: 509）

早期乳がん女性において乳房切除術施行例が増加している理由の一つに、術前の磁気共鳴画像検査の増加が関係している可能性がある

Increase in mastectomies among women with early-stage breast cancer may be partially related to greater use of preoperative magnetic resonance imaging

あるメディカルセンターにおいて早期乳がん女性の乳房切除術施行例が増加している理由の一つは、術前の磁気共鳴画像（MRI）検査が増加したためである可能性がある、とAmerican Society of Clinical Oncology学会で発表された。Mayo Clinicの研究者らは1997～2006年の間に治療を受けた患者5,464人のデータを評価した。全体の乳房切除術施行率は1997年の45%から2003年は30%に低下したが、2006年には43%に増加した。MRI検査を施行された女性の割合は2003年の11%から2006年の22%に増加した。MRI検査を施行された患者の52%が乳房切除術を選択したのに比べ、同検査を施行されなかった患者におけるその割合は38%であった。しかし、同期間中の乳房切除術施行率はMRI検査を施行されなかった患者においても増加した。筆者らは、前向き研究により患者の意思決定因子や、乳房切除術と臨床転帰および全生存率の関連の有無を見極めることができるであろうと述べている。

Full Text

The increase in mastectomies documented among women with early-stage breast cancer at one major medical center may be partially related to greater use of preoperative magnetic resonance imaging, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

Researchers at the Mayo Clinic (Rochester, Minnesota) reported that the number of mastectomies performed at their institution increased 13 percent from 2003 to 2006: Mastectomy accounted for 43 percent of procedures for early-stage breast cancer in 2006 compared with 30 percent of procedures in 2003.

The study also found that women who underwent preoperative breast magnetic resonance imaging were significantly more likely to undergo mastectomy than those who did not, although the rise in mastectomy rates was observed in both groups.

Preoperative breast examination with magnetic resonance imaging (MRI) may find cancer in more than one part of the breast, which may lead physicians and patients to choose mastectomy more often than lumpectomy. About half of the lesions detected by MRI are benign and only need to be monitored, but some women with such lesions may still choose mastectomy because they feel anxious or do not want to undergo periodic breast biopsies.

"This study demonstrates that a significant number of women with early-stage breast cancer are undergoing mastectomy, and it appears to be partially related to the introduction of pre-operative MRI," said Rajini Katipamula, MD, senior clinical fellow in hematology/oncology at Mayo Clinic and the study's lead author.

Breast-conserving surgery (lumpectomy) plus radiation therapy has been the treatment of choice for most American women with early-stage disease since 1990, when a National Institutes of Health Consensus Panel reported that it was as effective as mastectomy for overall survival for most women with stage I and II breast cancer.

Shortly thereafter, mastectomy rates began to decline. But in recent years, surgeons have performed more mastectomies, prompting Mayo Clinic researchers to conduct this retrospective study.

The researchers evaluated mastectomy trends in relation to surgical year and use of preoperative breast MRI using findings from a database of breast data started at the institution in 2003 among 5,464 women who had surgery for early-stage breast cancer at the Mayo Clinic between 1997 and 2006.

Mastectomy rates had declined from 45 percent in 1997 to 30 percent in 2003, but then rose to 43 percent in 2006. The percentage of women who had breast MRI doubled from 11 percent in 2003 to 22 percent in 2006. More than half (52 percent) of the patients receiving MRI underwent mastectomy compared with 38 percent of the patients who did not have MRI.

ASCO2008 特集

ホジキンリンパ腫罹患後の死亡（Abstract #: 10006）

小児ホジキンリンパ腫既往者の長期経過観察の結果から、これらの患者は早期死亡のリスクが高いことが示唆された

Long-term follow-up of survivors of childhood Hodgkin's lymphoma suggests these patients have an increased risk of premature death

小児ホジキンリンパ腫既往者は早期死亡のリスクが高い可能性があることが示唆された、とAmerican Society of Clinical Oncology学会で発表された。研究者らは1970～1986年の間に診断された患者1,927人のデータを解析した（5年後以降の再発、別の悪性疾患、および3～4度の心血管疾患を目的とした追跡期間中央値は23年）。20年間の再発率は13.2%であった。他の悪性腫瘍の30年間の累積発症率は男性で10.6%であり女性で10.9%（乳がん症例を除く）であった。3～4度の心血管疾患発現率に性差はなかった。他の悪性腫瘍および心血管疾患は男女ともに死亡の主要原因であった。再発は女性において死亡の有意な予測因子であり、3～4度の心血管疾患は男女ともに死亡率増加と相関した。他の悪性腫瘍もまた全患者の生存率を低下させたが、その影響は女性よりも男性においてより強固であった。

Full Text

Long-term follow-up of survivors of childhood Hodgkin's lymphoma suggests these patients have an increased risk of premature death, according to a presentation at the annual meeting of the American Society of Clinical Oncology.

Although the incidence of second malignancies among survivors is well known, few studies prior to the current analysis had specifically addressed treatment-associated mortality after childhood Hodgkin's lymphoma.

The Childhood Cancer Survivor Study (CCSS) followed a cohort of survivors of childhood cancer diagnosed between 1970 and 1986. Childhood survivors of Hodgkin's lymphoma had a standardized mortality ratio of 8.3 compared with the overall population of the United States.

Presenter Sharon M. Castellino, MD, of the Wake Forest University School of Medicine, presented an analysis of mortality risk factors for these survivors. The overall study, a retrospectively assembled cohort with subsequent prospective follow-up, included 1,927 survivors of Hodgkin's lymphoma (13 percent of all participants). Patients have been followed for a median of 23 years for relapse beyond 5 years, occurrence of second malignancy, and grade 3 or 4 cardiovascular conditions.

The incidence of relapse by 20 years after diagnosis was 13.2 percent. The 30-year cumulative incidence of second malignancies was 25.3 percent in women and 10.6 percent in men. When breast cancer was eliminated from the analysis, the 30-year cumulative incidence of second malignancies in women was 10.9 percent, comparable with that for men.

There was no significant difference by gender in cumulative incidence of grade 3 and 4 cardiovascular conditions. Second malignancy and cardiac conditions were the leading causes of death for both men and women.

Results for all patients were analyzed separately in Cox proportional hazard models adjusted for patient demographics. In a multivariate analysis, chemotherapy with anthracyclines was a significant risk factor for mortality in men. Supradiaphragmatic and infradiaphragmatic radiotherapy were significant risk factors for mortality in women patients at all radiation doses.

Relapse was a significant predictor of mortality in women, whereas grade 3 and 4 cardiovascular conditions were associated with an increased mortality risk in all patients. Second malignancies also decreased survival for all patients, with a stronger effect in men than women.

Castellino concluded that therapy-related morbidity and premature mortality is a trend as the cohort ages. She suggested that aging survivors and their health care providers should have a heightened awareness of second malignancies and cardiovascular risks and perform earlier targeted screening for these conditions.

ASCO2008 特集

メラノーマの生存率改善（Abstract #: 20027）

Phase IIスタディの結果、sargramostimによるアジュバント療法を受けたハイリスクメラノーマ患者のほとんどが無増悪生存期間または全生存期間の改善を認めた

Phase II study suggests that most high-risk patients with melanoma who receive adjuvant treatment with sargramostim achieve disease-free or overall survival

Sargramostimおよびインターロイキン2同時投与によるアジュバント療法を受けたハイリスクメラノーマ患者のほとんどが、無増悪生存期間または全生存期間の改善を認めたとのphase IIスタディの結果がAmerican Society of Clinical Oncology学会で発表された。治癒を目的とした手術を施行された患者計45人がsargramostimおよびインターロイキン2による治療を1年間とその後sargramostimでの治療を1年間受けた。経過観察期間は1～50ヵ月であった（中央値15.9ヵ月）。トライアル終了時に45人中32人が生存していた（stage IV 13人中9人、stage III 25人中16人、stage II（3B/4C）7人中7人）。研究者らは、21ヵ月後に60%の患者が無増悪生存を、64%が生存を達成したと報告した。Sargramostimは免疫細胞機能を増強する増殖因子製剤である。筆者らはさらに大規模なphase IIIトライアルの施行を提案している。

Full Text

The majority of high-risk patients with melanoma who receive adjuvant treatment with sargramostim and the synergistic cytokine Interleukin-2 (IL-2) achieve disease-free or overall survival, according to results of a phase II trial presented at the annual meeting of the American Society of Clinical Oncology.

"Previous findings suggest that sargramostim may be a potential adjuvant therapy for high-risk melanoma patients," said E. George Elias MD, PhD, Director of Maryland Melanoma Center.

"The percentage of patients who achieved disease-free and overall survival in this trial provides further evidence that sargramostim may prove to be a viable treatment option for this patient population and that further study in Phase III trials is needed."

The study was a single-arm, open-label design in which safety, tolerability, and efficacy were tested for the combination of sargramostim and IL-2 for one year, followed by sargramostim alone for a second year.

In the first year, sargramostim was administered subcutaneously at 125mcg/m^2/day for 14 consecutive days, followed by IL-2 subcutaneously at nine million IU/m^2/day for four days. Patients then received no treatment for 10 days. Patients with resected large metastases that yielded approximately 100 x 106 tumor cells also received autologous whole cell vaccine starting at the second cycle.

During the second year, each patient received sargramostim alone two times per week. In patients who experienced resected recurrence, the same adjuvant therapy was re-administered.

Adjuvant therapy with sargramostim and IL-2 was generally well-tolerated in the 45 patients, all of whom started therapy following potentially curative surgery. Toxicities were mild to moderate and no hospitalizations were required.

Researchers reported that 60 percent of the patients experienced disease-free survival and 64 percent of patients achieved overall survival at 21 months.

Follow-up ranged from 1 to 50 months (median, 15.9 months). At the end of the trial, 32 of the original 45 patients were alive [9/13 stage IV, 16/25 stage III, and 7/7 stage II (3B/4C)].

Survival data were expressed by the Kaplan- Meier method, and showed disease-free survival of 0.60 and overall survival of 0.64 at 21 months. There was no statistical difference in survival by Log Rank testing between those who received only sargramostim versus those treated by sargramostim and IL-2, and there was no increase in the number of dendritic cells during or after sargramostim administration in the 11 patients who donated blood for dendritic cell counts.

Sargramostim is a growth factor that helps fight infection and disease in appropriate patients by enhancing immune cell function. It was approved in the United States in 1991, and is marketed by Bayer HealthCare Pharmaceuticals. It is the only growth factor approved in the U.S. for use following induction chemotherapy in older adults (greater than or equal to 55 years) with acute myelogenous leukemia to shorten the time to neutrophil recovery and reduce the incidence of severe and life-threatening and fatal infections.

ASCO2008 特集