

JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

Journal of Clinical Oncology (ISSN 0732-183X) is published 36 times a year, three times monthly, by the American Society of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314. Periodicals postage is paid at Alexandria, VA, and at additional mailing offices.

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Duration of Chemotherapy for Advanced Non–Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis of Randomized Trials . . . Yu Yang Soon, Martin R. Stockler, Lisa M. Askie, et al pp 3277-3283

Purpose: To determine if it is preferable to extend chemotherapy beyond a standard number of cycles in patients receiving first-line chemotherapy for advanced non–small-cell lung cancer.

Methods: We searched biomedical literature databases and conference proceedings for randomized controlled trials (RCTs) comparing a defined number of cycles with continuation of the same chemotherapy until disease progression, a larger defined number of cycles of identical chemotherapy, and a defined number of cycles of identical initial chemotherapy followed by additional cycles of an alternative chemotherapy. Meta-analysis was performed using the fixed effect model. The primary outcome was overall survival (OS); secondary outcomes included progression-free survival (PFS), adverse events (AE), and health-related quality of life (HRQL).

Results: We found 13 RCTs including 3,027 patients. Extending chemotherapy improved PFS substantially (hazard ratio [HR], 0.75; 95% CI, 0.69 to 0.81; $P < .00001$) and OS modestly (HR, 0.92; 95% CI, 0.86 to 0.99; $P = .03$). Subgroup analysis revealed that effects on PFS were greater for trials extending chemotherapy with third-generation regimens rather than older regimens (HR, 0.70 interaction v 0.92 interaction; $P = .003$). Extending chemotherapy was associated with more frequent AE in all trials where it was reported and impaired HRQL in two of seven trials.

Conclusion: Extending chemotherapy, particularly with a third-generation regimen, improved PFS substantially, but OS less so. Future trials should test extending treatment with more effective and/or better-tolerated agents.

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Phase II Study of Pemetrexed and Carboplatin Plus Bevacizumab With Maintenance Pemetrexed and Bevacizumab As First-Line Therapy for Nonsquamous Non–Small-Cell Lung Cancer . . . Jyoti D. Patel, Thomas A. Hensing, Alfred Rademaker, et al pp 3284-3289

Purpose: This study evaluated the efficacy and safety of pemetrexed, carboplatin, and bevacizumab followed by maintenance pemetrexed and bevacizumab in patients with chemotherapy-naïve stage IIIB (effusion) or stage IV nonsquamous non–small-cell lung cancer (NSCLC).

Patients and Methods: Patients received pemetrexed 500 mg/m², carboplatin area under the concentration-time curve of 6, and bevacizumab 15 mg/kg every 3 weeks for six cycles. For patients with response or stable disease, pemetrexed and bevacizumab were continued until disease progression or unacceptable toxicity.

Results: Fifty patients were enrolled and received treatment. The median follow-up was 13.0 months, and the median number of treatment cycles was seven (range, one to 51). Thirty patients (60%) completed \geq six treatment cycles, and nine (18%) completed \geq 18 treatment cycles. Among the 49 patients assessable for response, the objective response rate was 55% (95% CI, 41% to 69%). Median progression-free and overall survival rates were 7.8 months (95% CI, 5.2 to 11.5 months) and 14.1 months (95% CI, 10.8 to 19.6 months), respectively. Grade 3/4 hematologic toxicity was modest— anemia (6%; 0), neutropenia (4%; 0), and thrombocytopenia (0; 8%). Grade 3/4 nonhematologic toxicities were proteinuria (2%; 0), venous thrombosis (4%; 2%), arterial thrombosis (2%; 0), fatigue (8%; 0), infection (8%; 2%), nephrotoxicity (2%; 0), and diverticulitis (6%; 2%). There were no grade 3 or greater hemorrhagic events or hypertension cases.

Conclusion: This regimen, involving a maintenance component, was associated with acceptable toxicity and relatively long survival in patients with advanced nonsquamous NSCLC. These results justify a phase III comparison against the standard-of-care in this patient population.

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Outcome in a Prospective Phase II Trial of Medically Inoperable Stage I Non–Small-Cell Lung Cancer Patients Treated With Stereotactic Body Radiotherapy . . . Pia Baumann, Jan Nyman, Morten Hoyer, et al pp 3290-3296

Purpose: The impact of stereotactic body radiotherapy (SBRT) on 3-year progression-free survival of medically inoperable patients with stage I non–small-cell lung cancer (NSCLC) was analyzed in a prospective phase II study.

Patients and Methods: Fifty-seven patients with T1N0M0 (70%) and T2N0M0 (30%) were included between August 2003 and September 2005 at seven different centers in Sweden, Norway, and Denmark and observed up to 36 months. SBRT was delivered with 15 Gy times three at the 67% isodose of the planning target volume.

Results: Progression-free survival at 3 years was 52%. Overall- and cancer-specific survival at 1, 2, and 3 years was 86%, 65%, 60%, and 93%, 88%, 88%, respectively. There was no statistically significant difference in survival between patients with T1 or T2 tumors. At a median follow-up of 35 months (range, 4 to 47 months), 27 patients (47%) were deceased, seven as a result of lung cancer and 20 as a result of concurrent disease. Kaplan-Meier estimated local control at 3 years was 92%. Local relapse was observed in four patients (7%). Regional relapse was observed in three patients (5%). Nine patients (16%) developed distant metastases. The estimated risk of all failure (local, regional, or distant metastases) was increased in patients with T2 (41%) compared with those with T1 (18%) tumors ($P = .027$).

Conclusion: With a 3-year local tumor control rate higher than 90% with limited toxicity, SBRT emerges as state-of-the-art treatment for medically inoperable stage I NSCLC and may even challenge surgery in operable instances.

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Metformin and Pathologic Complete Responses to Neoadjuvant Chemotherapy in Diabetic Patients With Breast Cancer . . .*Sao Jiralerspong, Shana L. Palla, Sharon H. Giordano, et al* **pp 3297-3302**

Purpose: Population studies have suggested that metformin use in diabetic patients decreases cancer incidence and mortality. Metformin inhibits the growth of cancer cells in vitro and tumors in vivo. However, there is little clinical data to support this. Our purpose was to determine whether metformin use was associated with a change in pathologic complete response (pCR) rates in diabetic patients with breast cancer receiving neoadjuvant chemotherapy.

Patients and Methods: We identified 2,529 patients who received neoadjuvant chemotherapy for early-stage breast cancer between 1990 and 2007. Patients were compared by groups: 68 diabetic patients taking metformin, 87 diabetic patients not taking metformin, and 2,374 nondiabetic patients. pCR rates were compared between the three groups using χ^2 tests of independence and compared pairwise using a binomial test of proportions. Factors predictive of pCR were assessed using a multivariate logistic regression model.

Results: The rate of pCR was 24% in the metformin group, 8.0% in the nonmetformin group, and 16% in the nondiabetic group ($P = .02$). Pairwise comparisons between the metformin and nonmetformin groups ($P = .007$) and the nonmetformin and nondiabetic groups ($P = .04$) were significant. Comparison of the pCR rates between the metformin and nondiabetic groups trended toward but did not meet significance ($P = .10$). Metformin use was independently predictive of pCR (odds ratio, 2.95; $P = .04$) after adjustment for diabetes, body mass index, age, stage, grade, receptor status, and neoadjuvant taxane use.

Conclusion: Diabetic patients with breast cancer receiving metformin and neoadjuvant chemotherapy have a higher pCR rate than do diabetics not receiving metformin. Additional studies to evaluate the potential of metformin as an antitumor agent are warranted.

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Circulating Tumor Cells and [¹⁸F]Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography for Outcome Prediction in Metastatic Breast Cancer . . .*Ugo De Giorgi, Vicente Valero, Eric Rohren, et al* **pp 3303-3311**

Purpose: Circulating tumor cells (CTCs) and [¹⁸F]fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) are two new promising tools for therapeutic monitoring. In this study, we compared the prognostic value of CTC and FDG-PET/CT monitoring during systemic therapy for metastatic breast cancer (MBC).

Patients and Methods: A retrospective analyses of 115 MBC patients who started a new line of therapy and who had CTC counts and FDG-PET/CT scans performed at baseline and at 9 to 12 weeks during therapy (midtherapy) was performed. Patients were categorized according to midtherapy CTC counts as favorable (ie, < five CTCs/7.5 mL blood) or unfavorable (\geq five CTCs/7.5 mL blood) outcomes. CTC counts and FDG-PET/CT response at midtherapy were compared, and univariate and multivariate analyses were performed to identify factors associated with survival.

Results: In 102 evaluable patients, the median overall survival time was 14 months (range, 1 to > 41 months). Midtherapy CTC levels correlated with FDG-PET/CT response in 68 (67%) of 102 evaluable patients. In univariate analysis, midtherapy CTC counts and FDG-PET/CT response predicted overall survival ($P < .001$ and $P = .001$, respectively). FDG-PET/CT predicted overall survival ($P = .0086$) in 31 (91%) of 34 discordant patients who had fewer than five CTCs at midtherapy. Only midtherapy CTC levels remained significant in a multivariate analysis ($P = .004$).

Conclusion: Detection of five or more CTCs during therapeutic monitoring can accurately predict prognosis in MBC beyond metabolic response. FDG-PET/CT deserves a role in patients who have fewer than five CTCs at midtherapy. Prospective trials should evaluate the most sensitive and cost-effective modality for therapeutic monitoring in MBC.

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Sorafenib for Treatment of Renal Cell Carcinoma: Final Efficacy and Safety Results of the Phase III Treatment Approaches in Renal Cancer Global Evaluation Trial . . .*Bernard Escudier, Tim Eisen, Walter M. Stadler, et al* **pp 3312-3318**

Purpose: Mature survival data and evaluation of vascular endothelial growth factor (VEGF) as a prognostic biomarker from the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) study in patients with renal cell carcinoma (RCC) are reported.

Patients and Methods: Nine hundred three previously treated patients were randomly assigned to receive sorafenib versus placebo. On demonstration of progression-free survival (PFS) benefit with sorafenib, patients assigned to placebo were offered sorafenib. Overall survival (OS) was determined at two planned interim analyses and one final analysis, with a secondary OS analysis conducted by censoring placebo patients who crossed over to sorafenib. The relationships between baseline VEGF level and prognosis and efficacy were evaluated.

Results: The final OS of patients receiving sorafenib was comparable with that of patients receiving placebo (17.8 v 15.2 months, respectively; hazard ratio [HR] = 0.88; $P = .146$); however, when post-cross-over placebo survival data were censored, the difference became significant (17.8 v 14.3 months, respectively; HR = 0.78; $P = .029$). Adverse events at 16 months after cross over were similar to those previously reported. Baseline VEGF levels correlated with Eastern Cooperative Oncology Group performance status ($P < .0001$), Memorial Sloan-Kettering Cancer Center score ($P < .0001$), and PFS and OS in univariate (PFS, $P = .0013$; OS, $P = .0009$) and multivariate (PFS, $P = .0231$; OS, $P = .0416$) analyses of placebo patients and with short OS by multivariate analysis of patients receiving sorafenib ($P = .0145$). Both high-VEGF ($P < .01$) and low-VEGF ($P < .01$) groups benefited from sorafenib.

Conclusion: Although an OS benefit was not seen on a primary intent-to-treat analysis, results of a secondary OS analysis censoring placebo patients demonstrated a survival advantage for those receiving sorafenib, suggesting an important cross-over effect. VEGF levels are prognostic for PFS and OS in RCC. The results of TARGET establish the efficacy and safety of sorafenib in advanced RCC.

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Phase I Study of Concurrent Weekly Docetaxel and Repeated Samarium-153 Lexidronam in Patients With Castration-Resistant Metastatic Prostate Cancer . . . Shi-Ming Tu, Paul Mathew, Franklin C. Wong, et al pp 3319-3324

Purpose: Samarium-153 (¹⁵³Sm) lexidronam is a bone-targeting radiopharmaceutical with a short physical half-life and a favorable toxicity profile. We evaluated the safety and feasibility of a concurrent combination of weekly docetaxel with repeated ¹⁵³Sm-lexidronam in patients with castration-resistant prostate cancer (CRPC).

Patients and Methods: A conventional 3 + 3 dose-escalation design was used for this study. Patients were treated in three cohorts comprising two cycles of weekly docetaxel at 25, 30, and 35 mg/m², respectively, on days 1, 8, and 15 of a 28-day cycle in combination with ¹⁵³Sm (1 mCi/kg) on day 1. Unacceptable hematologic toxicity (UHT) was defined as more than 7 days delay in therapy for inadequate counts: an absolute neutrophil count (ANC) more than 1,000/ μ L and platelets more than 70,000/ μ L were required at days 8 and 15 and ANC more than 1,500/ μ L and platelets more than 100,000/ μ L were required at cycle 2, day 1. If counts had not recovered by day 56 of either combination cycle, UHT was declared.

Results: Eighteen patients were treated in three cohorts. Two patients in separate cohorts experienced UHT; the maximum-tolerated dose for this regimen was not reached. The median interval between ¹⁵³Sm doses was 35 days (range, 27 to 57 days). The only significant toxicity was mild, transient myelosuppression. Five patients (28%) experienced grade 3 hematologic toxicity. There were no grade \geq 4 hematologic or nonhematologic toxicities.

Conclusion: Two dosing cycles consisting of weekly docetaxel and monthly ¹⁵³Sm-lexidronam were well tolerated and feasible in this CRPC population.

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Two-Center Evaluation of Dynamic Sentinel Node Biopsy for Squamous Cell Carcinoma of the Penis . . . Joost A.P. Leijte, Ben Hughes, Niels M. Graafland, et al pp 3325-3329

Purpose: Sentinel node biopsy is used to evaluate the nodal status of patients with clinically node-negative penile carcinoma. Its use is not widespread, and the majority of patients with clinically node-negative disease undergo an elective inguinal lymph node dissection. Reservations about the use of sentinel node biopsy include the fact that most current results come from one institution and the supposedly long learning curve associated with the procedure. The purpose of this study was to address these issues by analyzing results from two centers and by evaluating the learning curve.

Patients and Methods: All patients undergoing sentinel node biopsy for penile carcinoma at two centers were included. The sentinel node identification rate, false-negative rate, and morbidity of the procedure were calculated. Results from the first 30 procedures were assessed for a potential learning curve.

Results: A total of 323 patients with penile squamous cell carcinoma, which included 611 clinically node-negative groins, were scheduled for sentinel node biopsy. A sentinel node was found in 572 of the 592 groins (97%) that proceeded to sentinel node biopsy. In 79 groins, a sentinel node was positive for tumor. Six inguinal node recurrences occurred after a negative sentinel node procedure, all within 15 months after sentinel node biopsy. The combined false-negative rate was 7%. Complications occurred in 4.7% of explored groins. None of the false-negative procedures occurred in the initial 30 procedures.

Conclusion: Sentinel node biopsy is a suitable procedure to stage clinically node-negative penile cancer, and it has a low complication rate. No learning curve was demonstrated in this study.

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Macrophage Markers in Serum and Tumor Have Prognostic Impact in American Joint Committee on Cancer Stage I/II Melanoma . . . Trine O. Jensen, Henrik Schmidt, Holger Jon Møller, et al pp 3330-3337

Purpose: To evaluate the prognostic role of soluble CD163 (sCD163) in serum and macrophage infiltration in primary melanomas from patients with American Joint Committee on Cancer (AJCC) stage I/II melanoma. The scavenger receptor CD163 is associated with anti-inflammatory macrophages, and it is shed from their surface.

Patients and Methods: Serum samples from 227 patients with stage I/II melanoma obtained before definitive surgery (baseline) and during 5 years of follow-up were analyzed for sCD163 by enzyme-linked immunosorbent assay. Excised formalin-fixed, paraffin-embedded primary melanomas from 190 patients were available for immunohistochemical analyzes of CD163⁺ and CD68⁺ macrophage infiltration. They were estimated semiquantitatively in three different tumor compartments: tumor nests, tumor stroma, and at the invasive front of the tumor.

Results: Serum sCD163 treated as an updated continuous covariate as well as the baseline value were analyzed together with the covariate's ulceration and thickness in a Cox proportional hazards model. sCD163 was an independent prognostic factor for overall survival (baseline, hazard ratio [HR] = 1.4; 95% CI, 1.1 to 1.7; *P* = .01; and updated, HR = 1.4; 95% CI, 1.1 to 1.8; *P* = .003). Melanomas with dense CD163⁺ macrophage infiltration in tumor stroma and CD68⁺ macrophage infiltration at the invasive front were associated with poor overall survival (CD163, HR = 2.7; 95% CI, 0.8 to 9.3; *P* = .11; and CD68, HR = 2.8; 95% CI, 1.2 to 6.8; *P* = .02) independent (borderline for CD163) of thickness and ulceration.

Conclusion: Both serum levels of sCD163 and the presence of CD68⁺ macrophage infiltration at the tumor invasive front are independent predictors of survival in AJCC stage I/II melanoma. CD163⁺ cell infiltration in tumor stroma may be predictive of survival.

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Primary Care Physicians' Views of Routine Follow-Up Care of Cancer Survivors . . . M. Elisabeth Del Giudice, Eva Grunfeld, Bart J. Harvey, et al pp 3338-3345

Purpose: Routine follow-up of adult cancer survivors is an important clinical and health service issue. Because of a lack of evidence supporting advantages of long-term follow-up care in oncology clinics, there is increasing interest for the locus of this care to be provided by primary care physicians (PCPs). However, current Canadian PCP views on this issue have been largely unknown.

Methods: A mail survey of a random sample of PCPs across Canada, stratified by region and proximity to urban centers, was conducted. Views on routine follow-up of adult cancer survivors and modalities to facilitate PCPs in providing this care were determined.

Results: A total of 330 PCPs responded (adjusted response rate, 51.7%). After completion of active treatment, PCPs were willing to assume exclusive responsibility for routine follow-up care after 2.4 ± 2.3 years had elapsed for prostate cancer, 2.6 ± 2.6 years for colorectal cancer, 2.8 ± 2.5 years for breast cancer, and 3.2 ± 2.7 years for lymphoma. PCPs already providing this care were willing to provide exclusive care sooner. The most useful modalities PCPs felt would assist them in assuming exclusive responsibility for follow-up cancer care were (1) a patient-specific letter from the specialist, (2) printed guidelines, (3) expedited routes of rereferral, and (4) expedited access to investigations for suspected recurrence.

Conclusion: With appropriate information and support in place, PCPs reported being willing to assume exclusive responsibility for the follow-up care of adult cancer survivors. Insights gained from this survey may ultimately help guide strategies in providing optimal care to these patients. *J Clin Oncol* 27:3338-3345. © 2009 by American Society of Clinical Oncology

Humanized Anti-CD20 Antibody, Veltuzumab, in Refractory/Recurrent Non-Hodgkin's Lymphoma: Phase I/II Results

Franck Morschhauser, John P. Leonard, Luis Fayad, et al pp 3346-3353

Purpose: This is a multicenter phase I/II dose-finding study in relapsed/refractory B-cell non-Hodgkin's lymphoma (NHL) evaluating veltuzumab, a humanized anti-CD20 antibody with structure-function differences from chimeric rituximab.

Patients and Methods: Eighty-two patients (median age, 64 years; 79% stage III/IV, one to nine prior treatments) received four once-weekly doses of 80 to 750 mg/m² of veltuzumab and were assessed for safety, efficacy, pharmacodynamics, pharmacokinetics, and immunogenicity.

Results: Veltuzumab was well tolerated, with no grade 3 to 4 drug-related adverse events despite short infusion times (typically 2 hours initially, 1 hour subsequently at doses < 375 mg/m²). In follicular lymphoma, 24 (44%) of 55 patients had objective responses (OR), with 15 (27%) complete responses (CRs) or CRs unconfirmed (CRus) by International Working Group criteria, and with some responses occurring despite two to five prior rituximab-containing regimens, less favorable prognosis (elevated lactate dehydrogenase, tumors > 5 cm, and Follicular Lymphoma International Prognostic Index ≥ 2), and at all dose levels. The CRs/CRus were durable (median duration, 19.7 months), with five patients still ongoing (15.9 to 37.6 months duration). In marginal zone lymphoma, five (83%) of six patients had ORs, with two CRs/CRus (33%), and in diffuse large B-cell lymphoma, three (43%) of seven patients achieved partial responses. At all dose levels studied, B cells were depleted after the first infusion, veltuzumab serum half-lives were similar after the fourth infusion, and mean antibody serum levels exceeded values considered important for anti-CD20 therapy (ie, 25 µg/mL).

Conclusion: Veltuzumab appeared safe and active at all tested doses, encouraging further study, including dose levels less than those typically used with rituximab.

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Lymphoma After Solid Organ Transplantation: Risk, Response to Therapy, and Survival at a Transplantation Center

Jason S. Knight, Alexander Tsodikov, Diane M. Cibrik, et al pp 3354-3362

Purpose: We studied the incidence, risk factors, treatment, and outcomes of post-transplantation lymphoproliferative disorder (PTLD) that occurred at the University of Michigan since 1964.

Patients and Methods: We identified 7,040 patients who received solid organ transplantation (SOT) and post-transplantation immunosuppressive therapy. Seventy-eight patients developed PTLD.

Results: Diffuse large B-cell lymphoma (n = 43), polymorphic PTLD (n = 10), Hodgkin's lymphoma (n = 7), Burkitt's lymphoma (n = 6), plasmacytoma (n = 5), and mucosa-associated lymphoid tissue lymphoma (n = 3) were all over-represented in the SOT population compared with a population sample from the Surveillance, Epidemiology, and End Results (SEER) database; follicular lymphoma (n = 0) was underrepresented. Negative pretransplantation Epstein-Barr virus (EBV) serology was a risk factor for PTLD. Available histologic analysis of tumor tissue showed that 75% were CD20 positive and that 62% were EBV positive; EBV-positive tumors occurred sooner after SOT than EBV-negative tumors (mean, 29 v 66 months). Extralymphatic disease (79%), poor performance status (68%), elevated lactate dehydrogenase (LDH; 71%), and advanced stage (68%) disease were all common at the time of lymphoma diagnosis. Two thirds of patients had a complete response when treated with cyclophosphamide, doxorubicin, vincristine, and prednisone-like chemotherapy (either with or without rituximab). Median overall survival in all patients with PTLD was 8.23 years (95% CI, 2.28 to 30.0 years).

Conclusion: EBV-naïve patients who receive a donor organ from an EBV-infected donor are in the highest-risk situation for PTLD development. Most of these lymphomas are CD20 positive. Follicular lymphoma is unusual. With treatment, survival of patients with PTLD was indistinguishable from that of the SEER population sample.

J Clin Oncol 27:3354-3362. © 2009 by American Society of Clinical Oncology

Poor Outcome for Children and Adolescents With Progressive Disease or Relapse of Lymphoblastic Lymphoma: A Report From the Berlin-Frankfurt-Muenster Group . . . *Birgit Burkhardt, Alfred Reiter, Eva Landmann, et al* **pp 3363-3369**

Purpose: Little is known about the outcome of pediatric patients with lymphoblastic lymphoma (LBL) who suffer from progressive disease or relapse.

Patients and Methods: We analyzed the pattern of LBL relapses after current non-Hodgkin's lymphoma Berlin-Frankfurt-Muenster (BFM) frontline therapy between April 1990 and March 2003. Relapse therapy was according to acute lymphoblastic leukemia (ALL) –Relapse-BFM protocols or ALL-BFM protocols for high-risk patients.

Results: Twenty-eight (11%) of 251 registered patients with precursor T-cell LBL (T-LBL) and six (8%) of 73 patients with precursor B-cell LBL (pB-LBL) suffered from relapse. Of the 28 patients with T-LBL, one died from infection during relapse chemotherapy, 18 failed to achieve stable remission and died from disease progression, and nine reached allogeneic stem-cell transplantation (SCT). Two of these nine patients who underwent SCT died from transplantation-associated toxicity, three died from disease progression, and four are still alive. These four patients are in second remission of their lymphoma for 48, 68, 125, and 131 months, respectively, after allogeneic SCT. One of the four patients developed colon adenocarcinoma 47 months after SCT. Of the six patients with pB-LBL who experienced relapse, one patient died as a result of toxicity of relapse chemotherapy, two died from disease progression after chemotherapy, and three received allogeneic SCT. Of these, two died from subsequent disease progression, and one is still alive 57 months after allogeneic SCT.

Conclusion: Using modern conventional therapy in the frontline treatment of LBL, 10% of patients suffer from progressive disease or relapse. Because of the extremely poor reinduction success, the salvage rate for these patients is poor, with only a 14% (SE = 6%) overall survival. Long-term survival was only achieved in those few patients who were able to undergo an allogeneic SCT.

J Clin Oncol 27:3363-3369. © 2009 by American Society of Clinical Oncology

Single Nucleotide Polymorphism at rs1982073:T869C of the *TGFβ1* Gene Is Associated With the Risk of Radiation Pneumonitis in Patients With Non–Small-Cell Lung Cancer Treated With Definitive Radiotherapy . . . *Xianglin Yuan,*

Zhongxing Liao, Zhensheng Liu, et al **pp 3370-3378**

Purpose: In search of reliable biologic markers to predict the risk of normal tissue damage by radio(chemo)therapy before treatment, we investigated the association between single nucleotide polymorphisms (SNPs) in the transforming growth factor 1 (*TGFβ1*) gene and risk of radiation pneumonitis (RP) in patients with non–small-cell lung cancer (NSCLC).

Patients and Methods: Using 164 available genomic DNA samples from patients with NSCLC treated with definitive radio(chemo)therapy, we genotyped three SNPs of the *TGFβ1* gene (rs1800469:C-509T, rs1800471:G915C, and rs1982073:T869C) by polymerase chain reaction restriction fragment length polymorphism method. We used Kaplan-Meier cumulative probability to assess the risk of grade ≥ 3 RP and Cox proportional hazards analyses to evaluate the effect of *TGFβ1* genotypes on such risk.

Results: There were 90 men and 74 women in the study, with median age of 63 years. Radiation doses ranging from 60 to 70 Gy (median = 63 Gy) in 30 to 58 fractions were given to 158 patients (96.3%) and platinum-based chemotherapy to 147 (89.6%). Grade ≥ 2 and grade ≥ 3 RP were observed in 74 (45.1%) and 36 patients (22.0%), respectively. Multivariate analysis found CT/CC genotypes of *TGFβ1* rs1982073:T869C to be associated with a statistically significantly lower risk of RP grades ≥ 2 (hazard ratio [HR] = 0.489; 95% CI, 0.227 to 0.861; $P = .013$) and grades ≥ 3 (HR = 0.390; 95% CI, 0.197 to .774; $P = 0.007$), respectively, compared with the TT genotype, after adjustment for Karnofsky performance status, smoking status, pulmonary function, and dosimetric parameters.

Conclusion: Our results showed that CT/CC genotypes of *TGFβ1* rs1982073:T869C gene were associated with lower risk of RP in patients with NSCLC treated with definitive radio(chemo)therapy and thus may serve as a reliable predictor of RP.

J Clin Oncol 27:3370-3378. © 2009 by American Society of Clinical Oncology

Outcome of Primary Tumor in Patients With Synchronous Stage IV Colorectal Cancer Receiving Combination Chemotherapy Without Surgery As Initial Treatment . . . *George A. Poultsides, Elliot L. Servais, Leonard B. Saltz, et al* **pp 3379-3384**

Purpose: The purpose of this study was to describe the frequency of interventions necessary to palliate the intact primary tumor in patients who present with synchronous, stage IV colorectal cancer (CRC) and who receive up-front modern combination chemotherapy without prophylactic surgery.

Patients and Methods: By using a prospective institutional database, we identified 233 consecutive patients from 2000 through 2006 with synchronous metastatic CRC and an unresected primary tumor who received oxaliplatin- or irinotecan-based, triple-drug chemotherapy (infusional fluorouracil, leucovorin, and oxaliplatin; bolus fluorouracil, leucovorin, and irinotecan; or fluorouracil, leucovorin, and irinotecan) with or without bevacizumab as their initial treatment. The incidence of subsequent use of surgery, radiotherapy, and/or endoluminal stenting to manage primary tumor complications was recorded.

Results: Of 233 patients, 217 (93%) never required surgical palliation of their primary tumor. Sixteen patients (7%) required emergent surgery for primary tumor obstruction or perforation, 10 patients (4%) required nonoperative intervention (ie, stent or radiotherapy), and 213 (89%) never required any direct symptomatic management for their intact primary tumor. Of those 213 patients, 47 patients (20%) ultimately underwent elective colon resection at the time of metastasectomy, and eight patients (3%) underwent this resection during laparotomy for hepatic artery infusion pump placement. Use of bevacizumab, location of the primary tumor in the rectum, and metastatic disease burden were not associated with increased intervention rate.

Conclusion: Most patients with synchronous, stage IV CRC who receive up-front modern combination chemotherapy never require palliative surgery for their intact primary tumor. These data support the use of chemotherapy, without routine prophylactic resection, as the appropriate standard practice for patients with neither obstructed nor hemorrhaging primary colorectal tumors in the setting of metastatic disease.

J Clin Oncol 27:3379-3384. © 2009 by American Society of Clinical Oncology

Initial Safety Report of NSABP C-08: A Randomized Phase III Study of Modified FOLFOX6 With or Without Bevacizumab for the Adjuvant Treatment of Patients With Stage II or III Colon Cancer . . .

Carmen J. Allegra, Greg Yothers, Michael J. O'Connell, et al pp 3385-3390

Purpose: The National Surgical Adjuvant Breast and Bowel Project C-08 trial was designed to investigate the safety and effectiveness of adding bevacizumab to modified infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) 6 regimen for the adjuvant treatment of patients with stage II or III colon cancer. We present safety information in advance of the planned analysis of efficacy.

Patients and Methods: Among 2,710 randomly assigned patients, demographic factors were balanced. Patients received modified FOLFOX6 every 2 weeks \times 12 or modified FOLFOX6 plus bevacizumab (5 mg/kg every 2 weeks \times 26, experimental group).

Results: Overall rates of grade 4 or 5 toxicities were nearly identical in the FOLFOX6 and FOLFOX6 plus bevacizumab arms (15.2% and 15.0%, respectively). Six-month mortality rates were 0.96% and 0.90% for the control and experimental groups, respectively. Grade 3+ toxicities that occurred more often in the experimental arm versus control arm included hypertension (12% v 1.8%, respectively), wound complications (abdominal incisional hernia or infusion port dehiscence/inflammation; 1.7% v 0.3%, respectively), pain (11.1% v 6.3%, respectively), and proteinuria (2.7% v 0.8%, respectively). Grade 2+ neuropathy was increased in the experimental arm versus the control arm (grade 2, 33% v 29%, respectively; grade 3, 16% v 14%, respectively; and grade 4, < 1% each). In the experimental arm versus control arm, significantly less thrombocytopenia (1.4% v 3.4%, respectively) and fewer allergic reactions (3.1% v 4.7%, respectively) were observed. Advanced age was associated with a significantly greater rate of grade 4 and 5 toxicities regardless of treatment.

Conclusion: Bevacizumab with modified FOLFOX6 is well tolerated in the surgical adjuvant setting in these patients. No significant increase in GI perforation, hemorrhage, arterial or venous thrombotic events, or death with the addition of bevacizumab to modified FOLFOX6 has been observed. Follow-up for potential delayed adverse effects and efficacy is ongoing.

J Clin Oncol 27:3385-3390. © 2009 by American Society of Clinical Oncology



Comparing Adult and Pediatric Rhabdomyosarcoma in the Surveillance, Epidemiology and End Results Program, 1973 to 2005: An Analysis of 2,600 Patients . . .

Iyad Sultan, Ibrahim Qaddoumi, Sameer Yaser, et al pp 3391-3397

Purpose: To compare clinical features and outcomes of adults and children reported to have rhabdomyosarcoma.

Patients and Methods: We analyzed data from 1,071 adults (age > 19 years) and 1,529 children (age \leq 19 years) reported in the public-access Surveillance, Epidemiology and End Results database as having rhabdomyosarcoma, diagnosed from 1973 to 2005. Survival estimates were determined using survival time with the end point being death from any cause.

Results: Adults with rhabdomyosarcoma had significantly worse outcome than children (5-year overall survival rates, 27% \pm 1.4% and 61% \pm 1.4%, respectively; $P < .0001$). Tumors in adults were more likely to be at an unfavorable site (65% v 55%; $P < .0001$) and to have histologies that are unusual during childhood, particularly the pleomorphic subtype (19%) and not otherwise specified (43%). Regional and distant spread was not more frequent in adults. Adults had significantly worse outcome than children with similar tumors. The most significant difference was in localized disease; 5-year survival estimates were 82% \pm 2.0% for children and 47% \pm 2.9% for adults ($P < .0001$). Multivariate analysis showed that age, histologic subtype, primary site location, stage, and local control with surgery and/or radiation were significant predictors of survival. However, alveolar subtype and unfavorable primary site lost significance when analysis was restricted to adults.

Conclusion: Adults reported to have rhabdomyosarcoma had worse survival than children with similar tumors. Predictors of poor outcome in children were valid in adults except for alveolar histology and unfavorable tumor site.

J Clin Oncol 27:3391-3397. © 2009 by American Society of Clinical Oncology



Approaches to the Management of Invasive Fungal Infections in Hematologic Malignancy and Hematopoietic Cell Transplantation . . .

Mauricette Michallet and James I. Ito pp 3398-3409

Patients with hematologic malignancy and hematopoietic cell transplant (HCT) recipients are at increased risk for invasive fungal infection (IFI) as a result of immunosuppression or organ damage stemming from their underlying disease, its treatment, or both. Such IFIs can cause significant morbidity and mortality, and the diagnosis and treatment of infected patients frequently are clinically challenging. This article discusses the epidemiology and risk factors for IFI in patients with hematologic malignancy and HCT recipients. The pros and cons of available antifungal agents are discussed, and evolving treatment strategies and recent prophylaxis guidelines from various professional organizations are reviewed. Finally, recommendations are offered for antifungal prophylaxis according to risk group.

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