Predictive Biomarkers and Personalized Medicine

Serum Insulin-Like Growth Factor-1 Levels Predict Outcomes of Patients with Advanced Hepatocellular Carcinoma Receiving Antiangiogenic Therapy

Yu-Yun Shao1,3, Chien-Chung Huang1, Shiou-Der Lin1, Chih-Hung Hsu1,3, and Ann-Lii Cheng1,2,3

Abstract

Purpose: Patients with liver cirrhosis or hepatocellular carcinoma (HCC) have decreased serum insulin-like growth factor (IGF)-1 levels. We evaluated whether IGF-1 levels were associated with the outcomes of patients with advanced HCC treated with systemic antiangiogenic therapy.

Experimental Design: The study was based on patients with advanced HCC who were enrolled in two clinical trials evaluating first-line combination antiangiogenic therapy. Serum samples were collected before treatment and four to six weeks after the start of treatment. The levels of IGF-1, IGF-2, and IGF-binding protein-3 (IGFBP3) were analyzed for their associations with treatment outcomes.

Results: A total of 83 patients were included in the study. Patients who had high (≥ median level) baseline IGF-1 levels had significantly higher disease control rate (DCR) than patients who had low (< median level) levels (71% vs. 39%, \( P = 0.003 \)). The levels of posttreatment IGF-1, and pre- or posttreatment IGF-2 and IGFBP3 were not associated with DCR. Patients with high baseline IGF-1 levels, compared with patients with low levels, had significantly longer progression-free survival (PFS; median, 4.3 vs. 1.9 months, \( P = 0.014 \)) and overall survival (OS; median, 10.7 vs. 3.9 months, \( P = 0.009 \)). The high baseline IGF-1 level remains an independent factor associated with favorable PFS and OS in multivariate analysis.

Conclusions: High pretreatment IGF-1 levels were associated with better DCR, PFS, and OS of patients who received antiangiogenic therapy for advanced HCC. This finding warrants validation in large studies.

Clin Cancer Res; 18(14); 3992–7. ©2012 AACR.

Introduction

Insulin-like growth factor (IGF) signaling pathways are key regulators of energy metabolism and growth (1, 2). Substantial evidence indicates that IGF-1 and its signaling networks play an important role in the carcinogenesis of many cancer types. Although the vast majority of the ligands in circulation, including IGF-1 and IGF-2, are synthesized by the liver (3, 4), these ligands are frequently expressed in neoplastic tissues (1). Many cancer cells also overexpress the IGF-1 receptor (IGFR; ref. 5). Activation of IGF-1 signaling promotes mitogenesis and inhibits apoptosis (1, 2). In epidemiologic studies, high blood IGF-1 concentration was associated with an increased risk of breast cancer, prostate cancer, esophageal cancer, and colon cancer (6–9).

The relevance of IGF signaling to hepatocellular carcinoma (HCC) is unique. Unlike other cancer types, patients with HCC have lower circulating IGF-1 levels than healthy controls (10). Regular monitoring of serum IGF-1 level in patients with chronic hepatitis C showed that patients with declining serum IGF-1 levels were more likely to develop HCC (11). In addition, low serum IGF-1 levels were associated with extensive liver involvement and vascular invasion in patients with HCC (12, 13). The inclusion of serum IGF-1 level into the common HCC staging systems improves their prognostic stratification (13, 14).

In the past, advanced HCC was a disease with very poor prognosis and few treatment options. In 2007, sorafenib, a multitargeted inhibitor with antiangiogenic activity, became the first approved systemic therapy for HCC after it was shown to provide survival benefit in patients with advanced HCC (15, 16). Many other antiangiogenic compounds or combinations are under active investigation (17–19). However, biomarkers that predict the efficacy or prognosis of patients treated with these therapies for advanced HCC are still lacking.
Translational Relevance

Although the insulin-like growth factor (IGF)-1 signaling network is associated with carcinogenesis, IGF-1 may also serve as a surrogate for the liver function reserve because it is mainly produced by the liver. IGF-1 levels have been found to decrease in patients with liver cirrhosis or hepatocellular carcinoma (HCC). Here we showed that high pretreatment IGF-1 levels were associated with better disease control rates and can independently predict better progression-free survival and overall survival of patients with advanced HCC who received first-line antiangiogenic therapy.

Because serum IGF-1 has been shown to be associated with the risk and disease extent of HCC, we planned this study to explore the significance of serum factors related to IGF signaling in patients with advanced HCC, focusing on their association with treatment outcomes.

Materials and Methods

Study population

This study was based on patients who were enrolled in 2 phase II clinical trials at the National Taiwan University Hospital (NTUH), Taipei, Taiwan. Both studies tested first-line combination systemic therapy for advanced HCC using an antiangiogenic targeted agent plus metronomic chemotherapy, which was defined as the uninterrupted administration of low-dose chemotherapeutic agents for a prolonged period (20). Metronomic chemotherapy was found with antiangiogenic activity, rather than cytoxicity to the tumor cells (21). One clinical trial studied sorafenib plus metronomic tegafur/uracil (S + T), and the other studied bevacizumab plus capcetabine (B + C). The eligibility criteria for both trials were similar. Patients were required to have pathologically proven metastatic or locally advanced HCC not amenable to locoregional therapies, with adequate liver reserve [Child–Pugh Class A, liver transaminases levels ≤ 5 × upper limit of normal (ULN)] and organ functions (serum creatinine level ≤ 1.5 × ULN; platelet counts ≥ 100,000/µL for the study with S + T and ≥ 150,000/µL for the study with B + C). Tumor assessment was done every 6 to 8 weeks following RECIST 1.0. The results of the 2 clinical trials have been published (17, 18).

Measurement of IGF-1, IGF-2, and IGF-binding protein-3

Patients who were enrolled in the clinical trials could choose whether or not to participate in the current biomarker study. Those patients who provided written informed consent had serum samples collected before treatment started and again at 4 to 6 weeks after the start of therapy. All sera were aliquoted and stored at -80°C. Measurement of serum levels of IGF-1 (R&D), IGF-2 (Diagnostic Systems Laboratories), and IGF-binding protein-3 (IGFBP3; R&D) were carried out by ELISA following the manufacturers’ instructions. This biomarker study was approved by the Research Ethical Committee of NTUH.

Statistical methods

Statistical analyses were carried out with SAS statistical software (version 9.1.3; The SAS Institute). A 2-sided P value of 0.05 or less was considered statistically significant. The associations between IGF-1, IGF-2, or IGFBP3 levels and disease control rate (DCR), which was defined as complete response, partial response, or stable disease, were examined by the independent t test. This test was also applied to examine the associations between IGF-1 levels and patient characteristics.

Baseline IGF-1 levels were further dichotomized into high (>median levels) and low (<median levels) for further analysis. The association between disease control and high or low IGF-1 was examined by the χ² test or by Fisher exact test if any expected values of cells were less than 5. The Kaplan–Meier method was used to estimate survival. The survival of patients with high and low IGF-1 levels was compared by the log-rank test.

The Cox proportional hazards model was used to calculate the HR of baseline IGF-1, IGF-2, and IGFBP3 levels, and other potential clinicopathologic parameters including treatment regimens, gender, age, body mass index (BMI), hepatitis etiologies, macrovascular invasion, extrahepatic metastasis, α-fetoprotein > 400 ng/mL, Barcelona Clinic Liver Cancer stage, Cancer of the Liver Italian Program (CLIP) scores, Eastern Cooperative Oncology Group (ECOG) performance status, and prior treatment in univariate and multivariate analyses. In the stepwise variable selection procedure during multivariate analysis, all the significant and nonsignificant covariates were considered by their P values. The significance levels for entry and for stay were set as P less than 0.15.

Results

Patient characteristics and treatment outcomes

A total of 83 patients were enrolled into the current study; 64 received S + T, and 19 received B + C. The median age was 54 years; 75% had chronic hepatitis B virus infection, and 90% had either extrahepatic metastasis (60%) or macrovascular invasion (59%; Table 1). The basic characteristics of these patients were similar to the entire groups in the 2 clinical trials (17, 18). All patients in the current study had Child–Pugh class A liver cirrhosis, bilirubin level < 2 mg/dL, platelet counts > 100,000, and INR < 1.5. Eleven patients had mild ascites, and the other 72 patients had no ascites.

There were no complete responses, but 7 (8%) patients had partial responses to treatment (Table 2). Another 39 patients had stable disease, yielding a DCR of 55%. Median progression-free survival (PPS) was 3.3 months.
and median overall survival (OS) was 6.3 months (95% CI, 4.1–8.5). DCR, PFS, and OS were not significantly different between patients who were enrolled in the biomarker study and those who were not. In addition, within the current study population, patients who received different treatment regimens had similar DCR ($P = 0.421$), PFS ($P = 0.141$), and OS ($P = 0.218$).

**IGF-1 levels and treatment outcomes**

Patients with disease control had significantly higher baseline IGF-1 levels than did patients without disease control (mean 78.2 vs. 56.5 ng/mL, $P = 0.006$; Fig. 1A). When baseline IGF-1 levels were dichotomized to high ($\geq$median level (63.6 ng/mL)) or low ($<$median level), patients with high IGF-1 levels had significantly higher DCR than patients with low IGF-1 levels (71% vs. 39%, $P = 0.003$). The higher DCR in patients with high IGF-1 levels could be attributed to more stable diseases compared with patients with low IGF-1 levels (62% vs. 32%, $P = 0.003$). The baseline levels of IGF-2 and IGFBP3 were not associated with DCR ($P = 0.415$, 0.295, and 0.099, respectively), either.

Patients with high baseline IGF-1 levels, compared with patients with low levels, had significantly longer PFS (median, 4.3 vs. 1.9 months, $P = 0.014$; Fig. 2A) and OS (median, 10.7 vs. 3.9 months, $P = 0.009$; Fig. 2B). All the variables in Table 1, along with the baseline levels of IGF-1, IGF-2, and IGFBP3 were then analyzed in the Cox proportional hazard model. Treatment regimens, BMI, and prior treatment were also included. Univariate

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Total</th>
<th>High</th>
<th>Low</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>83 (100)</td>
<td>42 (100)</td>
<td>41 (100)</td>
<td></td>
</tr>
<tr>
<td>Median age (range, y)</td>
<td>54 (24–83)</td>
<td>52 (24–73)</td>
<td>56 (28–83)</td>
<td>0.065</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (11)</td>
<td>5 (12)</td>
<td>4 (10)</td>
<td>1.000</td>
</tr>
<tr>
<td>Male</td>
<td>74 (89)</td>
<td>37 (88)</td>
<td>37 (90)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>62 (75)</td>
<td>33 (79)</td>
<td>29 (71)</td>
<td>0.411</td>
</tr>
<tr>
<td>Anti-HCV positive</td>
<td>16 (19)</td>
<td>4 (10)</td>
<td>12 (29)</td>
<td>0.028</td>
</tr>
<tr>
<td>Extrahepatic metastasis</td>
<td>50 (60)</td>
<td>26 (62)</td>
<td>24 (59)</td>
<td>0.754</td>
</tr>
<tr>
<td>Macrovascular invasion</td>
<td>49 (59)</td>
<td>18 (43)</td>
<td>31 (76)</td>
<td>0.002</td>
</tr>
<tr>
<td>AFP &gt; 400 ng/mL</td>
<td>45 (54)</td>
<td>21 (50)</td>
<td>24 (59)</td>
<td>0.435</td>
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<tr>
<td>BCLC stage</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5 (6)</td>
<td>4 (10)</td>
<td>1 (2)</td>
<td>0.360</td>
</tr>
<tr>
<td>C</td>
<td>78 (94)</td>
<td>38 (80)</td>
<td>40 (98)</td>
<td></td>
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<tr>
<td>CLIP score</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0–2</td>
<td>43 (52)</td>
<td>27 (64)</td>
<td>16 (39)</td>
<td>0.021</td>
</tr>
<tr>
<td>3–4</td>
<td>40 (48)</td>
<td>15 (36)</td>
<td>25 (61)</td>
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</tr>
<tr>
<td>ECOG PS</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>70 (84)</td>
<td>39 (93)</td>
<td>31 (76)</td>
<td>0.038</td>
</tr>
<tr>
<td>1</td>
<td>13 (16)</td>
<td>3 (7)</td>
<td>10 (24)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, ECOG performance status.

### Table 2. Treatment response of studied patients according to RECIST

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Total</th>
<th>High</th>
<th>Low</th>
<th>$P$</th>
</tr>
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<tr>
<td>Total</td>
<td>83 (100)</td>
<td>42 (100)</td>
<td>41 (100)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (8)</td>
<td>4 (10)</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>39 (47)</td>
<td>26 (62)</td>
<td>13 (32)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>33 (40)</td>
<td>10 (24)</td>
<td>23 (56)</td>
<td></td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (5)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Response rate$^a$</td>
<td>7 (8)</td>
<td>4 (10)</td>
<td>3 (7)</td>
<td>1.000</td>
</tr>
<tr>
<td>DCR$^b$</td>
<td>46 (55)</td>
<td>30 (71)</td>
<td>16 (39)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

$^a$Defined as the percentage of patients with complete response or partial response.

$^b$Defined as the percentage of patients with complete response, partial response, or stable disease.

[95% confidence interval (CI), 2.2–4.3] and median overall survival (OS) was 6.3 months (95% CI, 4.1–8.5).
In multivariate analysis, high baseline IGF-1 remained an independent predictor for better PFS (HR, 0.375; \( P < 0.001 \)) and OS (HR, 0.577, \( P = 0.029 \); Table 3) in the final fitting model.

**Discussion**

In this study, we found that high pretreatment serum IGF-1 levels were associated with better DCR, PFS, and OS in patients who received first-line systemic therapy for advanced HCC. The associations were independent of other clinicopathologic variables such as hepatitis etiologies, performance status, \( \alpha \)-fetoprotein levels, and CLIP scores. Although previous studies have shown that blood IGF-1 levels are a prognostic marker for HCC (13, 14, 22), this is the first study showing the potential association between serum IGF-1 levels and the efficacy of systemic therapy for advanced HCC. The study was a retrospective analysis and did not include a control group of patients who did not receive therapy. However, the adherence of this study to levels were not associated with the BMI, bilirubin level, and the presence of ascites or encephalopathy. As discussed above, these and other potential prognostic factors were adjusted in the multivariate analysis for PFS and OS, and the baseline IGF-1 level remained an independent predictor.

**IGF-1 levels and patient characteristics**

Patients with low baseline IGF-1 levels were more likely to have chronic hepatitis C (\( P = 0.028 \)), macrovascular tumor invasion (\( P = 0.002 \)), CLIP scores \( \geq 3 \) (\( P = 0.021 \)), or ECOG = 1 (vs. 0, \( P = 0.027 \); Table 1). Baseline IGF-1 levels were not associated with the BMI, bilirubin level, and the presence of ascites or encephalopathy. As discussed above, these and other potential prognostic factors were adjusted in the multivariate analysis for PFS and OS, and the baseline IGF-1 level remained an independent predictor.

**Figure 1.** Baseline levels of (A) IGF-1, (B) IGF-2, and (C) IGFBP3, grouped by disease control or not. The lines marked mean levels and 95% CIs. \( P \) values were calculated by independent \( t \) test to compare the mean levels of biomarker between patients with disease control and with disease progression.

**Figure 2.** Kaplan–Meier analysis of (A) PFS and (B) OS, grouped by high (>median level) and low (<median level) baseline IGF-1 levels. \( P \) values were calculated by log-rank tests.
modified RECIST for tumor assessment, the probable 2 phase II clinical trials our study had adopted prediction for patients with advanced HCC (23, 24). If identify more responders and have improved prognosis by RECIST. Recent data indicated that RECIST may not be attributed to the low response rate (8%) determined from better therapeutic efficacy. Alternatively, this may from better tumor behavior or prognosis, rather than associations between IGF-1 levels and response rates. Although we identified the high IGF-1 levels were associated with better treatment efficacy and patient outcomes may be counterintuitive because elevated IGF-1 levels and activation of the IGFR signaling pathway have been linked to tumorigenesis and the development of many cancer types (1, 2). However, patients with HCC had lower circulating IGF-1 levels than healthy controls (10). On the basis of an HCC patient cohort with heterogeneous disease status and treatment, Kaseb and colleagues found that low plasma IGF-1 levels were associated with extensive liver involvement, vascular invasion, and poorer OS (13, 14). Most circulating IGF-1 is produced in the liver (3, 4). It was therefore postulated that IGF-1 levels reflect the functional reserve of the liver. We also found the correlation between high IGF-1 levels and less advanced disease status (CLIP score <3) or better performance status, which may contribute to the better PFS and OS of patients with high IGF-1 levels.

Table 3. Cox proportional hazards model for predictors of PFS and OS

<table>
<thead>
<tr>
<th>Variables</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (vs. female)</td>
<td>&lt;0.001</td>
<td>5.294 (2.172–12.903)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>0.958 (0.941–0.974)</td>
</tr>
<tr>
<td>High baseline</td>
<td>&lt;0.001</td>
<td>0.375 (0.230–0.612)</td>
</tr>
<tr>
<td>IGF-1 levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (vs. female)</td>
<td>0.047</td>
<td>2.557 (1.012–6.461)</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>0.014</td>
<td>2.087 (1.157–3.763)</td>
</tr>
<tr>
<td>CLIP score ≥ 3</td>
<td>&lt;0.001</td>
<td>2.821 (1.674–4.754)</td>
</tr>
<tr>
<td>High baseline</td>
<td>0.029</td>
<td>0.577 (0.352–0.945)</td>
</tr>
<tr>
<td>IGF-1 levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HBsAg, hepatitis B virus surface antigen.

The finding that high IGF-1 levels were associated with better treatment efficacy and patient outcomes may be counterintuitive because elevated IGF-1 levels and activation of the IGFR signaling pathway have been linked to tumorigenesis and the development of many cancer types (1, 2). However, patients with HCC had lower circulating IGF-1 levels than healthy controls (10). On the basis of an HCC patient cohort with heterogeneous disease status and treatment, Kaseb and colleagues found that low plasma IGF-1 levels were associated with extensive liver involvement, vascular invasion, and poorer OS (13, 14). Most circulating IGF-1 is produced in the liver (3, 4). It was therefore postulated that IGF-1 levels reflect the functional reserve of the liver. We also found the correlation between high IGF-1 levels and less advanced disease status (CLIP score <3) or better performance status, which may contribute to the better PFS and OS of patients with high IGF-1 levels.

Although we identified the high IGF-1 levels were associated with better DCR, PFS, and OS, we did not find associations between IGF-1 levels and response rates. This observation may imply that better survival outcomes in HCC patients with high IGF-1 levels may derive from better tumor behavior or prognosis, rather than from better therapeutic efficacy. Alternatively, this may be attributed to the low response rate (8%) determined by RECIST. Recent data indicated that RECIST may not be adequate in evaluating the efficacy of systemic therapy, especially antiangiogenic agents, in patients with advanced HCC (23, 24). Modified RECIST, which incorporates the measurements of viable tumors in liver, could identify more responders and have improved prognosis prediction for patients with advanced HCC (23, 24). If the 2 phase II clinical trials our study had adopted modified RECIST for tumor assessment, the probable association between response rates and IGF-1 levels might have been found.

The other potential mechanism underlying the associations between treatment outcomes of antiangiogenic therapy and serum IGF-1 levels is the cross-talk between the IGF pathway and tumor angiogenesis. IGF-1 has been shown to stimulate hypoxia-inducible factor-1α activity and VEGF expression in several cancer models (25–28). Blockade of the IGF-1 pathway inhibited angiogenesis and tumor growth in experimental animals (29–32). It is plausible that our HCC patients who had high serum IGF-1 levels might have tumors with higher angiogenic activity, which renders them more likely to benefit from antiangiogenic therapy. We also found that the association of IGF-1 levels with DCR, PFS, and OS held true for patients receiving either bevacizumab or sorafenib-based regimens. This implies that the mechanism underlying the predictive values of IGF-1 levels is possibly linked to antiangiogenesis, the common mechanism of action shared by bevacizumab and sorafenib. However, because of the lack of a control group not receiving antiangiogenic therapy, this hypothesis awaits further exploration.

Approximately 99% of IGF-1 circulates bound to IGFBPs, with most bound to IGFBP3. Less than 1% of IGF-1 circulates unbound (1). In our analysis, serum levels of IGFBP3 had no association with the treatment outcomes. We measured free serum IGF-1 levels and found them also to be associated with DCR. Patients with high levels of free serum IGF-1 had better PFS and OS, although this was not statistically significant (data not shown).

In conclusion, we have shown that high pretreatment serum IGF-1 levels were associated with better DCR, PFS, and OS of patients who received systemic therapy for advanced HCC. These findings warrant validation in large studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: Y.-Y. Shao, C.-H. Hsu
Development of methodology: C.-C. Huang, C.-H. Hsu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y.-Y. Shao, C.-C. Huang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y.-Y. Shao, S.-D. Lin, C.-H. Hsu
Writing, review, and/or revision of the manuscript: Y.-Y. Shao, C.-H. Hsu, A.-L. Cheng
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.-C. Huang, A.-L. Cheng
Study supervision: C.-H. Hsu

Grant Support

This study was supported by grants NSC 98-3112-B-002-038, DOH98-TD-B-111-001, DOH99-TD-B-111-001, and 100CAP1020-2.

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Received November 6, 2011; revised April 12, 2012; accepted May 4, 2012; published OnlineFirst May 23, 2012.
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References

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