Therapy of Adenocarcinoma of Unknown Primary: Are We Making Progress?

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Key Words
Unknown primary carcinoma, therapy, adenocarcinoma, treatment, CUP therapy

Abstract
Therapy for patients with unknown primary carcinoma is evolving and requires a detailed understanding of the various clinicopathologic subsets with more favorable prognoses. For the remainder, and most patients with unfavorable prognoses, data on current empiric chemotherapy with the newer drugs seems to show improved overall survival compared with older historical data, including comparisons with large retrospective series and prospective phase II trial results. Several recent clinical trials have recently documented long-term survival for a minority of patients. The survival of patients with several metastatic adenocarcinomas of known primary sites, including colon/rectum, lung, and pancreas, has been improved by the administration of chemotherapy alone or combined with biologic targeted drugs (bevacizumab, erlotinib). Approximately 60% of the patients with unknown primary adenocarcinoma have clinically occult primary sites of colon/rectum, lung, and pancreas. Many of these patients will also benefit from therapeutic regimens now proven to be useful for patients with these known primary sites. All available data make a convincing argument that progress is being made for the commonly seen patients with adenocarcinoma of unknown primary site, and is likely to continue as understanding of these and other neoplasms further evolves. (JNCCN 2008;6:1061–1067)

Unknown Primary Adenocarcinoma and the Occult Primary

Many patients with adenocarcinoma of unknown primary site have clinically occult primaries. Autopsy series have identified occult primary sites in approximately 73% of these patients, most commonly in the lung (non–small cell), pancreas, liver/bile ducts, kidney/adrenal, and colon/rectum. All reported autopsy series were recently reviewed. From 1944 to 2000, 12 series of 884 unknown primary patients were reported, including 7 (622 patients) from 1944 to 1980 and 5 (262 patients) from 1980 to 2000. In the older series (1944–1980) clinically occult primary sites found at autopsy in the pancreas and colon/rectum were more common than in the more recent series (1980–2000), as might be expected because CT and colonoscopy were not available in the earlier years. Occult primaries from other sites have remained about the same over this time span. Furthermore, most primaries found at autopsy were small (< 1 cm) and thus represent clinical biology. Over the past 3 decades, several subsets of patients have shown distinct clinical or pathologic features distinguishing them from the group as a whole. Patients in many of these subsets (favorable) are treatable and their recognition is clinically relevant (Table 1), because their prognosis is individually much better than for all patients with unknown primary cancer.

Most patients with unknown primary cancer have carcinoma, and of these, most are adenocarcinomas. After patients in favorable subsets are excluded, the prognosis for the remaining patients has been poor. Is progress being made in the treatment of these patients? Before answering this question several other issues must be considered, including the current and evolving therapy for patients with several common advanced adenocarcinomas with known primary sites.
Table 1 Favorable Prognostic Subsets in Cancer of Unknown Primary Site

| Extragonadal germ cell syndrome (PDA or PDC) | Poorly differentiated malignant neoplasm (not otherwise classified; 60% lymphomas) | Retroperitoneal, mediastinal, and/or peripheral lymph node involvement (PDA, PDC, WDA) | Squamous cell carcinomas (head/neck or inguinal area) | Isolated axillary adenopathy: women, rare in men (WDA, PDC, PDA) | Peritoneal carcinoma: women, rare in men (WDA, PDC, PDA) | Blastic bone metastasis or increased PSA in serum or tumor: men (WDA, PDA, PDC) | Neuroendocrine carcinoma: low-grade or well-differentiated (carcinoid/islet cell type) | Neuroendocrine carcinoma: high-grade or poorly differentiated (small cell and others) | Single site (one lesion; WDA, PDC, PDA) |

Abbreviations: PDA, poorly differentiated adenocarcinoma; PDC, poorly differentiated carcinoma; PSA, prostate-specific antigen; WDA, well-differentiated adenocarcinoma.


occult clinically undetectable primary sites that would probably not be detected during life with diagnostic testing. Approximately 60% of clinically occult primary tumors were from the colon/rectum, lung, and pancreas.

Patients with known primary adenocarcinomas are now more treatable. Significant improvements in survival have been documented for various systemic therapies. These data are unequivocal and derived from large randomized, prospective phase III studies (level I evidence). Treatments for patients with advanced cancers continue to improve, as shown by the recent introduction of several new and useful biologic targeted agents (trastuzumab, imatinib, erlotinib, bevacizumab, cetuximab, sorafenib, sunitinib, lapatinib, and tensirolimus), alone or with cytotoxics.

Current survival data, including median, 1-, 2-, and 3-year survivals for patients with metastatic colon/rectum, non–small cell lung, pancreatic, and unknown primary carcinomas, are shown in Table 2. The use of bevacizumab (colonic/rectal, non–small cell lung) and erlotinib (pancreas) combined with cytotoxic chemotherapy in selected patients has shown improved survival over chemotherapy alone.

Because approximately 60% of patients with unknown primary carcinomas harbor a “treatable” occult primary carcinoma, some of these patients should benefit from the same treatments for patients with known primary tumors. This is particularly understandable if sometime during the course of their disease, patients with unknown primary carcinomas undergo various sequential combination regimens containing cisplatin or carboplatin, taxanes, gemcitabine, irinotecan, 5-fluorouracil, oxaliplatin, and bevacizumab/erlotinib.

No level I evidence proves that any form of chemotherapy versus best supportive care improves survival for these patients. However, considerable aggregate data (level II evidence) make a compelling argument that regimens developed in the past several years have improved survival for these patients.

Table 2 Survival of Patients with Several Metastatic Adenocarcinomas After Systemic Therapy

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Median Survival Range (mo)</th>
<th>1-y Survival Range (%)</th>
<th>2-y Survival Range (%)</th>
<th>3-y Survival Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon/rectum*</td>
<td>18–22</td>
<td>72–76</td>
<td>38–42</td>
<td>18–22</td>
</tr>
<tr>
<td>Non–small cell lung*</td>
<td>10–12</td>
<td>35–50</td>
<td>20–25</td>
<td>5–10</td>
</tr>
<tr>
<td>Pancreas*</td>
<td>5–7</td>
<td>20–25</td>
<td>5–10</td>
<td>0–5</td>
</tr>
<tr>
<td>Unknown primary†</td>
<td>7–13</td>
<td>26–52</td>
<td>7–20</td>
<td>7–16</td>
</tr>
</tbody>
</table>

*Combined data from several randomized prospective phase III trials.†Combined data from several prospective phase II trials.
Two randomized comparisons of regimens showed a response rate of approximately 20% and a median survival of approximately 6 months. Survival at 2 years and beyond was rarely reported and progression-free survival beyond 2 years was not reported.

Only 4 small randomized phase II studies were reported. Two randomized comparisons of regimens with or without cisplatin showed no difference in median survival. A third randomized trial showed the superiority of cisplatin, mitomycin C, and epirubicin compared with mitomycin C alone (median survival, 9.4 vs. 5.4 months). The fourth trial compared cyclophosphamide, methotrexate, and 5-fluorouracil with doxorubicin and mitomycin C. The response rate and median survival favored the doxorubicin-based regimen (36% vs. 5%; 4.5 vs. 1.7 months). Survival beyond 1 year was not reported.

Several factors should be considered when viewing these data. The studies were small, large randomized phase III comparisons are lacking, and long-term survival was not reported from any study. Many of these studies included some patients with favorable subsets. These results all reflect older chemotherapy and none included an arm for best supportive care. The patients were not evaluated or stratified in references to sites of metastasis (nodal vs. visceral), performance status, sex, age, or other now-known prognostic factors. No convincing evidence showed that survival was prolonged by any therapy.

### Prospective Clinical Trials Review After 2000

Several new cytostatic drugs with rather broad-spectrum antineoplastic activity and targeted mechanism-based therapies have recently improved standard treatment for patients with several common advanced epithelial cancers. Some drugs include the taxanes, gemcitabine, irinotecan, vinorelbine, topotecan, oxaliplatin, and several biologic targeted agents (including bevacizumab and erlotinib).

The Minnie Pearl Cancer Research Network (MPCRN) completed 9 sequential prospective phase II trials since 1997, incorporating paclitaxel, docetaxel,
gemcitabine, irinotecan, capecitabine, oxaliplatin, and bevacizumab/erlotinib into the first-, second-, or third-line therapy for 692 patients (most with good performance status) with carcinoma of an unknown primary site. One additional phase III randomized, prospective first-line trial is in progress comparing paclitaxel, carboplatin, and etoposide with gemcitabine and irinotecan, with 185 patients accrued. Only patients with carcinoma (any histology) who were not defined in a favorable subset were eligible for the first-line trials. All patients underwent a standard evaluation to detect a primary.

The chemotherapy regimens for the first 5 phase II MPCRN studies (396 previously untreated patients) were as follows: 1) paclitaxel, carboplatin, and gemcitabine (120 patients); 2) docetaxel, cisplatin (26 patients); 3) docetaxel and carboplatin (47 patients); 4) paclitaxel, carboplatin, and gemcitabine (120 patients); and 5) paclitaxel, carboplatin, and etoposide followed by gemcitabine and irinotecan (132 patients). The response rate for all patients was 30% (107 of 353 evaluable patients), with 85 (24%) partial and 22 (6%) complete responders. With a minimum and maximum follow-up of 2.5 and 9.5 years, respectively, the median survival was 9.1 months. The 1-, 2-, 3-, 5-, 8-, and 10-year survivals were 38%, 19%, 12%, 10%, 8%, and 8%, respectively (Figure 1). The median progression-free survival was 5 months and the 1-, 2-, 3-, 5-, 8-, and 10-year progression-free survival was 17%, 7%, 5%, 4%, 3%, and 3%, respectively. The toxicity of all regimens was generally moderate, primarily myelosuppression. A total of 8 (2%) treatment-related deaths occurred.

Long-term follow-up of the 264 patients in the first 4 trials is as follows: minimum follow-up was 4.5 years (maximum 9.5 years), median survival was 10.2 months, and the 1-, 2-, 3-, 5-, 8-, and 10-year survivals were 41%, 24%, 15%, 11%, 8%, and 8%, respectively. The actuarial survival for the 428 additional patients treated in 5 subsequent phase II trials and 185 patients in an ongoing phase III trial look similar. No significant survival differences were seen between the survival curves of first-line phase II studies. The central element in evaluating therapy for these patients has been survival at 1 year and beyond.

The FDA approved bevacizumab (an inhibitor of vascular endothelial growth factor receptor) for advanced non–small cell lung and pancreatic carcinomas. The MPCRN recently reported a phase II trial of bevacizumab/erlotinib in 51 patients with unknown primary carcinoma; 37 underwent previous chemotherapy and 14 were previously untreated but all had poor prognostic features (advanced liver metastasis, bone metastasis, or ≥ 3 visceral sites of involvement). All received bevacizumab 10 mg/kg intravenously every 2 weeks along with erlotinib 150 mg orally daily, and 47 underwent at least 8 weeks of therapy. Among patients undergoing treatment, 5 (10%) experienced a partial response and 29 (61%) had stable disease (many with some tumor shrinkage). Median survival was 7.4 months and 1-year survival was 33%. Patients tolerated this therapy relatively well (grade 3/4 toxicity of any type < 10%, except fatigue at 16%). Median and 1-year survivals seem superior to second-line chemotherapy and are similar to early results of many recent first-line chemotherapy trials. These results prompted an ongoing MPCRN phase II study of the 4-drug combination of paclitaxel/carboplatin plus bevacizumab/erlotinib in previously untreated patients.

Analysis of all previously untreated patients in the MPCRN trials shows no difference in survival for patients with adenocarcinomas versus those with poorly differentiated carcinomas. Women survived longer than men, and those with ECOG performance status 0 or 1 lived longer than those with performance status 2. Progress was recently made in identifying prognostic factors in common patients who are not in the favorable subset groups. Several studies with multivariate
analyses identified poor performance status, elevated serum lactate dehydrogenase, low serum albumin, and liver metastases as major independent negative prognostic factors. It now seems that these factors can separate patients into at least 2 groups with significantly different survivals after therapy (median survival, 4 vs. 12 months), and additional prospective validation of these results is warranted. Prognostic factors are important in assessing the impact of a treatment.

Several other investigators have also reported on phase II trials since 2000 (Table 4). These trials usually involved the newer cytotoxic drugs, including platinum-, paclitaxel-, docetaxel-, gemcitabine-, irinotecan-, and vinorelbine-based regimens. In 12 phase II studies (530 total patients), patients with well-recognized favorable prognostic factors were excluded, and most patients had multiple sites of metastases, often with liver, bone, and lung involvement. A minority of the patients (about 15%) had poor functional status (ECOG = 2). Although clinical characteristics and pathology were variable, most patients in these studies (2000–2007) had unfavorable prognostic features, and represent a relatively similar group. The primary end points were usually response rate or median survival. The median survivals (approximately 9 months; range, 6–13.6 months) are very similar to those in the MPCRIN trials. Furthermore, survival at 1 year reported by all 12 trials ranged from 25% to 52% (mean, 34.6%) and survival at both 1 and 2 years was also reported by 8 of these studies, including 405 patients. Survival at 1 and 2 years ranged from 26% to 52% (mean, 37%) and 9% to 20% (mean, 14%), respectively. Only 1 study reported a 3-year survival rate of 11%. These recent data are very similar, although with shorter follow-up, to the 396 patients reported and previously discussed MPCRIN studies, and document survival of a small minority of patients at 2 and 3 years (Table 4). Survival at 2 years and beyond has not been previously reported, and these data support progress in the therapy of these patients.

The efficiency of these therapies as assessed in relatively small clinical trials is best seen and documented

Table 4 Recent Trials in Unknown Primary Carcinoma and Unfavorable Prognostic Factors: Long-Term Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Regimen</th>
<th>Median Survival (mo)</th>
<th>1-Year Survival (%)</th>
<th>2-Year Survival (%)</th>
<th>3-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briasoulis et al., 2000</td>
<td>33</td>
<td>PCb</td>
<td>10</td>
<td>25</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>Dowell et al., 2001</td>
<td>34</td>
<td>PSFUL (17)</td>
<td>8.3</td>
<td>26</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CbE (17)</td>
<td>6.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balaña et al., 2003</td>
<td>30</td>
<td>GCE</td>
<td>7.2</td>
<td>36</td>
<td>14</td>
<td>NR</td>
</tr>
<tr>
<td>Pouessel et al., 2004</td>
<td>35</td>
<td>GD</td>
<td>10</td>
<td>43</td>
<td>7</td>
<td>NR</td>
</tr>
<tr>
<td>Piga et al., 2004</td>
<td>102</td>
<td>CbDoxE</td>
<td>9</td>
<td>35.3</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Park et al., 2004</td>
<td>37</td>
<td>PC</td>
<td>11</td>
<td>38</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>El-Rayas et al., 2005</td>
<td>22</td>
<td>PCb</td>
<td>6.5</td>
<td>27</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Palmeri et al., 2006</td>
<td>66</td>
<td>GPC (33)</td>
<td>9.6</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GVC (33)</td>
<td>13.6</td>
<td>52</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pittman et al., 2006</td>
<td>51</td>
<td>Gcb</td>
<td>7.8</td>
<td>26</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Schneider et al., 2007</td>
<td>33</td>
<td>GCaCb</td>
<td>7.6</td>
<td>35.6</td>
<td>14.2</td>
<td>NR</td>
</tr>
<tr>
<td>Briasoulis et al., 2007</td>
<td>47</td>
<td>OxIr</td>
<td>9.5</td>
<td>40</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Berry et al., 2007</td>
<td>42</td>
<td>PCb</td>
<td>8.5</td>
<td>33</td>
<td>17</td>
<td>NR</td>
</tr>
<tr>
<td>MPCRIN trials (5) 1997–2008</td>
<td>396</td>
<td>Multiple regimens (see text)</td>
<td>9.1</td>
<td>38</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>928</td>
<td></td>
<td>8.9</td>
<td>34.6</td>
<td>13*</td>
<td>12*</td>
</tr>
</tbody>
</table>

Abbreviations: 5FUL, 5-fluorouracil/leucovorin; C, cisplatin; Ca, capecitabine;Cb, carboplatin; D, docetaxel; Dox, doxorubicin; E, etoposide; G, gemcitabine; Ir, irinotecan; MPCRIN, Minnie Pearl Cancer Research Network; NR, not reported; Ox, oxaliplatin; P, paclitaxel; V, vinorelbine.

*Mean survivals of all studies.
at 1-, 2-, and 3-year survival end points. Fewer than 50% of the patients survive for 1 year; consequently, important and perhaps significant improvements in survival beyond 1 year cannot be appreciated when comparing only median survival data. Unless the trial is of phase III design and very large, concluding that a new therapy is not better based on lack of differences in median survival alone may be erroneous. After a particular treatment, 1-, 2-, and 3-year survival rates may be superior, but the median survival may not significantly change. Although survival is generally not the appropriate end point for phase II studies, this is all that is currently available to evaluate.

Long-term survival data from several hundred patients in MPCRN studies and the 1- and 2-year survivals of several hundred patients recently reported by others are encouraging. Initial results with the targeted combination of bevacizumab/erlotinib are also provocative, and warrant further study of biologic targeted agents combined with chemotherapy.

Survival reported from multiple recent phase II studies of these patients, most with unfavorable prognostic features, receiving the newer cytotoxic drugs, seem superior to not only the historical retrospective control data but also the combined data from multiple previous prospective clinical trials reported from 1964 to 2002. Large prospective, randomized phase III trials could provide definitive confirmation, but a no-treatment control (best supportive care) arm study will doubtfully ever be completed. Furthermore, the use of combined clinical, pathologic, and molecular profiling data is likely to be a more rational framework to design future clinical trials, rather than using empirically derived chemotherapy regimens.

Conclusions
Is progress being made in the treatment of carcinoma of unknown primary site? These data reported in this article, including the documentation of long-term survival in a minority of patients in the past decade, provide a solid argument for progress. When also considering that several of these patients harbor occult carcinomas from the colon, rectum, pancreas, lung, kidney, breast, and other treatable sites, the argument is strengthened even further. Many common patients with unknown primary adenocarcinoma who are not in a previously defined favorable subset now experience significant clinical benefit and survival from the new drug combinations. Survival for these patients now compares favorably to that of several other patients with known metastatic primary carcinomas, including those with pancreatic and non–small cell lung carcinomas.

Much more improvement is needed, but the question of whether progress has been made in the therapy for these patients is no longer a relevant clinical question. More important questions are whether molecular profiling of a metastatic lesion will enable the primary site to be defined, and whether patients with primary sites identified through molecular profiling will respond to site-directed therapy and experience similar survival to those with a known primary site. Both questions should be answered in the next few years, and hopefully a better molecular understanding of each patient’s individual neoplasm, when used with clinical and pathologic findings, will also lead to more specific and effective therapy.

References
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