The Winning Formulation: The Development of Paclitaxel in Pancreatic Cancer

Wen Wee Ma¹ and Manuel Hidalgo²

Abstract
Paclitaxel has wide application in anticancer therapy but was never considered an efficacious agent in pancreatic cancer. A review of the experience with the Cremaphor formulation hinted at paclitaxel’s activity in pancreatic cancer, but the early development was hampered by significant toxicities such as neutropenia and infection at clinically tolerable doses. However, such efficacy was confirmed in the recently completed phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT), in which the addition of nab-paclitaxel to gemcitabine significantly improved the survival of patients with metastatic pancreatic cancer. Several other Cremaphor-free formulations of paclitaxel had also been evaluated in pancreatic cancer, and the reasons for the success of the albumin nanoparticulate are examined here. In the era of biologic and molecularly targeted agents, the success of nab-paclitaxel in recalcitrant pancreatic cancer is a timely reminder of the importance and relevance of pharmacology and novel drug delivery technology in the development of anticancer drugs. Clin Cancer Res; 19(20); 5572–9. ©2013 AACR.

Introduction
Pancreatic cancer is the eighth leading cause of cancer-related deaths worldwide, and approximately 266,000 patients died from the disease in 2008 (1). Gemcitabine was the first anticancer drug to achieve meaningful survival improvement in advanced pancreatic cancer and has been the standard bearer since the 1990s (2). Over the years, a large number of cytotoxic and molecularly targeted drugs were evaluated in combination with gemcitabine in clinical trials, but almost all failed to further improve the survival in advanced pancreatic cancer (3–5). In some instances, this was due to low intrinsic activity of the new agent, but some others might have been due to poor clinical trial design. A meta-analysis of 15 clinical trials involving 4,465 patients with advanced pancreatic cancer concluded that patients with good performance status should be offered gemcitabine-containing combinations. Erlotinib, given with gemcitabine, is the only other anticancer drug to receive regulatory approval for the treatment of advanced disease. However, the addition of erlotinib to gemcitabine achieved an improvement of only approximately 1 week in median survival compared with gemcitabine, as shown in the NCIC CTG PA.3 trial (6).

The success of FOLFIRINOX, an intensive cytotoxic regimen of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin, was a major milestone in pancreatic cancer therapy that extended the survival of patients with metastatic pancreatic cancer by 4.3 months compared with gemcitabine alone (7). However, toxicities related to FOLFIRINOX were significant and included febrile neutropenia, fatigue, diarrhea, and peripheral neuropathy, and is being used selectively. As such, there remains a need for therapies more tolerable than FOLFIRINOX that is yet still able to achieve clinically meaningful survival improvement. Positive results from the recently announced Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) showed that the nab-paclitaxel and gemcitabine combination may, in fact, fill this void (Table 1; ref. 8). This review contrasts the development of nab-paclitaxel in pancreatic cancer with that of other paclitaxel formulations and explores the question of why the nab formulation succeeded while others did not (Table 2). Experience on docetaxel in the context of “GTX” is also reviewed briefly.

Metastatic Pancreatic Adenocarcinoma Clinical Trial
The MPACT study was a multinational phase III trial launched following the encouraging result of a phase I/II trial of nab-paclitaxel plus gemcitabine in advanced pancreatic cancer (9). In the pivotal trial, 842 patients with metastatic pancreatic cancer and Karnofsky performance scores of 70 or higher were randomized to receive nab-paclitaxel, 125 mg/m² followed by gemcitabine, 1,000 mg/m² on days 1, 8, and 15 every 28 days or gemcitabine, 1,000 mg/m² weekly for 7 weeks followed by 1 week of rest, and then on days 1, 8, and 15 every 4 weeks thereafter (8). Forty-three percent of the patients had head of pancreas...
The addition of nab-paclitaxel to gemcitabine was well tolerated; patients in the combination arm received 71% and 63% of planned nab-paclitaxel and gemcitabine doses, respectively, and the gemcitabine-only arm received 79% of the planned gemcitabine dose. The added toxicity risks from nab-paclitaxel–gemcitabine did much better than those in the gemcitabine-only arm, with median survival of 8.5 months versus 6.7 months (HR, 0.72; \( P = 0.000015 \)), 1-year survival 35% versus 22%, 2-year survival 9% versus 4%, and objective response rate 23% versus 7%, respectively.

In summary, the addition of nab-paclitaxel to gemcitabine did achieve a statistically significant survival improvement for patients with metastatic pancreatic cancer, and the added toxicity risk was acceptable and manageable including neutropenia and neuropathy. The nab-paclitaxel–gemcitabine regimen should, therefore, be considered in patients with advanced pancreatic cancer and good physiological reserve who were not otherwise a candidate for the intensive FOLFIRINOX. In addition, the more favorable toxicity profile makes nab-paclitaxel plus gemcitabine a very attractive backbone for developing novel agents.

### Paclitaxel and Pancreatic Cancer

Paclitaxel has broad application in oncology and causes mitotic arrest in cancer cells by disrupting microtubule function (10). Due to the poor aqueous solubility, polyoxyethylated castor oil solvent (Cremaphor) was used to solubilize paclitaxel for intravenous administration (Cre-paclitaxel; Taxol). However, the formulation caused infusion hypersensitivity reaction requiring premedication with steroids and antihistamines (11, 12). The Cremaphor solvent also altered paclitaxel’s pharmacology, affecting the toxicity profile and anticancer efficacy (13–15). A number of strategies have, thus, been developed to better solubilize and improve the pharmacology of paclitaxel, including albumin nanoparticles, emulsions, and liposomes (Fig 1; refs. 13).

### Cremaphor formulation

Cre-paclitaxel was evaluated in pancreatic cancer but failed to show significant activity in general (Table 2). A phase II trial of Cre-paclitaxel 175 mg/m\(^2\) every 3 weeks in 14 patients with chemo-naive, locally advanced unresectable and metastatic pancreatic cancer was closed early when preplanned analysis showed no response (16). The median survival was 7.2 months. A higher dose of Cre-paclitaxel 250 mg/m\(^2\) every 3 weeks with G-CSF support was tested in patients with chemo-naive advanced pancreatic cancer. Although 1 complete response was observed, the median survival was 5 months and the regimen was declared inactive in pancreatic cancer (17). The median duration of treatment was 51 days, and 6 patients (15%) stopped due to treatment-related toxicities. Common grade 3 or worse toxicity included granulocytopenia (92%), anemia (23%), thrombocytopenia (21%), liver function anomalies (23%), and infection (21%), including one septic death.

A weekly schedule of Cre-paclitaxel 90 mg/m\(^2\) on days 1, 8, and 16 every 28 days was evaluated in combination with bryostatin, a protein kinase C inhibitor, in a phase II trial of 19 patients with advanced pancreatic cancer (5 were first-line; ref. 18). No confirmed response was observed, and time to treatment failure was 1.9 months. Several other weekly schedules of Cre-paclitaxel monotherapy in patients with gemcitabine-refractory advanced pancreatic cancer had been noted in several retrospective reports (19, 20). However, the results were difficult to interpret due to the nature of the reports although tumor responses had been observed, including 1 complete response.

A combination regimen of Cre-paclitaxel 175 mg/m\(^2\) every 4 weeks and 5-fluorouracil 1,000 mg/m\(^2\) on days 1, 2, and 3 was evaluated in a single-arm phase II study of 28 patients with gemcitabine-refractory advanced disease (21).
Table 2. Studies that evaluated paclitaxel in patients with advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Clinical trial (year; reference)</th>
<th>Design</th>
<th>Patients, N</th>
<th>Line(s) of therapy; patient population</th>
<th>Regimen</th>
<th>Overall response rate</th>
<th>Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cre-paclitaxel</td>
<td>Phase II</td>
<td>14</td>
<td>First-line; stage II/IV</td>
<td>Paclitaxel 175 mg/m² every 3 wks</td>
<td>0%</td>
<td>7.2</td>
</tr>
<tr>
<td>Gebbia (1996; ref. 16)</td>
<td>Phase II</td>
<td>39</td>
<td>First-line; stage II/IV</td>
<td>Paclitaxel 250 mg/m² every 3 wks + G-CSF</td>
<td>8%</td>
<td>5</td>
</tr>
<tr>
<td>Whitehead (1997; ref. 17)</td>
<td>Phase II</td>
<td>28</td>
<td>Gemcitabine-refractory; stage II/IV</td>
<td>Paclitaxel 175 mg/m² on day 1 every 4 wks + 5-fluourouracil 1,000 mg/m² iv. on days 1–3 every 4 wks</td>
<td>10%</td>
<td>2.5</td>
</tr>
<tr>
<td>Kim (2008; ref. 21)</td>
<td>Phase II</td>
<td>19</td>
<td>First-line and beyond; stage II/IV</td>
<td>Paclitaxel 90 mg/m² weekly × 3 every 4 wks + bryostatin</td>
<td>0%</td>
<td>1.9</td>
</tr>
<tr>
<td>Lam (2009; ref. 18)</td>
<td>Phase II</td>
<td>18</td>
<td>Second and third lines; stage IV</td>
<td>Paclitaxel 55–88 mg/m² weekly</td>
<td>5%</td>
<td>4.3</td>
</tr>
<tr>
<td>Oettle (2000; ref. 20)</td>
<td>Retrospective study</td>
<td>19</td>
<td>Gemcitabine-refractory; stage II/IV</td>
<td>Paclitaxel 80 mg/m² weekly × 3 every 4 wks</td>
<td>0%</td>
<td>3.4</td>
</tr>
<tr>
<td>Shukuya (2010; ref. 60)</td>
<td>Retrospective study</td>
<td>30</td>
<td>Gemcitabine-refractory; stage II/IV</td>
<td>Paclitaxel 80 mg/m² weekly × 3 every 4 wks</td>
<td>10%</td>
<td>6.7</td>
</tr>
<tr>
<td>Maeda (2012; ref. 19)</td>
<td>Retrospective study</td>
<td>30</td>
<td>Gemcitabine-refractory; stage II/IV</td>
<td>Paclitaxel 90 mg/m² weekly × 3 every 4 wks</td>
<td>10%</td>
<td>6.7</td>
</tr>
<tr>
<td>nab-paclitaxel</td>
<td>Phase II/II</td>
<td>67</td>
<td>First-line; stage IV</td>
<td>nab-paclitaxel 100, 125, 150 mg/m² + gemcitabine</td>
<td>46%</td>
<td>12.2</td>
</tr>
<tr>
<td>von Hoff (2011; ref. 9)</td>
<td>Phase II</td>
<td>15</td>
<td>First-line; stage IV</td>
<td>nab-paclitaxel 100 mg/m² (Day 4) + gemcitabine 750 mg/m² (day 4) + capcitabine 750 mg/m² twice daily (day 1–7) every 14 days</td>
<td>14%</td>
<td>7.5</td>
</tr>
<tr>
<td>Ko (2012; ref. 24)</td>
<td>Phase III</td>
<td>842</td>
<td>First-line; stage IV</td>
<td>nab-paclitaxel 125 mg/m² + gemcitabine</td>
<td>23%</td>
<td>8.5</td>
</tr>
<tr>
<td>MPACT (2013; ref. 8)</td>
<td>Phase III</td>
<td>19</td>
<td>Second and third lines; stage II/IV</td>
<td>nab-paclitaxel 100 mg/m² weekly × 3 every 4 wks</td>
<td>5%</td>
<td>7.3</td>
</tr>
<tr>
<td>Hosein (2012; ref. 25)</td>
<td>Phase II randomized</td>
<td>200</td>
<td>First-line; stage II/IV</td>
<td>ET-paclitaxel 11, 22, 44 mg/m² twice-weekly + gemcitabine 1,000 mg/m² vs. gemcitabine</td>
<td>14%/14%/16%</td>
<td>4.1/4.6/4.4/2.7, respectively</td>
</tr>
<tr>
<td>GPM-paclitaxel</td>
<td>Phase II randomized</td>
<td>2010</td>
<td>First-line; stage II/IV</td>
<td>GPM-paclitaxel 435/300/350 mg/m² every 3 wks</td>
<td>7%</td>
<td>6.5</td>
</tr>
</tbody>
</table>
The Development of Paclitaxel in Pancreatic Cancer

The majority of patients (89%) received only one previous line of gemcitabine-containing therapy. There were 2 partial responses, although the median time to progression and survival were 2.5 and 7.6 months, respectively. Grade 3 and worse adverse events included neutropenia (21.4%; including 1 grade 4 neutropenia associated with pneumonia), thrombocytopenia (3.6%), diarrhea (7.1%), and neuropathy (3.5%).

**Albumin-bound formulation: early-phase trials experience**

The albumin formulation of paclitaxel, nab-paclitaxel (Abraxane), is approved by the U.S. Food and Drug Administration for the treatment of breast and lung cancers (22). The solvent-free nab-paclitaxel is advantageous over Cremophor, with significantly lower risk of infusion hypersensitivity reactions and neutropenia, and faster recovery of peripheral neuropathy on stopping the treatment (23). The hint of activity of nab-paclitaxel–gemcitabine in pancreatic cancer came from a phase I/II trial (9). Sixty-seven treatment-naïve patients with advanced pancreatic cancer were treated with nab-paclitaxel dose levels of 100, 125, or 150 mg/m² in combination with gemcitabine, 1,000 mg/m² on days 1, 8, and 15 every 28 days. The dose-limiting toxicities were neutropenia and sepsis at the 150 mg/m² dose; thus, the 125 mg/m² dose level was determined tolerable and evaluated further in the phase III MPACT trial. The single-arm study had a respectable median survival of 12.2 months, 1-year survival rate of 48%, and overall response rate of 48% in patients treated at the maximum tolerated dose.

The feasibility of combining additional cytotoxic drug to nab-paclitaxel–gemcitabine was evaluated by Ko and colleagues (24). In the phase I trial, capecitabine was administered on days 1 to 7, and nab-paclitaxel and gemcitabine at fixed-dose rate infusion (FDR) on day 4 on an every-14-day cycle. Dose-limiting toxicities were grade 3 neutropenia and grade 3 alanine transaminase elevation. Capecitabine, 750 mg/m² twice daily; nab-paclitaxel, 100 mg/m²; and gemcitabine, FDR 750 mg/m² were determined to be the maximum tolerated dose. Of the 14 evaluable patients, the objective response rate was 14.3% and median survival was 7.5 months. The inferior efficacy observed for this regimen compared with the above-mentioned phase I/II study was most likely due to the lower dose intensity of component drugs.

Monotherapy with nab-paclitaxel, 100 mg/m² on days 1, 8, and 15 in every 28-day cycle, was evaluated in 19 patients previously treated with gemcitabine-based regimens (25). The treatment was tolerable and the toxicity profile was consistent with expectations. The median survival was 7.3 months, and 1 (5%) partial response was observed. The study was closed before reaching target accrual in view of the decision to develop the nab-paclitaxel and gemcitabine combination in a first-line setting. For comparison, Oettle and colleagues reported a case series of 18 metastatic patients previously treated with gemcitabine-based therapy (20). Patients received Cremophor-paclitaxel, 50 mg/m² weekly for...
6 weeks followed by a week of rest, and the dose was increased up to 85 mg/m² for patients with less than grade 3 toxicities. The median dose administered was 73 mg/m² (range, 55–88 mg/m²). The median survival observed was 4.4 months, and 1 patient (5.6%) achieved a complete response. The longer survival observed in the aforementioned nab-paclitaxel monotherapy study may be a result of improved supportive care over the decade although both studies consistently reported tumor responses, suggesting efficacy of paclitaxel in some patients, and biomarkers are needed to identify this subgroup.

Cationic liposomal formulation

Cationic liposomes have strong affinity for negatively charged tumor endothelial cells and are, theoretically, advantageous in selectively delivering paclitaxel to tumor vasculature (26). EndoTag-paclitaxel (ET-paclitaxel) is one such formulation in which paclitaxel is embedded in the cationic liposome membrane (27). The efficacy of adding ET-paclitaxel to gemcitabine was evaluated in a randomized phase II trial in which 212 patients with pancreatic cancer (80% metastatic and 20% locally advanced) were randomized to one of four arms: gemcitabine, 1,000 mg/m²; or gemcitabine plus twice weekly ET-paclitaxel, 11, 22, or 44 mg/m² for 7 weeks. The median survival durations achieved were 6.8 versus 8.1, 8.7, and 9.3 months, respectively, and 1-year survival rates were 15% versus 21%, 35%, and 30%, respectively. Partial response was the best response and the rates were similar between gemcitabine alone and ET-paclitaxel-containing arms. Grade 3 or worse adverse events during the first cycle were observed in 24%, 22%, 32%, and 40% of patients, respectively. There was a dose-dependent increase in grade 3 or worse thrombocytopenia (2% vs. 8%, 16%, and 18% respectively) whereas neutropenia risk was almost comparable across all arms. Infusion-related reactions (pyrexia, chills) were more frequent in the ET-paclitaxel-containing arms. The combination was reportedly planned for phase III evaluation.

Polymeric micelle formulation

Paclitaxel-loaded polymeric micelle (Genexol-PM; ref. 28) was evaluated as monotherapy in treatment-naive advanced pancreatic cancer in a single-arm phase II study (29). The initial 11 patients were treated at a dose of 435 mg/m² once every 3 weeks, and the dose was reduced to 300 or 350 mg/m² for the next 45 patients due to intolerance. The median survival achieved was 6.5 months and response rate was 6.7% (one complete and two partial responses). The dose of 300 mg/m² every 3 weeks was determined as the tolerable dose, and toxicities were comparable with that of the Cremaphor formulation. The most common adverse events were neutropenia (40%), fatigue (17.8%), infection, dehydration, neuropathy (13.3% each), and abdominal pain (11.1%). The formulation was reportedly being evaluated in combination with gemcitabine in advanced pancreatic cancer (ClinicalTrials.gov NCT00882973).

Docetaxel—In the Context of “GTX”

Docetaxel is a semisynthetic taxoid that also has wide application in anticancer therapy (30). The dose-limiting toxicity was neutropenia, and the initial recommended phase II dose was 100 mg/m² every 3 weeks although 75 mg/m² every 3 weeks was later determined to be more tolerable (31, 32). Like Cre-paclitaxel, docetaxel monotherapy did not show significant activity in pancreatic cancer (33–36). Several dosing schedules combining docetaxel and gemcitabine were evaluated in advanced pancreatic cancer, with median survival ranging from 4.7 to 10.5 months, and response rate from 6% to 30% (37–44). However, toxicities were significant in these phase II studies including neutropenia, infection, and septic death.

Fine and colleagues reported a single-arm phase II study of docetaxel, gemcitabine, and capecitabine (GTX) in first-line metastatic patients that achieved a median survival of 14.5 months and response rate of 38%, where the frequency of grade 3 or 4 neutropenia was 29%, febrile neutropenia was 3%, and anemia and thrombocytopenia was 12% (Table 3; ref. 45). A retrospective study of 154 patients with advanced pancreatic cancer treated with GTX reported a response rate of 11% and median survival of 11.6 months (in stage IV patients; ref. 46). The rate of grade 3 or worse hematologic toxicities was 41%. An alternate every-28-day cycle schedule of docetaxel, gemcitabine, and capecitabine was reported by Xenidis and colleagues that achieved a response rate of 40% and median survival of 9 months (47). Reni and colleagues evaluated an intensive four-drug regimen by adding cisplatin to docetaxel, gemcitabine, and capecitabine in first-line metastatic patients and achieved a response rate of 57% but a disappointing median survival of 5.8 months (48). The efficacy and toxicity profiles of GTX seemed comparable with those reported in the phase I/II trial of nab-paclitaxel–gemcitabine by von Hoff and colleagues (Table 2; ref. 9). Unfortunately, the GTX regimen had never been properly evaluated in a randomized trial.

The Winning Formula

Neutropenia was a significant hurdle, in addition to infusion reaction, in the development of paclitaxel (49). Through pharmacokinetic modeling, the risk for paclitaxel-induced neutropenia was found to correlate with the time interval in which free paclitaxel concentration was more than the 0.05 μmol/L threshold (50). Then, a recent meta-analysis of various paclitaxel formulations using population pharmacokinetic modeling showed that, at equivalent doses, this time interval by the nab-formulation was much shorter and correlated with a lower neutropenic risk than the Cremaphor formulation (51). As such, the nab-formulation seemed to confer a more favorable pharmacologic characteristic that allowed the delivery of a higher yet equitoxic dose of paclitaxel than Cremaphor. Furthermore, preclinical studies showed that the nab-formulation may enhance intratumoral paclitaxel accumulation through gp60–mediated uptake of the albumin moiety; moreover, Cremaphor also inhibits paclitaxel uptake by endothelial vasculature (26).
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Secreted protein, acidic, and rich in cysteine (SPARC) was found to be epigenetically silenced in pancreatic cancer cells but preferentially expressed in adjacent stromal fibroblasts (55). Increased SPARC expression had been associated with poorer prognosis in patients with pancreatic cancer (56). The increased expression of the albumin-binding protein in patients with pancreatic cancer stimulated the interest of researchers to initiate the phase I/II trial to evaluate nab-paclitaxel in the disease (9). Of the 36 evaluable patients from the phase I/II trial, high stromal SPRAC level was associated with longer survival in patients treated with the combination. The role of SPARC as a predictive biomarker for benefit from nab-paclitaxel treatment will be clarified when the investigators complete the analysis of patient tumor specimens from the MPACT trial.

In summary, the success of nab-paclitaxel–gemcitabine was a result of multiple factors mechanistically. The favorable pharmacologic characteristics of the nab-formulation enabled the delivery of a higher paclitaxel dose, which not only increased the cell kill but also synergized the effects of gemcitabine by enhancing intratumoral accumulation through several mechanisms, including depletion of stromal matrix, increasing tumor microvasculature, and inhibiting the catabolism of gemcitabine metabolites.

Conclusions

A review of the experience with Cre-paclitaxel hinted at the drug's activity in pancreatic cancer except that the dose of paclitaxel that could be safely administered was limited by the toxicities associated with the formulation. Interestingly, the combination of Cre-paclitaxel and gemcitabine had never been systematically evaluated in treatment-naive advanced pancreatic cancer except for a phase I study of this combination with radiation (57). As discussed above,
nab-paclitaxel had several pharmacologic advantages over the Cre formulation that eventually translated into superior clinical efficacy when combined with gemcitabine in pancreatic cancer.

Several factors influence one’s recommendation on which regimen (nab-paclitaxel–gemcitabine or FOLFIRINOX) to initiate in a newly diagnosed metastatic patient including the impact on quality of life. Unlike the PRODIGE 4/ACCORD 11 trial (58), formal quality-of-life assessment was not part of the MPACT trial. However, the relative tolerability of nab-paclitaxel–gemcitabine can be inferred from the fact that patients treated with nab-paclitaxel–gemcitabine maintained comparable dose intensity as the gemcitabine-alone arm. In terms of drug cost, nab-paclitaxel–gemcitabine is approximately 8 to 10 times more expensive than FOLFIRINOX although such a contrast is unlikely to be a deciding factor in the United States in the near future (59).

In an era when billions of dollars are spent developing novel biologic and molecular-targeted drugs, the success of nab-paclitaxel is a timely reminder that innovations to improve the pharmacologic characteristics of old drugs are still important and relevant in anticancer drug development although they may not be as catchy at scientific conferences.

Disclosure of Potential Conflicts of Interest
W.W. Ma received commercial research support from Celgene. M. Hidalgo received honoraria for service on the speakers’ bureau and is a consultant/advisory board member for Celgene.

Authors’ Contributions
Conception and design: W.W. Ma, M. Hidalgo
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.W. Ma
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W.W. Ma
Writing, review, and/or revision of the manuscript: W.W. Ma, M. Hidalgo
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W.W. Ma

Acknowledgments
The authors thank Mei Ka Fong for assisting in researching the cost of treatments and Deborah Donaldson for proofreading the manuscript.

Received May 17, 2013; revised July 17, 2013; accepted July 19, 2013; published OnlineFirst August 5, 2013.
polyethylated castor oil-based paclitaxel in women with breast cancer.


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