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D. Kudlowitz

E. Teplinsky
Zucker School of Medicine at Hofstra/Northwell

F. Muggia

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Review Article

Integrating targeted drugs with taxanes and platinums: opportunities and challenges

David Kudlowitz, Eleonora Teplinsky, Franco Muggia

New York University Cancer Institute, New York, NY 10016, USA

Correspondence to: Franco Muggia, MD. New York University Cancer Institute, Laura and Isaac Perlmutter Cancer Center, 160 East 34th Street, Room 429, New York, NY 10016, USA. Email: Franco.Muggia@nyumc.org.

Abstract: In ovarian cancer, multiple attempts to adjust the standard taxane/platinum doublet by adding cytotoxic therapy or varying scheduling, dosage, and delivery have been met with limited success. Alternative methods to improve the grim prognosis of ovarian cancer, including molecular therapies, are currently under investigation. Efforts have been made to study tyrosine kinase inhibitors (including imatinib and pazopanib), Src kinase inhibitors and histone deacetylase inhibitors (HDACi) in combination with taxanes/platinums in order to improve efficacy. Unfortunately, while many pre-clinical and early phase clinical trials argue that the utilization of these molecular targets may enhance survival, only modest benefit has been seen in larger clinical trials. Other agents that have been evaluated include proteasome inhibitors, folate receptor antagonists, MEK inhibitors and opiate antagonists. In this review, we discuss the mechanisms of these targeted therapies and highlight the current and ongoing clinical trials that utilize these targeted agents in combination with taxanes and platinums in advanced ovarian cancer.

Keywords: Targeted therapies; ovarian cancer; histone deacetylase inhibitors (HDACi); Src kinase inhibitors; tyrosine kinase inhibitors; platinums; taxanes

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Introduction

Ovarian cancer is the fifth leading cause of cancer death in women in the United States with a 5-year survival of only 30% in patients with advanced stage disease (1,2). For more than a decade, the standard treatment for advanced ovarian cancer has been optimal surgical debulking followed by a paclitaxel/platinum regimen. Attempts to improve on outcomes by adding cytotoxic therapies have only resulted in increased toxicity without significant benefit (3-7). Other pursuits such as intraperitoneal (IP) drug delivery, optimization of the platinum/taxane schedule, and consolidation with anti-angiogenic drugs, such as bevacizumab, or with poly-ADP-ribose polymerase (PARP) inhibitors, have been met with limited success and often increased toxicity (8-13). Given ovarian cancer's lethality, yet elusiveness to current treatments, the need for expanded, targeted therapies for this disease is crucial. This review will focus on various emerging molecular targets and therapeutic options that are being explored in combination with taxanes and platinums, including selective and multi-targeted tyrosine kinase inhibitors, Src kinase inhibitors, and histone deacetylase inhibitors (HDACi).

Tyrosine kinase inhibitors

With imatinib revolutionizing the treatment of chronic myelogenous leukemia (CML) in the late 1990s, interest and research dedicated to investigate its utility in solid tumors ensued (14). Imatinib is a tyrosine kinase inhibitor, which is specific for the ABL domain, c-KIT, and the platelet-derived growth factor receptor (PDGFR). Its mechanism of action prompted exploring its role in ovarian cancer (15). Of note, platelet derived growth factor (PDGF) and PDGFR-alpha (α)

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have poor prognostic value in ovarian cancer and PDGFR is active in tumor-associated endothelial cells and presumably contributes to tumor angiogenesis (16,17). This pre-clinical data led to several clinical trials of imatinib in ovarian cancer. Schilder *et al.* performed a phase II trial evaluating single agent imatinib in patients with recurrent or persistent epithelial ovarian or primary peritoneal carcinoma. Fifty-six patients received imatinib 400 mg twice daily. Imatinib had minimal activity and the median progression free survival (PFS) and overall survival (OS) were 2 and 16 months, respectively. Nine patients were progression free for at least 6 months, including one patient who had a complete response (CR). Imatinib was well tolerated; the most common grade 3 and 4 toxicities were neutropenia, gastrointestinal, dermatologic effects, pain and electrolyte disturbances. Biomarker analysis failed to identify any predictive markers of imatinib activity (18). In another phase II trial of single agent imatinib in 13 patients with recurrent, platinum-resistant low-grade serous carcinoma of the ovary, peritoneum, or fallopian tube, there were no CRs or partial responses (PRs) seen. In contrast to the previous trial, patients received imatinib 600 mg daily. The median PFS and OS were 1.3 and 4.9 months, respectively. Imatinib was well tolerated but again had no activity as a single agent in this population (19). Alberts *et al.* conducted a phase II trial of imatinib 400 mg daily in recurrent ovarian cancer in patients with biomarker positive c-Kit (11%) and PDGFR (89%). Of the 19 eligible patients, there were no objective responses. The median OS was 10 months and notably, 32% of patients came off study within the first month due to adverse events. Eleven percent of patients had grade 4 hematologic and 37% had grade 3 non-hematologic toxicity. Not only did this trial show a lack of activity in patients with imatinib specific mutations, but it also differed from the previous two in that there were significant adverse events (20).

While imatinib has limited activity as a single agent, a synergy between imatinib and paclitaxel has been hypothesized. Circulating endothelial progenitors (CEP) are mobilized after paclitaxel administration. CEPs assist tumor cell proliferation and angiogenesis, counteracting the effects of paclitaxel. However, imatinib dampens the CEP response by inhibiting PDGFR and subsequently, prevents additional tumor growth (16,21). Safra *et al.* evaluated intermittent imatinib in combination with paclitaxel in 14 patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Imatinib 300 mg twice daily was given for 4 consecutive days each week in combination with weekly paclitaxel at a dose of 80 mg/m^2 for a median of 5.7 cycles (range <1 to 12.3). Of 12 evaluable patients, nine were progression free at 12 weeks, and four had a PR [two by Response Evaluation Criteria in Solid Tumors (RECIST) and two by CA-125]. A PFS of longer than 6 months was seen in five patients and PFS of more than 12 months in two patients. Toxicities included grade 3 diarrhea (resolving after imatinib dose reduction), and two patients with grade 3 neutropenia or neutropenia/thrombocytopenia (resolving after paclitaxel dose reduction). Although it was a small trial, the combination was tolerable and demonstrated anti-tumor activity (22).

Docetaxel has also been studied in combination with imatinib. In a phase II study conducted by Matei *et al.*, 23 patients with advanced, platinum-resistant or refractory epithelial ovarian cancer and a median of 3 prior treatments received imatinib 600 mg daily with docetaxel 30 mg/m^2 weekly (weeks 1-4 of every 6-week cycle). The objective response rate (ORR) was 21.7%. Responses included one CR, three PRs, and three patients with stable disease (SD) at 4 months. Most adverse effects (AEs) were grade 1 or 2 and included fatigue, nausea, diarrhea, anorexia, and edema (23). Non-taxane agents are also being combined with imatinib. A trial of imatinib and gemcitabine has been completed and results are awaited (24).

Pazopanib is a multikinase inhibitor, which has multiple targets including PDGFR and vascular endothelial growth factor receptor (VEGFR). It has been studied in both recurrent ovarian cancer and as maintenance therapy. Friedlander *et al.* conducted a phase II trial of pazopanib monotherapy in 36 patients with low-volume recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. All had received initial platinum-based chemotherapy with a complete CA-125 response. Upon elevation of CA-125 to >2× the upper limit of normal, patients were treated with pazopanib 800 mg daily until progression of disease or unacceptable toxicity. ORR was 18% (95% CI, 4-43%) in patients with measurable disease at baseline. Thirty-one percent of patients had a CA-125 response and PFS at 6 months was 17%. Twenty-eight percent of patients experienced toxicity requiring pazopanib discontinuation. Only one grade 4 AE was seen (peripheral edema), but there were multiple grade 3 toxicities (56%), which included fatigue, diarrhea, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation, and γ-glutamyl transpeptidase (GGT) elevation (25).

More recently, the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) studied pazopanib as maintenance therapy for 2 years *vs.* placebo in 940 patients with stage II-IV ovarian, fallopian tube, or primary peritoneal carcinoma

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after initial debulking and at least five cycles of platinum-taxane chemotherapy. Patients had no evidence of disease progression after primary therapy and were randomized 1:1 to receive pazopanib 800 mg daily or placebo for up to 24 months. The primary endpoint was PFS. Maintenance pazopanib resulted in a significant improvement in PFS when compared to placebo (17.9 *vs.* 12.3 months; HR 0.77; 95% CI, 0.64-0.91; P=0.0021). There were significantly more AEs leading to treatment discontinuation in the pazopanib arm (33.3%) when compared to the placebo arm (5.6%). Grade 3/4 toxicities included hypertension, neutropenia, liver related toxicity, diarrhea, fatigue, thrombocytopenia, and palmar-plantar erthrodysesthesia. Unfortunately, there was no survival benefit between pazopanib and placebo (HR 1.08; 95% CI, 0.97-1.33; P=0.499) (26). Additional studies of pazopanib with topotecan, doxorubicin, cyclophosphomide, or paclitaxel in refractory or recurrent ovarian cancer are ongoing (27-30). Given the trials described above, future studies of pazopanib will certainly need to balance efficacy with toxicity.

Src kinase inhibitors

Src kinase is a non-receptor tyrosine kinase that is overexpressed and activated in late stage ovarian cancer (31). Src activation supports vascular endothelial growth factor A (VEGF-A) expression and inhibits transforming growth factor beta 1 (TGFβ1), a protein that modulates cancer-associated fibroblasts in the ovarian cancer microenvironment (32-34). In ovarian cancer models, the activation of Src prevents microtubule assembly and stabilization, leading to taxane resistance (35,36). In these models, inhibiting Src can reverse the taxane resistance (37). The mechanism of the resensitization to taxanes is unclear; however, it may be that Src inhibition decreases the concentration of intracellular paclitaxel required to disrupt microtubule dynamics (38).

Saracatinib (AZD0530), an oral inhibitor of Src kinase, was shown *in vitro* to reduce Src phosphorylation and prevent cell migration (39). In a phase I study done in 116 patients with multiple solid tumors, including 16% with ovarian cancer, patients were treated with saracatinib (once daily oral dosing from 125-300 mg) in combination with carboplatin and/or paclitaxel. Objective responses were seen in 5/44 of patients receiving saracatinib (125-300 mg), carboplatin, and paclitaxel every 3 weeks; two of those were in ovarian cancer patients. In those getting saracatinib and paclitaxel weekly, objective responses were seen in 5/24 patients (one was ovarian) (40). This then led to a phase II/III study where 107 patients with platinum resistant ovarian, fallopian, and primary peritoneal cancer were randomized to receive weekly paclitaxel 80 mg/m^2 with or without saracatinib 175 mg daily. There was no difference in PFS (4.7 *vs.* 5.3 months; HR 1.00; 95% CI, 0.65-1.54; P=0.99) or OS (10.1 *vs.* 12.3 months; HR 1.01; 95% CI, 0.56-1.58; P=0.81). Grade 3 and 4 toxicities attributed to saracatinib were abdominal pain and febrile neutropenia (41). Another phase II study of saracatinib, carboplatin and paclitaxel in advanced ovarian cancer has been completed and results are awaited (42).

Despite the lack of efficacy thus far with saracatinib in ovarian cancer, other Src kinase inhibitors, such as dasatinib, have been evaluated. In a phase I dose escalation study of 20 patients, dasatinib at doses of 100, 120, or 150 mg daily, was combined with paclitaxel 175 mg/m^2 and carboplatin area under the curve (AUC) 6 every 3 weeks. The recommended phase II dose (RP2D) of dasatinib was determined to be 150 mg. The median PFS and OS were 7.8 months and 16.2 months, respectively (43). Dasatinib will be in investigated in a phase II trial, GOG028, which was activated in February 2014 (44). Given the expression of Src in clear cell carcinoma (CCC), this clinical trial projects to enroll ovarian CCC patients recurred after initial platinum/taxane treatment. The patients will receive dasatinib 160 mg daily. Patients must be Wilms tumor 1 (WT1) and estrogen receptor (ER) negative by immunohistochemistry (IHC). The negative WT1 and ER expression are used to differentiate clear cell from epithelial ovarian tumors. *ARID1A* mutation status will be assessed in enrolled patients (44). *ARID1A* is the most frequently mutated gene in ovarian CCC, found in 46-75% of CCC. Loss of this gene's function is associated with a shorter PFS, worse OS, and greater chemotherapy resistance (45). The *ARID1A* gene codes for the BAF250a protein. This protein is part of a chromatin modeling family that binds to DNA and has roles in DNA repair (46,47). The expectation is that those patients that have the *ARID1A* mutation will be hypersensitive to dasatinib. *ARID1A* mutation status will be assessed using next-generation and exon-capture sequencing and will be tabulated to determine the correlation between BAF250a IHC and *ARID1A* mutations. This will help to identify whether IHC is predictive for better responses to the inhibitor.

Histone deacetylase inhibitors (HDACi)

Histones are proteins composed of positively charged

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amino acids. They are bound to negatively charged DNA and are regulators of gene expression. Modification of the histone proteins controls gene transcription, replication, and DNA repair. Methylation of histones turns off gene transcription, while histone acetylation, which occurs mostly on lysine residues, is associated with a morphology that facilitates transcription (48). HDACi, enzymes that remove an acetyl group from the histone protein and prevent gene transcription, have been shown to induce apoptosis, promote cell differentiation, and inhibit cancer cell growth (49). HDACi reduce the expression of homologous recombination genes, such as *BRCA 1* and *2* (50). Additionally, in ovarian cancer cells, the overexpression of HDAC is associated with cisplatin resistance (51). *In vitro*, HDACi have reversed cisplatin resistance and induced apoptosis (52,53). The inhibitors result in a depletion of HDAC, which leads to a decreased expression of chromatin maintenance proteins. Without these structural anchors, the chromatin's morphology transforms into a more receptive conformation, allowing for chemo-sensitization (54).

Currently available HDACi are vorinostat, belinostat, and romidepsin. HDACi as single agents for recurrent or persistent ovarian cancer have shown minimal efficacy. In a phase II study of 27 women with recurrent or persistent ovarian or primary peritoneal carcinoma, patients received vorinostat 400 mg daily and continued until disease progression or unacceptable toxicity. Of the 24/27 patients eligible for evaluation, only 1 had a PR, 9 had SD and 14 progressed within 2 months. Toxicity was minimal with 10 patients getting ≥3 cycles of treatment and only two grade 4 AEs (neutropenia and leukopenia) (55). In a phase II combination study vorinostat was used with paclitaxel and carboplatin as primary induction therapy in 18 patients with advanced stage ovarian cancer after cytoreductive surgery. Patients received a median of six cycles; there were two PRs and seven CRs. Unfortunately, there were significant AEs, resulting in early termination of the study. Three patients had either gastrointestinal perforation or fistula formation (notably, these patients all had bowel reanastomosis as part of their initial cytoreductive surgery). There were also significant hematologic toxicities (56).

In contrast, a combination study of belinostat, carboplatin, and paclitaxel in a phase I/II study had more promising results. Belinostat was given at 1,000 mg/m^2 daily for 4 days with carboplatin AUC 5 and paclitaxel 175 mg/m^2 on days 3 and 21. Of the 35 heavily pre-treated patients, 15 patients had a PR and 3 had a CR. The ORR was 43% among platinum resistant patients and 63% among platinum sensitive patients. There were no non-hematologic grade 4 toxicities but several episodes of grade 4 neutropenia (57). The difference in ORR between the platinum sensitive and resistant groups suggests that further studies need to separate these subtypes. However, a phase II study of belinostat with carboplatin (without paclitaxel) was terminated early for lack of activity (58). It is unclear if this finding of increased toxicity with vorinostat compared to belinostat was due to increased total dose, differing stages of therapy, a specific drug effect, or small sample sizes. Although current results with HDACi added to chemotherapy in ovarian cancer have yielded contradictory data, further investigations of these agents to reverse platinum resistance are not generating enthusiasm because of tolerance issues in platinum pretreated patients.

Other agents to reverse platinum and taxane resistance

Buthionine sulfoximine, an inhibitor of glutathione synthetase, was studied as a potential agent to reverse platinum resistance by down regulating intracellular thiols. However, in spite of strong *in vitro* data, the complexity of mechanisms associated with platinum resistance, interest in the development of buthionine sulfoximine and other intracellular thiol manipulations have not been pursued beyond phase I (59-61).

Another potential agent for reversal of platinum resistance has been bortezomib, presumably by interfering with ubiquination of copper transporter (CTR) 1, the CTR, which is also responsible for the influx of cisplatin and carboplatin (62). A phase I by Aghajanian *et al.* suggested activity of the combination of carboplatin and IV bortezomib. Here, the ORR was 47% with two CR and five PR. The recommended phase II dose of bortezomib was 1.3 mg/m^2 (63). More recently, in a phase I GOG study by Jandial *et al.*, responses were seen in platinum resistant patients receiving IP bortezomib and increasing doses of IP carboplatin. When IP bortezomib was given before IP cisplatin, platinum accumulation was increased in peritoneal tumors by 33% (P=0.006) (64). Cyclosporine has also been used for this purpose, although the mechanism of potentiation with platinum compounds is unclear (65,66). Finally, other DNA damaging chemotherapies, such as topoisomerase I or II inhibitors, may prove to be synergistic with cisplatin or carboplatin in a schedule dependent manner, as seen in preclinical studies and in the phase I study of the combination of topotecan and cisplatin (67). Unfortunately,

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the phase III GOG study 182 used the less toxic but also less effective schedule of topotecan on days 1-3 and carboplatin on day 3. There was no difference in PFS or OS when compared to the standard taxane-platinum doublet (3). By contrast, an IP schedule in a phase I study of IP cisplatin 50 mg on day 1 and escalating doses of topotecan on days 1-5 resulted in a PFS of 13 months for patients who had minimal or no disease at the end of induction. Five patients were alive at 4 years. Even given this considerable activity, these results have not been studied further (68).

With respect to paclitaxel resistance, the focus has been on inhibiting P-glycoprotein. P-glycoprotein is an efflux membrane pump that brings intracellular drugs, including chemotherapies such as paclitaxel, out of the cell. This process reduces the drug's intracellular concentration, and therefore its effect and toxicity (69). In a phase III study employing the inhibitor, valspodar (PSC-833) *vs.* placebo in first-line treatment of ovarian cancer, no advantage was seen (70).

Targeting the folate receptor

The folate receptor-α (FRA) is present on ovarian cancer but not in benign ovarian tissues (71,72). The function of this receptor is unknown as folate transport is mediated primarily by the highly-affinity reduced folate carrier (RFC). However, FRA may be a reasonable target for delivery of anticancer drugs via receptor-mediated endocytosis. The humanized monoclonal antibody, farletuzumab (MORAb-003), has been developed as a potential anticancer drug. In a phase I trial of single agent farletuzumab arm in 25 patients with platinum-refractory or platinum-resistant epithelial ovarian cancer, farletuzumab was generally safe and well-tolerated. Thirty-six percent of patients had SD but there were no objective responses (73). In a phase II study, farletuzumab was studied as a single agent or in combination with carboplatin and a taxanes in 54 patients with first-relapse, platinum-sensitive ovarian, fallopian tube, and primary peritoneal cancers. Patients with asymptomatic CA-125 relapse received single agent farletuzumab and could receive chemotherapy + farletuzumab upon single agent progression (n=28). Twenty-six subjects who had symptomatic relapse entered on the combination arm. Farletuzumab was well-tolerated as a single agent and there was no additional toxicity when it was combined with chemotherapy. Of 47 patients who ultimately received farletuzumab with chemotherapy, 80.9% normalized CA-125 levels. The complete or partial ORR was 75% with combination therapy (74). The results of this phase II trial were promising, leading to evaluation in phase III. However, a phase III study in platinum-resistant ovarian cancer was terminated at interim analysis because it did not meet pre-specified criteria for continuation after futility analysis (75). A similar phase III study in platinum-sensitive ovarian cancer was halted given failure to meet pre-specified criteria for significant PFS, the study's primary end point (76,77).

Vintafolide (EC145) is a folate antibody vinca alkaloid drug conjugate. In a phase II study, 149 patients with platinum-resistant ovarian cancer were randomized to pegylated liposomal doxorubicin (PLD) 50 mg/m^2 every 4 weeks with or without vintafolide at a dose of 2.5 mg intravenously three times weekly during weeks 1 and 3 on a 4-week cycle. The PFS was 5.0 months in the combination therapy arm as compared to 2.7 months in the PLD group (P=0.031). However, when patients' tumors were selected for folate receptors with EC20 imaging [a (99m)Tc-based folate peptide chelator that binds to folate receptor positive cells and tissues, making it useful for radiodiagnostics], PFS was non-significantly improved in the folate receptor positive group (median PFS 7.0 months; HR 0.873; 95% CI, 0.334-2.277; P=0.79) compared to the non-folate receptor positive group (median PFS 5.4 months; HR 1.806; 95% CI, 0.369-8.833; P=0.468). There was no significant difference in AEs (78). A randomized phase III study of PLD ± vintafolide has completed recruiting and results are pending (79).

MEK inhibitors

The mitogen activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway is a signal transduction pathway that regulates cellular growth and survival. In normal cells, an extracellular ligand is required to activate this pathway. After initiation, the signal is potentiated intracellularly via several activating kinases, communicating with various transcriptional factors to promote cell growth. However, in malignant cells, mutations in this pathway lead to constitutive activation and uninhibited growth. Multiple targets exist within the pathway, including MEK [also known as mitogen-activated protein kinase kinase (MAPKK)], which is a tyrosine/threonine kinase. While MEK inhibitors, such as trametinib, have seen success in BRAF mutated melanoma, their utility in other tumors is yet to be proven (80). A phase II study of single-agent selumetinib, a MEK inhibitor, in low-grade serous ovarian cancer was performed in 52 patients. ORR was 15% and an additional 34 patients (65%) had SD (81). These results demonstrate that MEK inhibition may have some effect in ovarian cancer. Combination with

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chemotherapy may improve the efficacy of these targeted agents. However, there is only one pending combination study of a MEK inhibitor (MEK162) and paclitaxel that is currently enrolling (82). A trial comparing MEK162 to chemotherapy of the physicians' choice in low grade serous ovarian cancer is also currently recruiting (83).

Methylnaltrexone

Opiate antagonists, specifically methylnaltrexone, have been shown to inhibit VEGF-induced angiogenesis (84). In fact, a synergistic effect between methylnaltrexone, a mu-opioid receptor antagonist, 5-fluorouracil (5-FU), and bevacizumab has been shown in preclinical models. This synergy is likely induced by the varied targets of these drugs. While bevacizumab inhibits VEGF binding to receptors, 5-FU inhibits Akt activation of VEGF, and methylnaltrexone simulates receptor protein tyrosine phosphatase mu (RPTPμ) activity that prevents VEGF induced Src activation (85). A phase I trial of dasatinib, bevacizumab, paclitaxel ± methylnaltrexone in advanced cancer is ongoing (86). It will ultimately be interesting to compare methylnaltrexone's capacity to inhibit tumor growth.

Conclusions

Given the grim prognosis in ovarian cancer, much effort has been dedicated to identify targeted therapies that may improve outcomes in combination with the standard chemotherapy 'backbone' of platinum and taxane agents. In this review, we discuss the conducted and ongoing studies of tyrosine kinase inhibitors, Src kinase inhibitors and HDACi. We also briefly discuss other targets including bortezomib, the folate receptor, MEK inhibitors, and methylnatrexone. Clinical trials of these agents have yielded mixed results ranging from differing efficacy data and issues with drug tolerance Future clinical trials and studies on drug and pathway resistance will pave the way to our understanding and use of these agents in ovarian cancer.

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