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ORIGINAL ARTICLE – PANCREATIC TUMORS

Neoadjuvant Chemotherapy with Gemcitabine Plus Nab-Paclitaxel for Borderline Resectable Pancreatic Cancer Potentially Improves Survival and Facilitates Surgery

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ABSTRACT

Background. Accumulation of evidence suggests that neoadjuvant chemotherapy improves the outcomes of borderline resectable pancreatic cancer (BRPC). Gemcitabine plus nab-paclitaxel (GnP) has been widely accepted as systemic chemotherapy for unresectable pancreatic cancer and reportedly results in remarkable tumor shrinkage. This study was performed to evaluate the safety and efficacy of neoadjuvant chemotherapy using neoadjuvant GnP for BRPC.

Methods. The medical records of 57 patients who underwent treatment of BRPC from 2010 to 2017 were retrospectively reviewed. The patient characteristics and short- and intermediate-term outcomes were compared between the GnP and upfront surgery (UFS) groups.

Results. The GnP group comprised 31 patients and the UFS group comprised 26 patients. The patient characteristics were comparable with the exception of a higher prevalence of arterial involvement in the GnP group. Twenty-seven of the 31 patients (87%) in the GnP group and all 26 patients in the UFS group underwent resection. The GnP group showed a significantly shorter operation time (429 vs. 509.5 min, $p = 0.0068$), less blood loss (760 vs. 1324 ml, $p = 0.0115$), and a higher R0 resection rate (100% vs. 77%, $p = 0.0100$) than the UFS group. Postoperative complications and hospital stay were comparable between the two groups, and no treatment-related mortality occurred in either group. Both the disease-free survival and overall survival times were significantly longer in the GnP group ($p = 0.0018$ and $p = 0.0024$, respectively).

Conclusions. Neoadjuvant GnP is a safe and effective treatment strategy for BRPC. It potentially improves patients' prognosis and facilitates surgical procedures.

Pancreatic cancer is the most aggressive and lethal malignancy of the digestive organs, and the 5-year overall survival (OS) rate of patients is only 8%.[1] Although surgical resection is the only curative treatment, approximately 80% of patients with pancreatic cancer have unresectable disease at diagnosis.[2] In addition, even if surgical resection is completed, local or metastatic recurrence occurs in most patients and results in a poor prognosis.

Borderline resectable pancreatic cancer (BRPC) has a high risk of surgical margin positivity when surgery is performed as initial treatment.[3,4] In fact, 34–40% of pancreatectomies for BRPC reportedly result in margin-positive resection.[5,6] Conversely, several studies have suggested that neoadjuvant therapy increases the R0 resection rate and improves the prognosis after treatment for BRPC compared with upfront surgery (UFS).[7,8]

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Gemcitabine plus nab-paclitaxel (GnP) therapy was initially reported to improve survival of patients with metastatic pancreatic cancer compared with gemcitabine alone.[9] A phase II study of GnP for metastatic pancreatic cancer conducted by Japanese investigators showed rapid and remarkable primary tumor shrinkage (response rate 58.5%), indicating that GnP therapy might be effective in the neoadjuvant setting for BRPC.[10] Since 2015, we have used GnP as neoadjuvant therapy for BRPC for the purpose of ensuring a negative resection margin and improving treatment outcomes. To evaluate the safety and efficacy of the GnP regimen as neoadjuvant chemotherapy for BRPC, we analyzed our initial experiences of patients with BRPC who were treated with neoadjuvant GnP, and compared their perioperative and intermediate-term outcomes with those who were treated with UFS.

METHODS

Study Design

This study was approved by the Institutional Review Board of Kyushu University Hospital. The medical records of patients who were diagnosed with pancreatic cancer and treated at the Department of Surgery and Oncology, Kyushu University Hospital, from January 2010 to December 2017 were retrospectively reviewed, and, among these patients, those with BRPC were selected for inclusion in our study. A diagnosis of BRPC was based on the findings of contrast-enhanced multidetector-row computed tomography, according to the definition of the resectability status in the National Comprehensive Cancer Network guideline version 2, 2017.[11] BRPC was subclassified into two types: BR-A, defined as BRPC contacting either the common hepatic artery (CHA), celiac axis (CA), or superior mesenteric artery (SMA; $\leq 180°$) regardless of venous involvement; and BR-V, defined as BRPC contacting or invading either the portal vein/superior mesenteric vein (PV/SMV; $> 180°$) or inferior vena cava without arterial involvement. A diagnosis of BRPC was made prospectively before treatment, and re-evaluation was performed by two surgeons (YM and RK) and one radiologist (DK). The collected data included age, sex, date of diagnosis, tumor location, tumor size, serum carbohydrate antigen 19-9 (CA19-9) level, biliary drainage, preoperative treatment, date of surgery, surgical procedures, combined arterial resection, PV/SMV resection, operation time, blood loss, postoperative complications, length of postoperative hospital stay, pathological outcomes (resection margin status, TNM status according to the 7th edition of the Union for International Cancer Control classification[12]), adjuvant therapy, recurrence, survival, and date of last follow-up. Postoperative complications of Clavien–Dindo classification grade IIIa or higher were included in this study. Among the patients with BRPC, those who underwent neoadjuvant GnP were categorized as the GnP group, and those who had undergone UFS were categorized as the UFS group. Patient characteristics and the short- and intermediate-term outcomes of the GnP group were analyzed and compared with those of the UFS group.

Neoadjuvant Chemotherapy with Gemcitabine Plus Nab-Paclitaxel (GnP)

The regimen was adopted from the protocol of a phase II trial for metastatic pancreatic cancer in Japan.[10] Patients received an intravenous infusion of nab-paclitaxel at a dose of 125 mg/m^2 followed by intravenous infusion of gemcitabine at a dose of 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks. If grade III or higher adverse events were recognized, the dose was reduced or the schedule was modified (days 1 and 8 every 3 weeks or biweekly) according to the physician's decision. Patients were re-evaluated using multidetector-row computed tomography every two or three courses. If no distant metastasis was present and the multidisciplinary conference judged that margin-negative resection was possible, then pancreatic resection was scheduled.

Surgical Procedures

Pancreatic resection with lymphadenectomy was performed with curative intent. Pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy were selected according to the tumor extension. SMV/PV resection was performed if tumor invasion was recognized or suspected during the operation. If the tumor contacted the CA or CHA and detachment was impossible, then combined resection of these arteries was carried out. In principle, combined resection of the SMA was not performed.

Adjuvant Chemotherapy

S-1 or gemcitabine was administered postoperatively unless the patient was in a poor condition or had a contraindication. The duration of adjuvant chemotherapy was usually 6 months.

Statistical Analyses

All statistical analyses were performed using JMP statistical software version 12.0 (SAS Institute, Cary, NC, USA). Continuous variables were compared using

Student's t test or the Mann–Whitney U test, and categorical variables were compared using the Chi square test or Fisher's exact test. Disease-free survival (DFS) was defined as the duration between the date of the operation and the date of recurrence, while OS was defined as the duration between the date of the initial diagnosis of cancer and the date of death or last follow-up, whichever came first. The Kaplan–Meier method was used to estimate survival, and the log-rank test was used for comparison. A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Sixty-nine patients with BRPC were treated during the study period, and 427 patients underwent pancreatic resection for pancreatic cancer during the same period. Figure 1 shows a flow diagram of the patients' treatment course. Thirty-one patients initially received the GnP regimen (GnP group) and 26 patients underwent UFS (UFS group). The remaining 12 patients who received other regimens (gemcitabine alone, S-1 alone, gemcitabine plus S-1, or FOLFOLINOX) were excluded from this study. Age, sex, tumor location, tumor size, biliary drainage, and the initial CA19-9 level were comparable between the GnP and UFS groups; however, arterial involvement (BR-A) was more frequent in the GnP group (27 [87%] in the GnP group vs. 6 [23%] in the UFS group; $p < 0.0001$) (Table 1).

Outcomes of Neoadjuvant Chemotherapy Using GnP

The median number of cycles of neoadjuvant GnP in the 31 patients was 3 (range 1–10), and the median percentage change in the size of the tumors from baseline was −23.3% (range − 51.4 to 28.0%) (Fig. 2). Of the 31 patients, 27 (87%) achieved surgical resection. Details of the four patients who did not undergo resection are as follows. One patient had cholangitis and a liver abscess during the first cycle and selected best supportive care; another two patients developed gastric outlet obstruction after the first cycle and were treated at affiliate hospitals, where the patients also selected best supportive care; and the remaining patient was found to have unresectable cancer at laparotomy because of multiple liver metastases, and subsequently underwent a bypass operation.

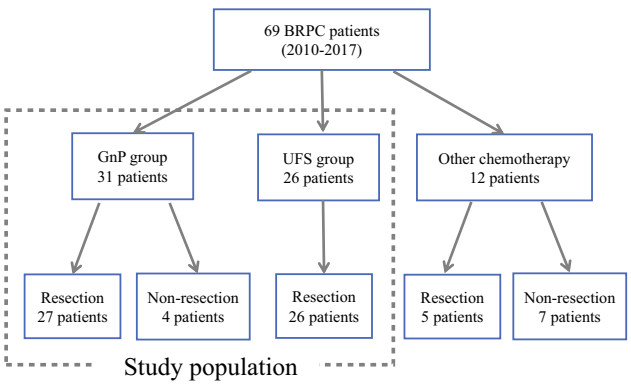

FIG. 1 Treatment courses of patients with BRPC treated in the Department of Surgery and Oncology, Kyushu University Hospital, from 2010 to 2017. *BRPC* borderline resectable pancreatic cancer, *GnP* gemcitabine plus nab-paclitaxel, *UFS* upfront surgery

Comparison of Surgical and Pathological Outcomes

The perioperative outcomes of the GnP and UFS groups are shown in Table 2. One patient in the GnP group who had a history of distal gastrectomy for gastric cancer with sacrifice of the left gastric artery underwent middle pancreatectomy to preserve the remnant stomach. SMV/PV resection and reconstruction was performed in 16 patients in both the GnP and UFS groups. Pancreatoduodenectomy with CHA resection and reconstruction was performed in two patients in the GnP group, while pancreatoduodenectomy with CHA resection and reconstruction was performed in three patients, and distal pancreatectomy with CA resection was performed in two patients, in the USF group. The operation time was significantly shorter and blood loss was significantly less in the GnP group than in the UFS group, and, as a result, significantly fewer patients in the GnP group required blood transfusion. Postoperative complications and postoperative hospital stay were comparable between the two groups. No postoperative mortality occurred in either group. All 27 patients who underwent resection in the GnP group achieved R0 resection, whereas 6 of the 26 patients in the UFS group underwent margin-positive resection. The R0 resection rate was significantly higher in the GnP group than in the UFS group (100% vs. 77%, $p = 0.0100$). Furthermore, lymph node metastases tended to be less frequent in the GnP group than in the UFS group ($p = 0.0581$). Adjuvant chemotherapy was performed for 26 (96%) patients in the GnP group (S-1 for all 26 patients) and 21 (81%) patients in the UFS group (S-1 for 9 patients and gemcitabine for 12 patients).

Comparison of Intermediate-Term Outcomes

The observation period from the time of diagnosis and from the time of resection were comparable between the two groups (Tables 1 and 2). Among the patients who underwent resection, recurrence was observed in 9 patients (33%) in the GnP group and 20 patients (77%) in the UFS

TABLE 1 Patient characteristics

	GnP group (n = 31)	UFS group (n = 26)	p value
Age, years [median (range)]	68 (44–80)	68.5 (43–80)	0.8916
Sex (male/female)	19/12	10/16	0.1135
Type (BR-A/BR-V)	27/4	6/20	< 0.0001
Location (head/body-tail)	23/8	24/2	0.0917
Tumor size, cm [median (range)]	3.0 (1.4–4.0)	3.0 (1.5–4.5)	0.6066
Biliary drainage	16 (52%)	17 (65%)	0.4197
CA19-9 level, U/mL [median (range)]	131 (0.8–2487)	150 (0.6–5154)	0.9872
Observation periods, days[a] [median (range)]	438 (109–1028)	367 (58–2104)	0.2977

GnP gemcitabine plus nab-paclitaxel, *UFS* upfront surgery, *BR-A* borderline resectable pancreatic cancer contacting either the common hepatic artery, celiac axis, or superior mesenteric artery (≤ 180°) regardless of venous involvement, *BR-V* borderline resectable pancreatic cancer contacting or invading either the portal vein/superior mesenteric vein (> 180°) or inferior vena cava without arterial involvement, *CA19-9* carbohydrate antigen 19-9

[a]From the date of the initial diagnosis

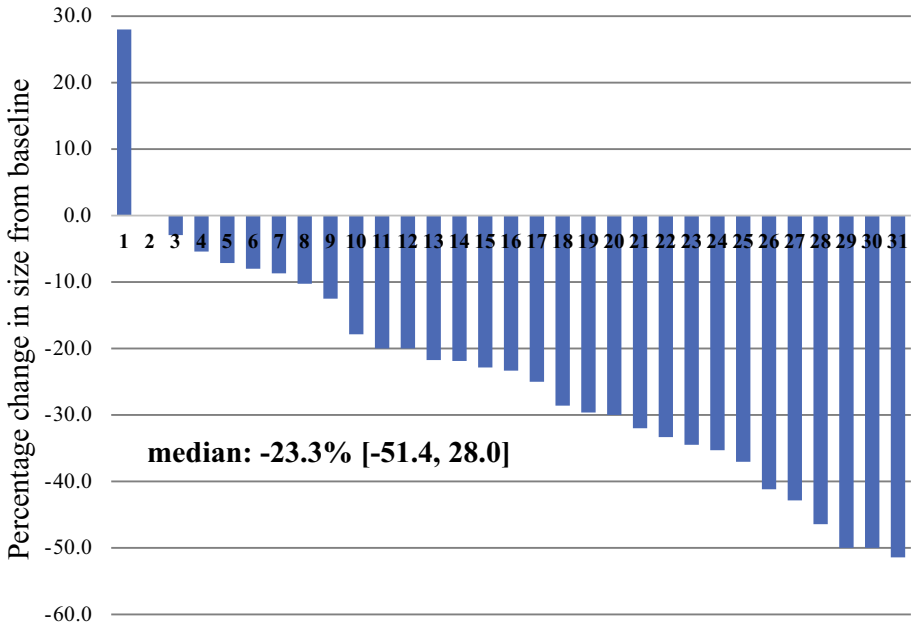

FIG. 2 Percentile changes in the size of tumors from baseline in 31 patients

group. The DFS time was significantly longer in the GnP group (median 633 days; 2-year DFS rate 35.6%) than in the UFS group (median 170 days; 2-year DFS rate 16.4%; p = 0.0018) (Fig. 3a). The intention-to-treat analysis showed that the OS time was also significantly longer in the GnP group (median 838 days; 2-year OS rate 73.0%) than in the UFS group (median 373 days; 2-year OS rate 25.0%; p = 0.0024) (Fig. 3b).

DISCUSSION

Accumulation of evidence suggests that neoadjuvant therapy improves the resectability and prognosis of BRPC;[13,14] however, no specific neoadjuvant therapy regimen is recommended for BRPC. This comparative study of patients who underwent neoadjuvant GnP or UFS for BRPC revealed several important findings: (1) neoadjuvant GnP demonstrated excellent disease control; (2) the GnP group showed a significantly shorter operative time, less blood loss, and a higher R0 resection rate than the UFS group; and (3) GnP was associated with significantly lower recurrence and a longer survival time than UFS.

Several studies have demonstrated a significant disease control effect of the GnP regimen. The disease control rate in a phase I/II study of the GnP regimen in Japan was 94.1% (32/34).[10] Muranaka et al.[15] reported that GnP showed a higher disease control rate than FOLFIRINOX in the first-line treatment of unresectable pancreatic cancer, although the difference was not statistically significant (86.4% vs. 56.3%, p = 0.062). In the present study, 94%

TABLE 2 Surgical and pathological outcomes

	GnP group (n = 27)	UFS group (n = 26)	p value
Procedure [PD/DP/TP/MP]	20/3/3/1	23/3/0/0	0.1252
Arterial resection	2 (7%)	5 (19%)	0.2501
SMV/PV resection	16 (59%)	16 (62%)	> 0.9999
Operation time, min [median (range)]	429 (173–639)	509.5 (283–900)	0.0068
Blood loss, mL [median (range)]	760 (110–3988)	1324 (285–7160)	0.0115
Blood transfusion	1 (4%)	13 (50%)	0.0001
Postoperative complication [≥ C–D grade IIIa]	3 (11%)	4 (15%)	0.7040
Postoperative hospital stay, days [median (range)]	20 (13–94)	22.5 (10–68)	0.9008
Margin status [R0/R1]	27/0	20/6	0.0100
Lymph node metastasis [pN1]	18 (67%)	23 (88%)	0.0581
Stage [IA/IB/IIA/IIB/III/IV]	1/0/7/18/1/0	0/0/3/22/1	0.3944
Adjuvant therapy	26 (96%)	21 (81%)	0.1003
Postoperative observation period, days [median (range)]	381 (43–920)	360.5 (38–2052)	0.7964

GnP gemcitabine plus nab-paclitaxel, *UFS* upfront surgery, *PD* pancreatoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *MP* middle pancreatectomy, *SMV* superior mesenteric vein, *PV* portal vein, *C-D* Clavien–Dindo classification

(29/31) of patients in the GnP group showed tumor reduction, and in 35% (11/31) of patients, the tumor shrunk by > 30%.

In this study, the GnP group showed a significantly shorter operative time and less blood loss, although the initial tumor size and distributions of the operative procedures were similar between the two groups. Most of the operations in the UFS group were performed in the first half of the study period (2010–2013, 20 cases; 2014–2017, 6 cases), and all operations in the GnP group were performed after 2015. Thus, improvement of surgical devices and changes in surgical techniques might have contributed to these differences. However, tumor shrinkage due to GnP was presumably involved in the facilitation of surgery. Ninety-two percent (22/24) of patients with BR-A in the GnP group did not require arterial resection, while 83% (5/6) of patients with BR-A in the UFS group underwent arterial resection. In addition, we feel that adhesion and fibrosis around vessels close to the tumor are not as severe after neoadjuvant GnP than after UFS, and that dissection around the vessels is therefore easier. In one study, nab-paclitaxel inhibited cancer-associated fibroblasts;[16] therefore, nab-paclitaxel might reduce fibrosis at the invasive front, making dissection easier. We therefore speculate that neoadjuvant GnP facilitates surgical procedures for BRPC.

If neoadjuvant therapy shows strong effects on the tumor, concerns may arise regarding the influence of neoadjuvant therapy on the postoperative course; however, neoadjuvant GnP did not increase either postoperative complications or hospital stay. Several authors also reported that neoadjuvant therapy for pancreatic cancer did not increase postoperative morbidity.[17,18] The administration rate of adjuvant chemotherapy was higher in the GnP group than in the UFS group. Our results suggest that neoadjuvant chemotherapy using the GnP regimen has no negative impact on the postoperative course.

One of the main purposes of neoadjuvant therapy for BRPC is to achieve margin-negative resection.[13] The current study demonstrated a significantly higher R0 resection rate in the GnP group than in the UFS group. Ielpo et al.[19] reported that all patients who underwent resection after neoadjuvant GnP for resectable pancreatic cancer and BRPC achieved R0 resection. Several studies on neoadjuvant therapy for BRPC also reported increased R0 resection rates after other neoadjuvant therapy regimens, compared with UFS.[7,8,20,21]

Recurrence frequently develops even after margin-negative resection for small resectable pancreatic cancer, and determines the patient's prognosis. Moreover, an analysis of the recurrence pattern after margin-positive resection revealed that most cases of recurrence were associated with distant metastasis.[22] Therefore, some investigators assert that pancreatic cancer should be considered a systemic disease and should be treated with 'systemic therapy'.[23] Another purpose of neoadjuvant chemotherapy is to eliminate micrometastatic cells prior to surgery and prevent metastatic recurrence. Our results suggest that neoadjuvant GnP potentially decreases recurrence during the intermediate-term postoperative period. Another comparative study of neoadjuvant GnP and UFS for potentially resectable pancreatic adenocarcinoma also showed significantly longer DFS after neoadjuvant GnP.[24]

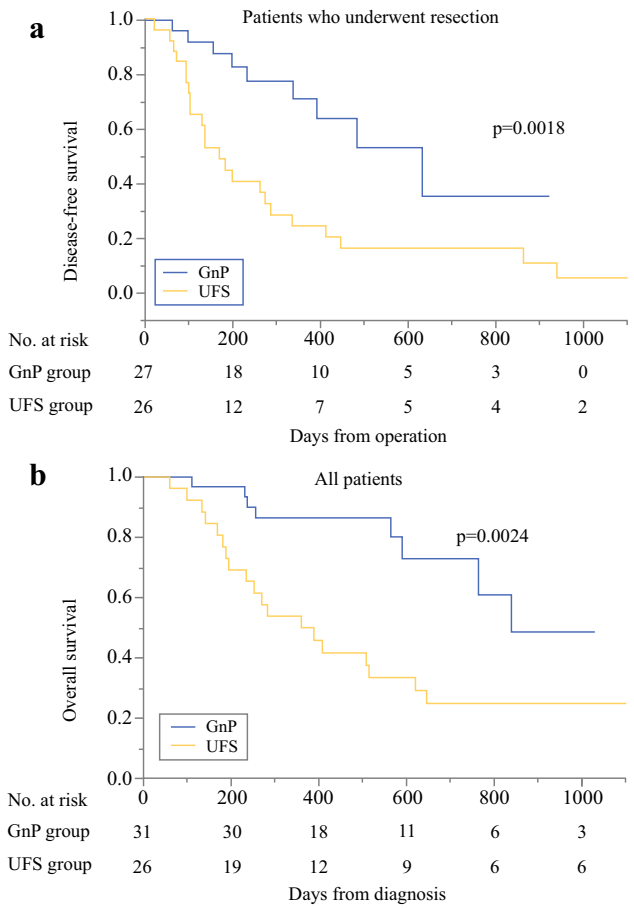

FIG. 3 **a** Kaplan–Meier curve for disease-free survival of patients with BRPC who underwent resection, in the GnP and UFS groups. **b** Kaplan–Meier curve for overall survival of all patients with BRPC in the GnP and UFS groups (intention-to-treat analysis). *BRPC* borderline resectable pancreatic cancer, *GnP* gemcitabine plus nab-paclitaxel, *UFS* upfront surgery

We performed UFS for BR-V until the late phase of the study period, while most patients with BR-A received neoadjuvant chemotherapy to avoid arterial resection. Therefore, the GnP group included a significantly larger population of patients with BR-A than the UFS group. Generally, the prognosis of BR-A is worse than that of BR-V.[5,25] However, the GnP group showed significantly better OS than the USF group, even in the intention-to-treat analysis. These outcomes suggest the prognosis-improving effects of neoadjuvant GnP for BRPC.

In addition, neoadjuvant chemotherapy provides the opportunity to select good candidates for surgery. Unnecessary laparotomy can be avoided if undetected metastasis becomes obvious during chemotherapy.

Our study has some limitations. This was a retrospective comparative study from a single institution and the sample size was small, especially considering the long 7-year study period. Notably, the findings of this study are susceptible to the effect of selection bias. Because most of the operations in the UFS group were performed in the former period, 12 of these patients received gemcitabine as adjuvant chemotherapy. Although adjuvant S-1 can reportedly improve the prognosis in patients with resectable pancreatic cancer compared with gemcitabine,[26] the matched analysis with patients who received adjuvant S-1 in this study also showed a significantly favorable prognosis in the GnP group (median not reached; 2-year OS rate 77.2%) compared with the UFS group (median 408 days; 2-year OS rate 33.3%; $p = 0.0301$). The GnP group comprised consecutive patients who underwent neoadjuvant GnP for BRPC as clinical care since the introduction of this regimen. The dose and schedule were modified according to the physician's decision, and the duration of neoadjuvant chemotherapy varied widely.

CONCLUSIONS

Neoadjuvant GnP was a safe and effective treatment strategy for BRPC. It has the possibility of not only improving the prognosis of patients but also facilitating surgical procedures. A prospective randomized trial is needed to establish solid evidence of the efficacy of neoadjuvant chemotherapy using the GnP regimen.

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