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Histology-based Combination Induction Chemotherapy for Elderly Patients with Clinical Stage III Non-small Cell Lung Cancer

GIUSEPPE L. BANNA[1], HECTOR JOSÈ SOTO PARRA[2], MARINE CASTAING[3], MARIA VITTORIA DIECI[4], GIUSEPPE ANILE[4], MAURIZIO NICOLOSI[5], SALVATORE STRANO[5], FRANCESCO MARLETTA[6], VALENTINA GUARNERI[4], PIERFRANCO CONTE[4] and ROHIT LAL[7]

Divisions of [1]Medical Oncology, [5]Thoracic Surgery, and [6]Radiotherapy, Cannizzaro Hospital, Catania, Italy;
[2]Division of Medical Oncology, A.O.U. Vittorio Emanuele Polyclinic, Catania, Italy;
[3]G.F. Ingrassia Department, University of Catania, Catania, Italy;
[4]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua, Italy;
[7]Lung Cancer Unit, Guy's and St Thomas' Hospital, London, U.K.

Abstract. *Aim: To explore the feasibility and activity of a histology-based induction combination chemotherapy for elderly patients with clinical stage III non-small cell lung cancer (NSCLC). Patients and Methods: Patients aged ≥70 years with stage IIIA and IIIB lung squamous cell carcinoma (SCC) or adenocarcinoma were treated with three cycles of carboplatin and gemcitabine or pemetrexed, respectively, followed by definitive radiotherapy or surgery. The primary endpoint was the overall response rate (ORR) following induction. Results: Twenty-seven patients, with a median age of 74 years (range=70-80 years) were treated for adenocarcinoma in 14 (52%) and SCC in 13 (48%), clinical stage IIIA in eight (30%) and IIIB in 19 (70%). Grade 3 or 4 toxicity was reported for five patients (18.5%). The ORR was 46% in 12 (partial responses) out of 26 assessable patients. Conclusion: Histology-based induction combination chemotherapy is active and feasible in elderly patients with stage III NSCLC.*

For elderly patients, aged ≥75 years, with unresectable locally advanced non-small cell lung cancer (NSCLC), definitive radiotherapy is considered an acceptable choice of treatment (1). Sequential chemoradiotherapy has demonstrated superior outcomes to those achieved by radiotherapy alone in the general population and is better-tolerated than concurrent chemoradiotherapy (CCRT), although specific data about sequential treatment in elderly patients are lacking and available data on CCRT are generally poor and retrospective (2). A similar overall survival (OS) following CCRT between elderly and younger patients has been reported in retrospective analyses, although the higher risk of haematological and non-haematological toxicity may overwhelm the possible benefits (2-4). In a randomised trial, CCRT with low-dose carboplatin *versus* radiotherapy alone resulted in survival benefit, but more grade 3-4 toxicities and infection in elderly Japanese patients (>70 years) with stage III NSCLC (5).

In the setting of advanced NSCLC disease, one randomised study showed that elderly patients may benefit more from a platinum doublet than from monotherapy (6). Whether this benefit can be translated to unresectable locally-advanced disease has not been prospectively studied to our knowledge.

The aim of this study was to explore the feasibility and activity of a histology-based induction combination chemotherapy for elderly patients with clinical stage III non-small cell lung cancer (NSCLC).

Patients and Methods

Study population. The eligibility criteria for the study included: histological or cytological diagnosis of NSCLC; unresectable locally advanced clinical stage IIIA or stage IIIB NSCLC according to TNM v7.0 (7); age ≥70 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2; adequate haematological, renal and hepatic function; no previous treatment with radiation or chemotherapy. All patients gave their written informed consent to this protocol. Pre-treatment evaluation and

Correspondence to: Giuseppe L. Banna, MD, Division of Medical Oncology, Cannizzaro Hospital, Via Messina 829, 95126, Catania, Italy. Tel: +39 0957262208, Fax: +39 0957262201, e-mail: gbanna@yahoo.com

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baseline clinical staging included: anamnesis; physical examination; computed tomography (CT) scan of brain, chest, abdomen and pelvis; ^{18}F-fluoro-deoxy-glucose (^{18}FDG)-positron-emission tomography (PET); laboratory tests for the evaluation of haematological, liver and kidney function; magnetic resonance imaging (MRI) of the brain with gadolinium, when clinically indicated.

For each case, the following criteria were followed for the definition of initial non-resectability: clinical N2 lymph node involvement; surgical indication for pneumonectomy; limiting comorbidities.

Induction chemotherapy. An induction chemotherapy regimen including three cycles delivered every 21 days was administered to all patients. In patients with squamous cell carcinoma, chemotherapy included: gemcitabine (at 1,000 mg/m^2 *i.v.* on days 1 and 8) in 250 cc saline solution over 30 minutes; carboplatin [at an area under the curve (AUC) of 5 *i.v.*, on day 1] in 500 cc saline solution over 1 hour. In patients with adenocarcinoma, the following drugs were administered: pemetrexed (at the dose of 500 mg/m^2 *i.v.*, on day 1) in 150 cc saline solution over 15 min; carboplatin (AUC 5 *i.v.*, on day 1) in 500 cc saline solution over 1 h.

As chemotherapy premedication, the following drugs were used *i.v.*: 100 mg ranitidine, 8 mg dexamethasone and 8 mg ondansetron 15 min before the chemotherapy of days 1 and 8. Patients treated with pemetrexed received folic acid, vitamin B12, and dexamethasone as recommended in the pemetrexed package insert (8).

On the day 8 of each cycle, a complete blood count and the determination of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were performed. On day 22, complete blood count (CBC) and laboratory tests for the assessment of haematological, hepatic and renal function were requested.

Patients received chemotherapy if the absolute neutrophil count (ANC) was ≥1,500/μl and platelet count was ≥100,000/μl; if ANC or platelet counts were less than these levels, the treatment was held, and a CBC was checked on a weekly basis. In the case of more than two weekly delays, chemotherapy was discontinued. In the case of febrile neutropenia or grade 3 non-haematological toxicity, a dose reduction of both agents (carboplatin AUC 4, pemetrexed or gemcitabine at 75% of the full dose) was carried out; in the case of recurrence of a grade 3 adverse event, chemotherapy was permanently discontinued. Patients who experienced haematological or non-haematological grade 4 adverse events were permanently discontinued from chemotherapy. In the case of grade 3 haematological toxicity, granulocyte-colony stimulating factors and haematopoietic growth factors were used; when clinically indicated transfusions of red blood cells or platelets were administered. If indicated, antibiotics and other supportive care were used.

Assessment of toxicity and response. Toxicity was recorded by clinical evaluation according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (9) before each subsequent chemotherapy administration. The assessment of response was performed using CT scan (with ^{18}FDG-PET only for stage IIIA NSCLC) within 3 weeks after the third cycle.

Locoregional treatment. Patients with stage IIIA disease and responding disease were re-evaluated for possible surgery, based on comorbidities and clinical conditions; in the case of non-resectability, or patient refusal, patients were sent for definitive radiotherapy. Patients with stage IIIB disease, with the responding or stable disease, were intended to be treated with definitive radiotherapy. Patients with disease progression dropped out of the study and were treated with a further line of chemotherapy if clinically indicated. Surgery or radiotherapy was intended to be started within 6 weeks of the response assessment.

Follow-up visits were performed every 3 months for the first 2 years and every 6 months thereafter and included clinical evaluation, a CT scan of the brain, thorax, abdomen and pelvis, and further investigations when clinically indicated.

Design of the study. The study was designed as a single-stage phase II study as described by A'Hern (10), with estimates based on the exact binomial distribution. In fact, designs for single-stage phase II trials commonly calculate the number of patients required using Fleming's single-stage procedure. However, this method is based on a normal approximation to the binomial distribution and is therefore technically incorrect for small trial sizes, as becomes apparent if exact binomial distributions are applied to these designs. Multi-stage designs, rather than single-stage designs, should be used in situations in which early termination is desirable if the treatment is ineffective.

The trial tested the null hypothesis H0: P<p0 against the alternative hypothesis H1: P>p1. For accepting that p1 is to be preferred to p0 (and therefore to accept that a phase III trial should be undertaken), for values of p0 of 0.15 and for values of p1 of 0.40, for one-sided alpha value of 0.05 and for power equal to 0.9, the trial size had to be 27 with a cut-off of eight patients not experiencing an overall response. All analyses were performed on an intention-to-treat basis.

Outcomes. The primary objective of the study was to evaluate the activity and feasibility of a histology-based combination induction chemotherapy for elderly patients with clinical stage III NSCLC. The primary endpoint was overall response rate (ORR), including complete response and partial response according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1 (11), following induction chemotherapy. Secondary endpoints were: toxicity according to the CTCAE v3.0 (9), need for chemotherapy dose reduction or withdrawal, the rate of patients who underwent definitive radiotherapy or surgery following induction chemotherapy, overall survival (OS), and progression-free survival (PFS).

Descriptive statistics were used to summarise the patient demographic and treatment characteristics. The disease responses were reported as relative proportions of the total number of patients. Percentages were approximated to the nearest unit. Statistical significance was investigated by the Fisher exact test with an acceptable significance value of $p<0.05$. The OS was calculated from the date of diagnosis until death or last date of follow-up. The PFS was calculated from the date of diagnosis until the date of progression, or death from any cause. Patients who had not died or whose disease progressed or who had failed to attend for follow-up at the time of the final analysis were censored at the date of the last contact. The PFS and OS were estimated using the Kaplan–Meier, reported as medians with confidence limits (95% CI) and compared using two-sided log-rank test (12). The 95% CI response rates were estimated according to Simon (13).

In order to study the possible influence of the main baseline characteristics (gender, stage of disease, histology/regimen of chemotherapy, age, PS, comorbidities, and radiotherapy) on the OS and PFS, univariate logistic regression model of Cox was used (14), considering differences statistically significant at $p<0.05$.

Table I. *Patient characteristics*.

Characteristic	Value
Age, median (range)	74 (70-80)
Gender, n (%)	
Male/Female	23/4 (85/15)
Histology, n (%)	
Adenocarcinoma	14 (52)
Squamous cell	13 (48)
Stage, n (%)	
IIIA/IIIB	8/19 (30/70)
T 1/2/3/4	3/2/8/14 (11/7/30/52)
N 1/2/3	4/15/8[a] (15/56/30)
ECOG PS, n (%)	
0/1/2	9/15/3 (33/56/11)
Active comorbidities, n (%)[b]	
0/1/2/3/4/5	2/6/8/5/5/1 (7/22/30/18.5/18.5/4)
Smoking history, n (%)[c]	
Heavy smoker	8 (30)
Ex-heavy smoker	15 (56)
Ex-light smoker	1 (4)
Never smoker	3[d] (11)

ECOG PS, Eastern Cooperative Group Performance Status; N, lymph node stage; T, tumor stage. [a]Contralateral (n=5) and supraclavicular (n=3) lymph nodes. [b]Requiring medical treatment: previous cardiac/cerebral ischemia in 8, chronic obstructive pulmonary disease in 6 and arrhythmia in 6. [c]Heavy smoker: >30 packs/year; ex-heavy smoker: >30 packs/year; ex-light smoker: 0.1-30 packs/year. [d]Two of these patients had adenocarcinoma, one with a del 19 epidermal growth factor receptor (*EGFR*) mutation, the only one observed among all 9 patients with adenocarcinoma studied.

Table II. *Treatment and disease response*.

Characteristic	Value
Treatment, n (%)	
Carboplatin-pemetrexed	14 (52)
Carboplatin-gemcitabine	13 (48)
Median no. of cycles of chemotherapy (range)	3 (1-4)
Dose reduction/withdrawal, n (%)	2/3 (7/11)
Response, n (%)	
PR	12 (46)
SD	4 (15)
PD	10 (38)
NA	1 (4)
PR according to regimen, n (%)	
Carboplatin-pemetrexed	7 (50)
Carboplatin-gemcitabine	5 (38)
Median OS (95% CI), months	12.6 (11.5-14.1)
Carboplatin-pemetrexed (adenocarcinoma)	13.1 (11.6-15.2)
Carboplatin-gemcitabine (SCC)	8.8 (7.8-10.3)
One-year OS probability (95% CI), %	52.7 (47.6-58.1)
Median PFS (95% CI), months	7.3 (6.7-8.2)
Carboplatin-pemetrexed (adenocarcinoma)	7.1 (6.4-8.3)
Carboplatin-gemcitabine (SCC)	7.8 (7.0-9.3)

CI: Confidence interval; NA: not assessable; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; SCC: squamous cell carcinoma; SD: stable disease.

Table III. *Treatment toxicity*.

	Grade 1-2	Grade 2	Grade 3	Grade 4
Toxicity	n (%)	n (%)	n (%)	n (%)
Neutropenia	1 (4)	11 (41)	0 (0)	1 (4)
Asthenia	5 (19)	7 (26)	1 (4)	0 (0)
Anaemia	1 (4)	8 (30)	2 (7)	0 (0)
Nausea/vomiting	8 (30)	1 (4)	-	-
Diarrhoea	6 (22)	1 (4)	-	-
Thrombocytopenia	0 (0)	2 (7)	1 (4)	0 (0)
Fever	0 (0)	2 (7)	1 (4)	0 (0)
Peripheral neuropathy	1 (4)	0 (0)	-	-
Pneumonia	-	-	1 (4)	0 (0)
Cerebral ischemia	-	-	0 (0)	1 (4)

Multivariate analysis of factors that were significant at univariate analysis was planned. All analyses were performed according to the intention-to-treat principle with two-sided tests. All statistical analyses were performed using the statistical software Statistica v6.1 (StatSoft Italia Srl, Vigonza, Italy).

Results

Characteristics of patients. From October 2009 to October 2015, 27 patients were consecutively enrolled in the study, with a median age of 74 (range=70-80) years and ECOG PS of 0/1/2 in 9/15/3 patients respectively. The characteristics of patients are shown in Table I. Fourteen patients (52%) had an adenocarcinoma, 13 patients (48%) a squamous cell carcinoma. Eight patients (42%) had clinical stage IIIB disease due to N3 involvement . Patients had a median of two (range=0-5) active comorbidities requiring medical treatment, with 41% of patients having three or more.

Treatment and outcome. The data related to the treatment and disease outcome are shown in Table II. The median number of induction chemotherapy cycles was 3 (range=1-4).

Three patients (11%) did not complete chemotherapy: one patient with SCC had a stroke after the administration of the second cycle, one patient with adenocarcinoma had protracted grade 3 anaemia following the second cycle and one patient with SCC had early clinical disease progression following the first cycle of chemotherapy. Two patients (7%) had chemotherapy dose reduction both following the second cycle of chemotherapy due to hospitalisation for pneumonia

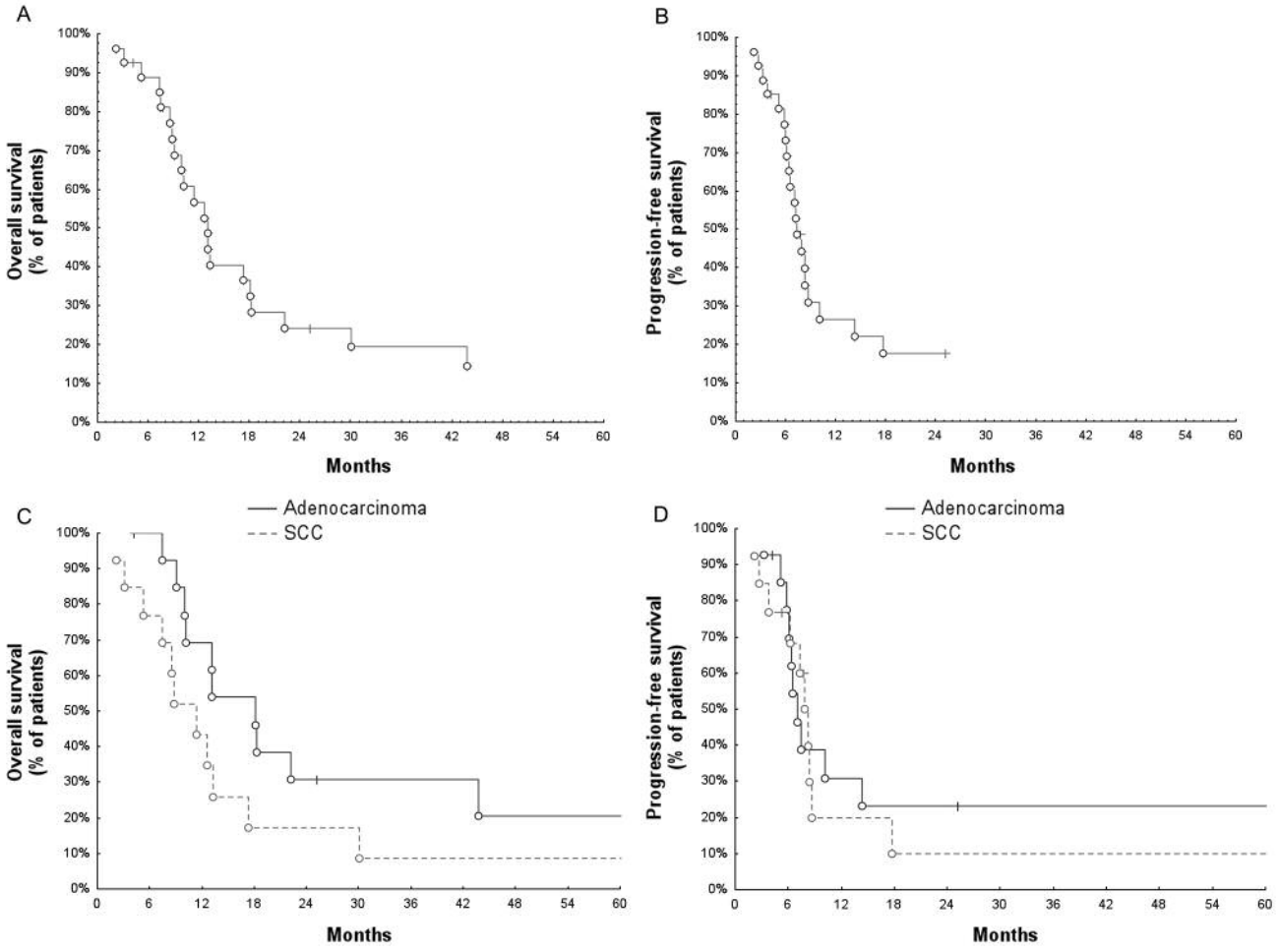

Figure 1. *Overall (OS) and progression-free (PFS) survival of patients. A: Median OS for the whole patient group: 12.6 [95% confidence interval (CI)=11.5-14.1] months. B: Median PFS for the whole patient group: 7.3 (95% CI=6.7-8.2) months; C: Median OS for patients with adenocarcinoma versus those with squamous cell carcinoma (SCC): 13.1 (95% CI=11.6-15.2) months versus 8.8 (95% CI=7.8-10.3) months (p=0.12). D: Median PFS for patients with adenocarcinoma versus those with SCC: 7.1 (95% CI=6.4-8.3) months versus 7.8 (95% CI=7.0-9.3) months (p=0.73).*

in one patient with adenocarcinoma and protracted grade 2 anaemia and asthenia in one patient with SCC.

Following chemotherapy, the ORR was 46% (12 out of 26 assessable patients). All disease responses, occurring in 12 patients, were partial. Ten patients (38%) had progressive disease and four patients (15%) stable disease. Seven patients with adenocarcinoma showed a partial response (ORR of 50%) *versus* five patients with SCC (ORR of 38%) (p=0.42). OS and PFS data are reported in Table II and shown in Figure 1. With a median follow-up of 71.1 months, 1-year probability of OS for patients with adenocarcinoma and SCC was 61.5% (95% CI=53.5-70.1) and 34.6% (95% CI=30.1-39.7), respectively (p=0.12).

Eleven patients (41%) received radiotherapy following induction chemotherapy, including 37% of all patients with initial stage IIIB disease and 50% of those with stage IIIA disease. Two patients (7%) with partial response after chemotherapy underwent lobectomy. No surgery or radiotherapy following chemotherapy was performed in 14 patients (52%) due to progressive disease in eight (57%) and clinical conditions or other comorbidities that led the remaining six patients (43%) to be deemed not suitable for radiotherapy.

Toxicity. The toxicity data are reported in Table III. Grade 3 or 4 toxicity was reported in five patients (18.5%). Two grade 4 and six grade 3 adverse events were reported, including one grade 4 neutropenia and one cerebral ischemia. Twenty-two patients (81%) had a grade 1 or 2 toxicity. The most frequent grade 1-2 toxicities were: neutropenia, asthenia, anaemia and nausea/vomiting and diarrhoea.

Table IV. *Univariate analysis for prognostic factors*.

Variable		OS			PFS		
	No. at risk	No. of events	1-Year	*p*-Value	No. events	1-Year	*p*-Value
Gender							
M	23	18	64%	0.62	3	30%	0.71
F	4	3	50%		17	25%	
Stage							
IIIB	19	17	53%	0.24	16	24%	0.16
IIIA	8	4	86%		4	43%	
Histology							
Adenocarcinoma	14	10	70%	0.12	10	33%	0.72
SCC	13	11	52%		10	25%	
Age, years							
≥75	11	9	52%	0.43	9	24%	0.26
<75	16	12	68%		11	33%	
ECOG PS							
1-2	18	14	65%	0.70	13	33%	0.91
0	9	7	56%		7	22%	
Comorbidities							
≥3	11	9	52%	0.40	9	14%	0.42
<3	16	12	68%		11	40%	
Radiotherapy							
Yes	11	6	70%	0.13	6	50%	0.03
No	16	15	56%		14	16%	

ECOG PS: Eastern Cooperative Group Performance Status; F: female; M: male; OS: overall survival; PFS: progression-free survival; SCC: squamous cell carcinoma.

Prognostic factors. None of the explored factors were found to be significant prognostic factors by univariate analysis of OS (see Table IV). The only factor found to be significantly associated with better PFS was the administration of radiotherapy following chemotherapy (p=0.03).

Discussion

For elderly patients, aged ≥70 years, with unresectable locally advanced NSCLC, the use of CCRT is recommended in selected fit cases by the European Organisation for Research and Treatment of Cancer Elderly Task Force and Lung Cancer Group (2) and the International Society of Geriatric Oncology (15), based on the results of a randomised study on Japanese patients >70 years (5) and retrospective data (2). Sequential chemoradiotherapy is better tolerated than CCRT and is more active than radiotherapy alone in the general population (2, 16), with reported median survival of 13.2-13.8 months compared to 9.7-11.4 months. In this study, sequential chemoradiotherapy with the use of a histology-based combination induction chemotherapy for elderly patients with stage III resulted in median OS and ORR consistent with data previously reported in the general population (2, 16), confirming the feasibility and activity of a doublet carboplatin-based induction chemotherapy in this setting, as was expected from data already available in the advanced disease setting (6, 17).

A trend toward better OS and ORR was observed in patients with adenocarcinoma, suggesting the choice of a histology-based chemotherapy with the use of pemetrexed instead of gemcitabine could be of some benefit in elderly patients with stage III adenocarcinoma, as already established in the advanced disease setting (18).

In this study, almost half of all patients had three or more active comorbidities, but this did not affect OS. This could suggest that sequential chemoradiotherapy with a carboplatin-based doublet induction should not be ruled out for those patients unsuitable for CCRT due to comorbidities, although many patients were thereafter excluded from definitive radiotherapy due to their cardiovascular and respiratory conditions and this could have negatively influenced their PFS.

Several limitations may have affected the results of this study, such as the limited number of patients, the lack of a multidimensional geriatric assessment, the low accrual rate and a selection bias due to enrolment of patients potentially not suitable for definitive radiation treatment. On the other hand, this was a mono-institutional study on a real-life population of elderly patients with several active comorbidities in a rare disease setting.

In summary, this study confirms the feasibility and activity of a histology-based induction doublet chemotherapy as a part of sequential chemoradiotherapy for the treatment of elderly patients with unresectable stage III NSCLC.

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