The C5R Protocol: A Regimen of High-Dose Chemotherapy and Radiotherapy in Primary Cerebral Non-Hodgkin’s Lymphoma of Patients With No Known Cause of Immunosuppression

By J.-Y. Blay, D. Bouhour, C. Carrie, E. Bouffet, M. Brunat-Mentigny, T. Philip, and P. Biron

In most reported series, less than 20% of patients with primary cerebral non-Hodgkin’s lymphoma (PCL) and no known cause of immunodepression are alive and disease-free 5 years after the initial diagnosis. Whether chemotherapy improves the outcome of these patients remains unclear. We report a pilot study of a protocol (C5R) with five courses of chemotherapy followed by cranial radiotherapy in 25 adult patients with PCL and no known cause of immunodepression. The median age was 51 years (range, 16 to 70 years) and the median performance status was 2 (range, 1 to 4) in this series. Fourteen patients (56%) achieved a complete response and 4 (16%) achieved a partial response 1 month after the completion of the treatment. Four patients died in the first month of treatment because of progression (n = 1) or toxicity (n = 3). In 3 patients, the treatment could not be performed because of patient refusal (n = 1) or severe infections (n = 2). Myelosuppression was the most frequent side effect; febrile neutropenia occurred in 96%, 89%, 69%, and 74% of the patients after the second, third, fourth, and fifth courses of chemotherapy, respectively. Grade 4 thrombocytopenia occurred in 20% of the patients. With a median follow-up of 24 months, the projected survival of the group at 4 years is 70% and 56%, respectively. The 4 early deaths occurred in the subgroup of 6 patients greater than 60 years of age with an international prognostic index (IPI) greater than 3. In the 19 remaining patients (76% of this series) less than 61 years of age or with an IPI less than 4, the projected overall survival at 2 and 5 years is 88% and 70%, respectively. The C5R protocol is a highly efficient regimen in nonimmunosuppressed patients with PCL less than 61 years of age or with an IPI less than 4.

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tary Cerebral non-Hodgkin’s lymphomas (PCL) occurring in patients with no known cause of immunodepression remain a therapeutic challenge. The median survival is in the range of 10 to 16 months in most series and only 5% to 15% of the patients are alive and disease-free at 5 years. Early relapses occur consistently when surgery alone is performed. Postoperative treatment has therefore been proposed almost consistently in the literature. Radiotherapy alone has been administered as a postoperative treatment in the majority of series, but yields only 5% to 10% of the patients alive and disease-free at 5 years. Long-term remissions have also been reported with chemotherapy alone or a combination of chemotherapy and radiotherapy. Although several reports suggest a superiority of combination therapy over radiotherapy alone in terms of survival, this has not been consistently observed. These discrepancies are probably due to the heterogeneity of treatments in retrospective series and to the limited number of patients in each series. In addition, chemotherapy regimens may improve survival only when they include drugs with a good penetration of the blood brain barrier (BBB) and/or administered with BBB disruption. Three recent prospective studies using these approaches have reported median overall survival close to 40 months. These results appear to be superior to those obtained with radiotherapy alone or radiotherapy combined with chemotherapies not directed towards the central nervous system (CNS).”

We report here the results of a pilot study of a high-dose chemotherapy regimen followed by radiotherapy in PCL that was conducted during two periods, from 1983 to 1986 and from 1991 to 1994, in the Centre Léon Bérard.

PATIENTS AND METHODS

Study group. Between 1983 and 1986 (period 1) and between 1991 and 1994 (period 2), all previously untreated human immunodeficiency virus (HIV)-negative nonimmunosuppressed patients less than 61 years of age with a newly diagnosed PCL seen at the Centre Léon Bérard were included in the prospective therapeutic protocol termed CSR. Between 1991 and 1994, the upper age limit was extended to 70 years of age. None of these patients had any known cause of congenital or acquired immunodepression, e.g., HIV infection, organ transplantation, and previous immunosuppressive treatment including long-term corticosteroid treatment. Between 1987 and 1992, the Centre Léon Bérard participated in a French multicentric study for NHL; all patients with PCL diagnosed and treated at the Centre Léon Bérard were included in this protocol and therefore not included in the CSR protocol.

The surgery performed for the initial diagnosis was either biopsy or complete macroscopic resection of the tumor (n = 4). All patients underwent a staging evaluation that included a lumbar puncture; an ophthalmologic examination, particularly of the vitreous and retina by slit-lamp examination; an abdominal and thoracic computer tomography (CT) scan; and HIV serology. Meningeal involvement was defined by the presence of lymphoma cells on cytologic examination of cerebrospinal fluid (CSF). All patients included were HIV-negative, as evaluated using one serologic test (Abbott HIV EIA; Abbott Diagnostic, Rungis, France) until 1989 and two serologic tests (Abbott HIV-1/HIV-2 EIA [Abbott Diagnostic] and Serodia-HIV [Bayer Diagnostic, Puteaux, France]) since 1989. Two patients included in 1983-1984 were tested for HIV serology after the completion of treatment. Table 1 shows the characteristics of these patients, including their status within the international prognostic index (IPI) for aggressive lymphomas (not age adjusted) that was recently reported. Briefly, this index is an algorithm obtained by adding the numbers associated with the following prognostic factors: (1) greater than 60 years of age; yes = 1, no = 0; (2) Ann Arbor clinical stage III-IV disease; yes = 1, no
CHEMOTHERAPY IN PRIMARY CEREBRAL LYMPHOMA

Table 1. Description of the Treatment

<table>
<thead>
<tr>
<th>COP (1 course)</th>
<th>CYM (2 courses at 21-day intervals from day 1 to day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>Cyclophosphamide: 300 mg/m², IV</td>
</tr>
<tr>
<td>D1</td>
<td>Methotrexate: 15 mg intrathecal</td>
</tr>
<tr>
<td>D2</td>
<td>Hydrocortisone: 15 mg intrathecal</td>
</tr>
<tr>
<td>D1 to D6</td>
<td>Methylprednisolone: 1 mg/kg every 12 hours, IV</td>
</tr>
<tr>
<td>Time between courses: 7 days (day 1 to day 1)</td>
<td></td>
</tr>
<tr>
<td>COPADEM (2 courses at 21-day intervals from day 1 to day 1)</td>
<td>CYM (2 courses at 21-day intervals from day 1 to day 1)</td>
</tr>
<tr>
<td>D1</td>
<td>Vincristine: 2 mg, IV</td>
</tr>
<tr>
<td>D1</td>
<td>Methotrexate: 3 g/m², IV</td>
</tr>
<tr>
<td>D2</td>
<td>Methotrexate: 15 mg, intrathecal</td>
</tr>
<tr>
<td>D2</td>
<td>Hydrocortisone: 15 mg, intrathecal</td>
</tr>
<tr>
<td>D2 to D4</td>
<td>Folinic acid: 25 mg every 6 hours, IV</td>
</tr>
<tr>
<td>D2</td>
<td>Adriamycin: 60 mg/m², IV</td>
</tr>
<tr>
<td>D2 to D4</td>
<td>Cyclophosphamide: 250 mg/m² every 12 hours, IV</td>
</tr>
<tr>
<td>D1 to D6</td>
<td>Methylprednisolone: 1 mg/kg every 12 hours, IV</td>
</tr>
<tr>
<td>D6</td>
<td>Methotrexate: 15 mg intrathecal</td>
</tr>
<tr>
<td>D8</td>
<td>Hydrocortisone: 15 mg intrathecal</td>
</tr>
<tr>
<td>Time between courses: 21 days</td>
<td></td>
</tr>
</tbody>
</table>

WBRT, whole-brain radiotherapy. Boost on tumor bed: 200 cGy x 15 (total 30 Gy)

Abbreviations: IV, intravenous; WBRT, whole-brain radiotherapy.

= 0; (3) serum lactate dehydrogenase (LDH) greater than normal; yes = 1, no = 0; (4) performance status greater than 1; yes = 1, no = 0; (5) more than one extranodal site: yes = 1, no = 0.** The CCR prognostic index for PCL is another index that was previously reported by our institute.**

The CCR protocol. The chemotherapy regimen was derived from the Lymphoma Malins B (LMB) regimens used for pediatric B lymphomas. This schedule was chosen because of its high efficacy for the treatment of Burkitt's lymphoma of children with CNS involvement and because of its feasibility in adult Burkitt's lymphoma. Chemotherapy consisted of one course of COP, followed 7 days after by the first course of the COPADEM. The second course of COPADEM and 2 courses of the CYM regimen were administered at 21-day intervals. Between the courses, the patients did not receive corticotherapy. The drugs and doses are indicated in Table 1. Radiotherapy was initiated 21 to 35 days after the last course of CYM and consisted of 20 Gy in 2-Gy fractions on the whole brain followed by 30 additional Gy in fractions of 2 Gy on the site of the primary tumor before chemotherapy. In cases of multiple CNS lymphoma sites, each site received 30 additional Gy. 5 patients received 50 Gy on the whole brain because of multiple PCL localizations within the CNS. The 3 patients with ocular involvement received 40 Gy of ocular radiotherapy in 2-Gy fractions. After the completion of the treatment, all patients underwent a physical examination, cranial CT scan, and/or magnetic resonance imaging (MRI) every 3 months in the first 2 years after diagnosis, every 4 months in years 3 and 4, and every 6 months thereafter.

Response to treatment. Response was assessed using planar CT scan and/or MRI scans according to the criteria defined by MacDonald et al.27 A complete response (CR) was defined as resolution of enhancing tumor in a patient who does not receive corticosteroid treatment. A partial response (PR) was defined as at least a 50% reduction in the size of the mass in the patient receiving a stable or decreasing dose of steroids. A minor response (MR) was defined as a less than 50% reduction in a patient receiving a stable or decreasing dose of steroids. Stable disease (SD) was defined as no objective change in the lesion(s). Progressive disease (PD) was defined as an unequivocal increase of tumor size and or appearance of new lesions.27 Although several patients received corticosteroids before the beginning of the treatment, continuous corticotherapy was interrupted after the first COPADEM course in all patients; none of the 25 patients received chronic corticosteroid therapy at the times of the evaluation using CT or MR scan. Evaluations were performed before the first course of COP, immediately before the initiation of the second course of COPADEM, 21 to 28 days after the second course of CYM, and 1 month after the end of radiotherapy.

Survival. Survival was calculated according to the Kaplan-Meier method.28 Survival duration was measured from the date of diagnosis to the date of death or last follow-up. The impact of prognostic factors on survival was calculated with the log-rank test.

RESULTS

Patient characteristics. Twenty-five patients were included in the CCR protocol, 5 in the first period (1983-1986) and 20 in the second period (1991-1994). The diagnosis was established after a histologic examination of the tumor (biopsies or complete resections) in all patients (Table 2). No patients are lost to follow-up. All patients alive at day 2 after the beginning of chemotherapy are evaluable for response to chemotherapy and survival. Table 2 shows the clinical and biologic characteristics of the patients included in the CCR protocol.

Feasibility and toxicity of the treatment. The treatment was completed as scheduled in 18 of the 25 patients (72%; Fig 1). Four patients (16%) died during the first month of treatment. A 53-year-old woman (unique patient no. [UPN] 122) died at day 22 because of rapid tumor progression diagnosed on CT scan. Three patients died in the first 28 days of the treatment without evidence of progressive disease (Fig 1). A 62-year-old woman (UPN 131) died of cerebral hematoma at day 32 after cranial trauma while in complete remission after the first course. A 62-year-old man (UPN 129) died suddenly of an unknown cause at day 27. This patient had previously experienced a febrile grade 4 neutropenia, was afebrile after complete hematologic recovery, and had negative blood culture results. Autopsy could not be performed. A 61-year-old man (UPN 087) died of septic shock due to Escherichia coli bacteremia at day 21. The treatment could not be performed as scheduled in 3 (12%) additional patients because of patient refusal (n = 1) or toxicity (n = 2). A 70-year-old man (UPN 087) refused the treatment after two courses and died 2 months later of tumor progression. A 45-year-old man (UPN 086) experienced a cerebral abscess after the second course and did not receive the second course of COPADEM. This patient received 2 additional courses of CYM and radiotherapy as...
scheduled in the protocol; the first course of CYM was administered 49 days after the first COPADEM course. A 49-year-old man (UPN 134) with diabetes mellitus experienced recurrent candida septicemia after the first course of COPADEM. Chemotherapy was then withdrawn and he received radiotherapy immediately after the first course of COPADEM.

Table 3 presents the toxicity of the 2 courses of COPADEM or CYM. Myelosuppression was the most frequent side effect of this treatment. Twenty-four of the 25 (96%) and 17 of the 19 (89%) evaluable patients experienced febrile neutropenia after the first and second courses of COPADEM, respectively (Table 3). The median duration of neutropenia level less than 500/μL was 3 days after both the first and second courses of COPADEM (range, 0 to 6 days). Febrile neutropenia occurred in 64% and 79% of the patients after the first and second course of CYM, respectively (Table 3). The median duration of neutropenia level less than 500/μL was 2 days after both the first and second courses of CYM (range, 0 to 5 days). Since 1992, recombinant granulocyte colony-stimulating factor (G-CSF) was administered in every patient as secondary prophylaxis after a first episode of febrile neutropenia. Seven patients experienced thrombocytopenia levels less than 25,000/μL (Table 3). Platelet transfusion was performed when counts were less than 20,000/μL. Respectively, 3 and 4 patients received a single platelet transfusion after the first and second COPADEM courses. One patient received 2 platelet transfusions after the second COPADEM course. Two patients received a single platelet transfusion after the first and second courses of CYM, respectively. None of the patients experienced acute neurologic toxicity. At the present time, with a median follow-up of 24 months for the complete series and 32 months for alive patients, none has experienced clinical, CT scan, or MRI symptoms of late neurologic toxicity, in particular chronic leukoencephalopathy.

Response to treatment. Among the 4 patients who died in the first 28 days, 2 were evaluable for response: 1 died of tumor progression at day 22 and 1 died in CR at day 32. Eighteen patients (72% of the 25) achieved an objective response: 14 (56%) achieved a CR and 4 (16%) a PR after the completion of the treatment. Actually, all 18 patients in whom the treatment could be completed and who were evaluated for response before the initiation of radiotherapy achieved a PR or a CR before radiotherapy (Table 4). Two patients were converted from a PR after chemotherapy to a CR after radiotherapy, whereas 5 remained in PR (Table 4). At the present time, overall survival is similar for patients in PR and in CR before and after the end of radiotherapy (not shown).

The 2 patients who did not complete the treatment after the first course of COPADEM were, respectively, in CR before and after radiotherapy (UPN 086) and in PR before and after radiotherapy (UPN 134; Fig 1).
Survival. Figure 2A presents the overall and progression-free survival of the 25 patients; with a median follow-up of 24 months, the projected 2- and 5-year overall survival rates are 70% and 56%, respectively, in this series (Fig 2A). Figure 2B presents the overall and progression-free survival of the 18 patients who completed the protocol as scheduled. With a median follow-up of 32 months, 2 of these 18 patients experienced a relapse (25 and 96 months after diagnosis, respectively; Fig 2B); the site of the relapses was the brain, without meningeal or extra-CNS involvement. The 3 patients in whom the treatment was interrupted after the first COPADEM course (UPN 138, 134, and 86) died of tumor progression, 4, 6, and 11 months after the initial diagnosis, respectively; relapses occurred in bone marrow and CSF (n = 1), in the brain and CSF (n = 1), and in the brain only (n = 1) in these patients. The overall survival rates of patients treated in periods 1 and 2 are not significantly different; 2 of the 5 patients of period 1 and 4 of the 20 patients in period 2 have progressed.

Prognostic factors for survival. Survival was then analyzed according to previously reported prognostic factors to identify patients at risk for an early death with this protocol. The four early deaths occurred in the subgroup of 6 patients more than 60 years of age with an IPI of 4 compared with none in the remaining group (Fisher’s exact test P < .001). This subgroup with an unfavorable outcome represents 24% of the complete series of patients and 60% of patients more than 60 years of age.

The projected overall survival rates of the subgroup of 19 patients less than 61 years of age or with an IPI less than 4 are 88% and 70% at 2 and 5 years, respectively, with a median follow up of 32 months (Fig 3). The overall survival of these 19 patients is significantly superior to that of the 6 patients more than 60 years of age and with an IPI greater than 3 (Fig 3; log-rank = 19.3, P = .00002).

DISCUSSION

Only 5% to 15% of the patients with PCL are alive and disease-free at 5 years when radiotherapy is used as the sole postoperative treatment. The capacity of chemotherapy to improve the outcome of PCL patients is still matter of debate. Chemotherapy regimens that do not include BBB-permeable drugs have only a limited efficacy in primary cerebral lymphoma and are most often associated with short-term relapses and limited survival. In contrast, chemotherapy regimens including BBB-permeable drugs have yielded
improved results, with a median survival close to 40 months in several reports.\textsuperscript{13-17}

A majority of PCL are intermediate or high-grade non-Hodgkin's lymphoma and most are diffuse large-cell lymphomas.\textsuperscript{2,4} The regimen used in this study were derived from the LMB regimen\textsuperscript{24-26} and combines drugs with a good penetration of the BBB (ie, high-dose methotrexate and cytosine arabinoside, administered either by systemic or intrathecal infusions) associated with cyclophosphamide and adriamycin, which are generally considered as the major components of chemotherapy regimens for diffuse large-cell lymphomas.\textsuperscript{29} Although adriamycin and cyclophosphamide poorly penetrate the BBB, the high response rates achieved by the LMB regimen in Burkitt's lymphoma of children and adults with CNS (mostly meningeal) involvement prompted us to investigate empirically a regimen with a similar schedule in PCL.\textsuperscript{24-26} In the C5R regimen, the doses of vincristine and cyclophosphamide were reduced as compared with the original LMB pediatric regimen to improve the tolerance in adult patients.\textsuperscript{24} In light of the pattern of relapses in PCL, which occur mostly in the CNS, it was decided to administer cranial radiotherapy after the completion of chemotherapy in this protocol.\textsuperscript{23}

It is important to note that the population of patients treated in this protocol was not selected. All previously untreated PCL patients less than 61 years of age (1983-1986) or less than 71 years of age (1991-1994) studied in the Centre Léon Bérard were treated according to the C5R protocol. These patients were similar in terms of age, sex, histologic subtype, and clinical presentation to PCL of nonimmunosuppressed patients seen in this institute outside these time frames\textsuperscript{13,29} or previously reported in the literature.\textsuperscript{1-4}

The C5R regimen was found highly efficient in terms of response rate. Eighteen patients (72% of the 25) who completed the entire program achieved a CR or a PR and only 1 patient experienced an early disease progression after the second course. This response rate compares favorably with those obtained with standard (eg, CHOP) chemotherapy regimens in PCL\textsuperscript{2,4,6,8-10,19,20} and appear to be similar to recently reported chemotherapy regimens for PCL,\textsuperscript{12-17} in particular regimens based on high-dose methotrexate.\textsuperscript{15,17} Six of these 25 patients have relapsed or progressed with a median fol-
low-up of 24 months. Interestingly, response was long-lasting in the 18 patients who completed the treatment and achieved CR/PR; with a median follow-up of 32 months in this subgroup, only 2 of these 18 patients have yet relapsed, respectively, 25 and 96 months after the initial treatment. These results are encouraging in view of the median times to progression generally reported in the literature for PCL, which are close to 8 months with radiotherapy only.\textsuperscript{2,3}

The toxicity of the C5R protocol was important. Febrile neutropenia occurred in all but 1 patient after the first COPADEM course. Therefore, most patients were readmitted during the intercourse; in 4 cases, treatment was performed in continuous hospitalization for the 2 courses of COPADEM. Although thrombocytopenia levels less than 25,000/μL occurred in 20% of the patients, only 1 case of severe bleeding was observed (with a platelet nadir of 34,000/μL) and resulted in 1 of the toxic deaths. In this case, an intracerebral hematoma occurred after severe cranial trauma; thrombocytopenia is likely to have contributed to this outcome. Twelve percent of the patients experienced severe mucositis; healing was obtained within day 21 in all cases.

Three deaths (12%) not due to disease progression occurred after the first COPADEM course. This death rate is comparable to that reported in most series of the literature, in which 10% to 20% of the patients with PCL die within the first 2 months of the diagnosis, most often of tumor progression.\textsuperscript{2,4} However, in these 3 cases, the treatment possibly or certainly contributed to the unfavorable outcome. It was therefore important to identify patients at risk for this toxicity to exclude them in the future. These 3 patients were found to be all more than 60 years of age and to have an IPI of 4. Six of the 25 patients of this series (24%) had these characteristics. Of note, 2 additional patients from this subgroup died within the 4 months of the treatment: 1 of tumor progression (UPN 122) and the other after treatment refusal (UPN 087). The survival of this subgroup is therefore very poor. This finding enables us to conclude that the subgroup of patients with an IPI of 4 who are more than 60 years of age should not receive this treatment.

The overall survival of this series is superior to that reported in series using postoperative radiotherapy only, for which the median survival is close to 10 to 16 months.\textsuperscript{1,10} The results achieved by the C5R regimen are consistent with those of reports using BBB-permeable chemotherapy, in which the median survival ranges from 32 to 44 months.\textsuperscript{13,15-17} They are also consistent with a recent report showing that treatment with high-dose methotrexate is associated with a significantly improved survival in a multicentric retrospective study of PCL.\textsuperscript{30} The projected 2-year overall survival is 70% in the C5R series as well as in the series reported by Neuwelt et al\textsuperscript{12} and De Angelis et al\textsuperscript{16} and 54% in the series of Glass et al.\textsuperscript{17} The projected 5-year survival is 56% in the C5R series, whereas it is close to 40% in the reports of Neuwelt et al,\textsuperscript{15} DeAngelis et al\textsuperscript{16} (at 56 months), and Glass et al.\textsuperscript{17} However, a longer follow-up will be required to compare the results achieved with these different regimens.

There are notable differences in terms of early death rates and toxicity between C5R and the three above-mentioned regimens.\textsuperscript{15-17} The hematologic toxicity of the C5R protocol is superior to that reported in the three other studies.\textsuperscript{15-17} No
early deaths are reported by De Angelis et al\textsuperscript{16} and Glass et al.,\textsuperscript{17} whereas 3 deaths in the first 30 days after chemotherapy are reported among 30 patients by Neuwelt et al\textsuperscript{15} and 4 (including 1 progression) are reported in the CSR series. The identification of the subgroup with a high risk of early death (ie, patients >60 years of age who have an IPI >3) will probably result in an important reduction of the early death rate for future patients treated with the CSR regimen. It is important to note that the outcome of patients either less than 61 years of age or with an IPI less than 4 (who represent 76% of PCL patients seen in our institute during this period) was particularly favorable. In this group with a median follow-up of 32 months, the projected 2- and 5-year overall survival rates are 88% and 70%, respectively, with no toxic deaths. The CSR regimen should therefore be compared with other modern treatments for PCL.\textsuperscript{15-17} It would be important, in particular, to analyze the outcome of the above-defined favorable subgroup of PCL patients in these three series.\textsuperscript{15-17}

An important possible concern with this regimen is the risk of leukoencephalopathy after this treatment, which combines systemic and intrathecal methotrexate, cytosine arabinoside, and cranial radiotherapy and is thus potentially highly neurotoxic.\textsuperscript{31} At the present time, none of the patients has experienced late neurologic complication, as evaluated by frequent (see the Patients and Methods) physical examination, CT scan, or MRI after the completion of the treatment. This apparently low incidence could be related to the administration of intrathecal and systemic chemotherapy before radiotherapy in this protocol, which has been reported to be possibly less neurotoxic than other combination modalities, such as simultaneous intrathecal methotrexate and radiotherapy.\textsuperscript{31} However, a longer follow-up will be needed to evaluate the risk of long-term neurotoxicity with the CSR regimen, because late neurologic toxicity, in particular leukoencephalopathy, may occur late after the initial treatment.\textsuperscript{31}

In conclusion, the CSR regimen is highly efficient in PCL and yields a projected 2-year survival rate of 70% in the whole group and of 88% in a properly selected subgroup of patients. These results compare favorably with those of previous reports and confirm that BBB-permeable chemotherapy regimens may improve survival in patients with PCL. The toxicity of the CSR regimen is manageable except in the subgroup of patients more than 60 years of age who had an IPI of 4, for whom less-intensive chemotherapy regimens should be considered.

REFERENCES
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The C5R protocol: a regimen of high-dose chemotherapy and radiotherapy in primary cerebral non-Hodgkin's lymphoma of patients with no known cause of immunosuppression [see comments]

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