High rate of prolonged remissions following combined modality therapy for patients with localized low-grade lymphoma


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Summary

Purpose: Involved field (IF) radiation can cure as many as 40% to 50% of patients with stage I-II low-grade lymphoma. We sought to improve these results by prospectively evaluating the combination of IF radiation and chemotherapy consisting of 10 courses of cyclophosphamide, vincristine, prednisone, and bleomycin, with doxorubicin added in a risk-adapted manner (COP/CHOP-Bleo).

Patients and methods: From 1984 until December 1992, 91 patients, median age 56 years (range 28 to 77 years), with clinical stage I-II low-grade lymphoma were treated. No patients were excluded on the basis of age or organ function.

Results: A complete response was attained in 99% of evaluable patients. Treatment-related toxicity was mild, and no deaths occurred during therapy. With a median follow-up of 60 months, there have been only 16 relapses. The actuarial freedom from relapse rate at five years is 82% (95% confidence interval 71% to 89%) and at 10 years is 73%. At five years the overall survival rate is 90% (95% confidence interval 81% to 95%) and at ten years it is 82%. Of the clinical features examined, only older age (>56 years; p = 0.07) was associated with shorter survival. No features examined were predictive of disease relapse.

Conclusion: The combination of IF radiation and risk-adapted COP/CHOP-Bleo chemotherapy is well-tolerated, produces a very high rate of complete remission, and with a median follow-up of five years, has produced lower rates of relapse and better overall survival than has been reported for IF radiation alone in patients with clinically-staged I-II low-grade lymphoma.

Key words: combined chemotherapy-radiotherapy, follicular small cleaved cell lymphoma, stage I-II low-grade lymphoma

Introduction

Since the low-grade lymphomas [1] are usually disseminated at the time of presentation, reported experience with stage I-II disease consists mainly of retrospective reviews of relatively small numbers of patients. These lymphomas are radiosensitive [2], and numerous investigators have documented the efficacy of involved field (IF) radiation therapy in stage I-II disease. Some centers, notably the Princess Margaret Hospital [3, 4], have accumulated experience in treating a large number of patients over many years. This group has recently reported [4] the results of IF radiation in 285 patients with clinical stage I-II low-grade lymphoma. With a median follow-up of 11 years, these patients have a 10-year actuarial relapse-free survival rate of 52% and a 10-year overall survival rate of 65%. Results such as these have led to IF radiation being considered the standard of care in this setting [5].

Occult disease may contribute significantly to relapse in patients with clinical stage I-II disease treated with IF radiation, as most relapses occur outside the radiation fields [4, 6]. Magnetic resonance imaging [7] or surgical staging by laparotomy [8, 9] may detect more widespread disease than is otherwise suspected. For patients whose lymphoma is characterized by bcl-2 gene rearrangement, the polymerase chain reaction (PCR) is an extremely sensitive method of detecting subclinical rearranged cells. Many clinical stage I-II follicular low-grade lymphoma patients have been shown by PCR to have cells with bcl-2 gene rearrangement in the bone marrow or blood at the time of diagnosis [10, 11]. But persistence of such rearranged cells after treatment has been clearly described in patients in long-term remission after radiation therapy [12], so PCR positivity does not necessarily indicate active disease. Both staging laparotomy and extended radiation fields have been employed with the intent of detecting and eradicating these sites of occult disease [13-15]. These studies have clearly shown an improved outcome for patients with laparotomy-staged compared to clinically-staged disease; however, the superiority of extended-field or total lymphoid irradiation over IF remains unsubstantiated, despite increased toxicity [6, 13-15].

An alternative approach to improve upon the effi-
cacy of IF radiation is the use of the combination of chemotherapy and radiation. In retrospective analyses, our group [16] and others [17] have suggested a superior outcome for patients treated with IF radiation and multi-agent chemotherapy. However, the few reported randomized studies that have compared IF radiation with combined modality therapy in stage I–II low-grade lymphoma have failed to confirm any statistically significant benefit for combined modality treatment [15, 18–22]. The largest of these studies was from the B.N.L.I. using low intensity oral chlorambucil for six months following IF radiation [22]. There was a non-significant trend towards fewer relapses in the combination arm (p = 0.14) without any survival benefit evident. The randomized studies that have examined multi-agent chemotherapy regimens all lacked meaningful statistical power to detect any difference, with no single study enrolling more than 26 patients with low-grade histology. Given the indolent natural history of these disorders and the rarity of localized presentations, it is unlikely that single-institution randomized trials can address this question in a timely manner.

Since 1984 we have evaluated prospectively the combination of IF radiation and multi-agent chemotherapy in patients with clinical stage I–II low-grade lymphoma. This report updates and extends the interim results published previously [23].

Patients and methods

Eligibility

Between February 1984 and December 1992, 114 patients with previously untreated Ann Arbor stage I–II low-grade lymphoma [1] were enrolled on this prospective study. At the time of initiation of the study, patients with two recently-described histologic variants not recognized as distinct entities within the International Working Formulation [1] were enrolled: 11 patients with lymphoma of mucosa-associated lymphoid tissue (MALT), and four patients with mantle cell lymphoma of mantle zone pattern [24]. With the recent recognition of the distinct natural history of these diseases, these patients have been excluded from this analysis and are reported separately [25]. There were no restrictions on the basis of patient age, organ function, or prior malignancy. All patients gave written informed consent in accordance with institutional policy. Of the remaining 99 patients enrolled on the study, eight patients were ineligible or inevaluable because of intermediate grade histology on pathology review in two, stage III-IV disease in four, and refusal of all therapy in two. The remaining 91 eligible and evaluable patients were included in all subsequent analyses.

Staging

The staging evaluation included computed tomography of the abdomen and pelvis, bipedal lymphangiography, or both, and bone marrow aspiration and biopsy (usually bilateral), in addition to a thorough history and physical examination. Staging laparotomy was performed in only one patient. After October 1985 serum β2-microglobulin determination was added to the pretreatment evaluation. Other imaging studies were performed as indicated in individual patients.

Follow-up evaluations were performed at three- to four-month intervals for the first two to three years and at yearly intervals there-

Therapy

Treatment included three cycles of chemotherapy, followed by IF radiation, and an additional seven cycles of chemotherapy for a total of 10 cycles (Fig. 1). When the abdomen was affected it was considered as two regions: the upper two-thirds, and the pelvis. The first region, usually the upper two-thirds, was irradiated after the initial three cycles of chemotherapy. The second region was treated between the six and seventh cycle of chemotherapy [23].

Chemotherapy consisted of cyclophosphamide 1000 mg/m², vincristine 1.4 mg/m² (maximum dose 2.0 mg), and bleomycin total dose 15 units; all given intravenously on day one, and prednisone 60 mg/m² given orally daily for five days (COP-Bleo). Chemotherapy cycles were repeated every 21 days, provided the patient's absolute neutrophil count was above 1.5 x 10⁹/µl and platelet count was above 100 x 10⁹/µl. Patients with any high-risk features [16], including extranodal involvement, bulky disease (adenopathy of 5 cm or more in the largest diameter), diffuse small lymphocytic lymphoma, or an elevated serum lactate dehydrogenase (LDH) level, additionally received doxorubicin 50 mg/m² intravenously on day one, with the cyclophosphamide dose reduced to 750 mg/m² (CHOP-Bleo). Doxorubicin was discontinued if there was any evidence of cardiac toxicity, or after a total dose of 450 mg/m². Bleomycin was not given to patients older than 60 years or to four patients with severe pre-existing pulmonary disease, and was discontinued if there was any evidence of pulmonary toxicity. Cyclophosphamide and doxorubicin dosages were reduced by 20% following abdominal radiation, in anticipation of reduced tolerance of myelosuppressive chemotherapy.

Radiotherapy for supradiaphragmatic disease using 6-MeV linear accelerator or cobalt 60 radiation was limited to the affected lymph node-bearing regions. The full mantle was not used unless the mediastinum was involved. Treatment to supradiaphragmatic fields was administered at a rate of 2 Gy per fraction to a total of 40 Gy in four weeks.

Treatment to the abdomen or pelvis was given at a rate of 1.5 Gy per fraction to a total of 30 Gy. The treatment fields for the upper two thirds of the abdomen extended from the dome of the diaphragm to the iliac crests. The right lobe of the liver was shielded anteriorly and posteriorly with five half-value layers of lead. The kidneys were shielded posteriorly with two HVL to reduce the received dose to approximately 18 Gy. Residual disease in the para-aortic and pelvic regions received additional 'boost' treatment of 10 Gy through reduced fields. In treatment of the pelvis, the inguinal

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**TREATMENT SCHEMA**

COP - Bleo x 3

x

XRT (Involved Field)

COP - Bleo x 7

- CHOP - Bleo was used for high risk patients ("E" sites; high LDH; bulky abdominal disease)

- XRT: Involved field 4000 cGy for upper torso sites, 3000 cGy for lower torso; for whole abdomen, XRT delivered in 2 sessions (upper 2/3; pelvis) in sandwich fashion, after the 3rd and 6th chemotherapy cycles

**Fig. 1.** Outline of planned treatment.
and femoral nodes were included in the anterior field only. However, the dose to these regions was supplemented through anterior involved fields.

**Data analysis**

Complete remission (CR) was defined as complete resolution of all clinical, radiographic, and endoscopic evidence of disease for a minimum of two months. Patients with stable minimal residual radiographic abnormalities at the site of previously bulky disease within the abdomen were considered to have an 'unconfirmed' CR (CRu) [26]. Partial remission (PR) was defined as a more than 50% reduction in the sum of the products of the two largest perpendicular diameters of all measurable lesions lasting a minimum of two months. Overall survival (OS) and relapse-free survival (RFS) were calculated from the date of commencement of therapy using the method of Kaplan and Meier. Comparisons were made using the log-rank method. All causes of death were included in the overall survival analysis. However, patients who died with no evidence of disease were censored in the analysis of RFS at the time of their death. Categorical data were compared using the x-square test. All p values given are two-sided.

**Results**

**Patient characteristics**

The clinical features of the 91 patients are presented in Table 1. The median age was 56 years (range 28 to 77 years). Patients with follicular mixed histology had a higher incidence of elevated LDH levels (29%) than patients with other histologies (13%) (p = 0.09). Extranodal involvement was more common in patients with diffuse small lymphocytic histology (86%) than in patients with either follicular mixed (14%; p < 0.01) or follicular small cleaved cell lymphoma (29%; p < 0.01). The incidence of bulky (≥5 cm) disease was greatest among those patients with follicular mixed histology (43%); this was significantly different from patients with other histologic types (21%; p = 0.05). Based on the risk-adapted guidelines prospectively defined by the protocol, 48 patients were allocated to receive COP-Bleo and 43 CHOP-Bleo.

**Table 1. Clinical features of patients.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>DSL (8)</th>
<th>FSC (63)</th>
<th>FM (21)</th>
<th>Total (91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5 (71)</td>
<td>23 (37)</td>
<td>11 (52)</td>
<td>39 (43)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (57)</td>
<td>30 (48)</td>
<td>7 (33)</td>
<td>41 (45)</td>
</tr>
<tr>
<td>II</td>
<td>3 (43)</td>
<td>33 (52)</td>
<td>14 (67)</td>
<td>50 (55)</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>0 (0)</td>
<td>4 (6)</td>
<td>1 (5)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Extranodal sites</td>
<td>6 (86)</td>
<td>18 (29)</td>
<td>3 (14)</td>
<td>27 (30)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>1 (14)</td>
<td>8 (13)</td>
<td>6 (29)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>β2-M ≥ 3 mg/l</td>
<td>0/7 (0)</td>
<td>4/50 (8)</td>
<td>0/12 (0)</td>
<td>4/69 (6)</td>
</tr>
<tr>
<td>Bulky tumor</td>
<td>1 (14)</td>
<td>14 (22)</td>
<td>9 (43)</td>
<td>24 (26)</td>
</tr>
</tbody>
</table>

DSL = diffuse small lymphocytic; FSC = follicular small cleaved; FM = follicular mixed.

* Normal range ≤ 2.0 mg/l; data available for 69 patients.

**Response**

Twenty-two patients (24%) had no evaluable disease following the diagnostic biopsy. Of the 69 patients with measurable disease, 66 (96%) attained a CR, and two (3%) attained a CRu. In subsequent analyses these 68 patients were considered collectively as having attained a CR. The single remaining patient attained a PR. Because the CR rate was so high, it was not possible to identify factors associated with response. The one patient who did not attain a CR had stage I follicular mixed lymphoma with an abdominal mass of greater than 10 cm diameter with elevated levels of both LDH and β2-microglobulin.

**Relapse-free survival**

The median duration of follow-up of surviving patients was 60 months (range 20 to 127 months). Disease relapse has occurred in 16 patients, including the one patient who attained a PR. At five years the actuarial RFS rate for all 91 patients was 82% (95% confidence interval 71% to 89%, Fig. 2). Of the 16 relapses observed, 14 (88%) occurred within the first five years. Patients who had no evidence of disease at the initiation of therapy were as likely to develop relapsing disease as those who attained a CR (p = 0.4). Patients who were older than 56 years, the median age of the group, had a marginally inferior RFS compared to younger patients (76% vs. 88% at 5 years; p = 0.12). The risk of relapse was not influenced significantly by gender, histology (Fig. 3), Ann Arbor stage, B-symptoms, upper compared to lower torso presentations, bulky disease (>5 cm), extranodal disease, serum β2-microglobulin values ≥3 mg/l, or an elevated serum LDH level (p > 0.3 for all comparisons, Table 2).

**Sites of failure**

Of the 16 relapses that have occurred, three recurred first at the sites of initial disease. Two of these three patients did not receive radiation therapy, one on the
performed at relapse. At five years the actuarial overall survival was 79% (95% confidence interval 78% to 81%) (Fig. 2). Patients who were older than 56 years had a marginally inferior survival compared to younger patients (83% vs. 98% at five years; p = 0.07). Both intercurrent illnesses (three deaths among 45 older patients, compared to one death among 46 younger patients) and disease-related deaths (four and two, respectively) contributed to the observed difference. The following features did not correlate with survival: gender, histology, Ann Arbor stage, upper compared to lower torso presentation, B-symptoms, bulky disease, extranodal disease, serum LDH level (p > 0.14 for all comparisons, Table 2). Survival rate, including all causes of death, was 90% (95% confidence interval 81% to 95%) (Fig. 2). Patients who were older than 56 years had a marginally inferior survival compared to younger patients (83% vs. 98% at five years; p = 0.07). Both intercurrent illnesses (three deaths among 45 older patients, compared to one death among 46 younger patients) and disease-related deaths (four and two, respectively) contributed to the observed difference. The following features did not correlate with survival: gender, histology, Ann Arbor stage, upper compared to lower torso presentation, B-symptoms, bulky disease, extranodal disease, serum LDH level (p > 0.14 for all comparisons, Table 2).

Complications and treatment modifications

Therapy for nine patients diverged significantly from protocol requirements. Radiation was omitted in five patients (5.5%)—two on the recommendation of the treating physician (one because of the risk of intra-abdominal adhesions in the setting of prior abdominal surgery, and one because of prior abdominal radiation therapy for a retroperitoneal sarcoma), and three due to patient refusal. One patient refused chemotherapy and was treated with IF radiation only, and two patients refused to continue chemotherapy after three cycles in the absence of objective toxicity.

The program was generally very well tolerated. Modest myelosuppression, mainly neutropenia, was the most commonly observed toxicity. For 626 cycles of chemotherapy that were evaluable for toxicity, brief neutropenia of less than 1.0 × 10^9/μl occurred in 40% of cycles (<0.5 × 10^9/μl in 21%). Thrombocytopenia of less than 100 × 10^9/μl occurred in only 5% of cycles. Hematologic tolerance of therapy following radiation,
with appropriate dose modifications, was not qualitatively different.

No patients died during therapy, and only eight patients (8.8%) required hospital admission for the treatment of complications: neutropenic fever (eight episodes), pneumonia (two), uncontrolled diabetes (one), and diverticulitis (one). Other toxicities, generally of grade 1 or 2, were observed in 45 patients (49%) (Table 3). The three cases of radiation pneumonitis resolved with corticosteroid therapy. In 18 patients (20%), 22 drugs were withdrawn prior to the planned completion of therapy due to a perceived increased risk of toxicity. The drugs involved were doxorubicin in two cases, bleomycin in ten, vincristine in eight, prednisone in one, and cyclophosphamide in one.

**Table 3. Nonhematologic toxicity of therapy.**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of episodes observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic neuropathy</td>
<td>19</td>
</tr>
<tr>
<td>Dermatomal herpes zoster</td>
<td>12</td>
</tr>
<tr>
<td>Symptomatic cardiac failure</td>
<td>2</td>
</tr>
<tr>
<td>Symptomatic bleomycin toxicity</td>
<td>1</td>
</tr>
<tr>
<td>Venous thrombosis (catheter-related in 2)</td>
<td>3</td>
</tr>
<tr>
<td>Cystitis attributed to cyclophosphamide</td>
<td>3</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>3</td>
</tr>
<tr>
<td>Pancreatitis during radiation</td>
<td>1</td>
</tr>
<tr>
<td>Arterial stenosis in the irradiated field</td>
<td>2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6</td>
</tr>
<tr>
<td>Myelodyplasia</td>
<td>2</td>
</tr>
</tbody>
</table>

**Second malignancies**

The case of myelodysplasia, occurring three years after therapy, and the case of refractory anemia with ringed sideroblasts eight years after therapy, in whom marrow cytogenetics were normal, are both considered treatment-related deaths. Five other patients have developed second malignancies after therapy for their lymphoma: two were lung carcinomas in ex-smokers, two were gastrointestinal (colon and stomach), and one was Kaposi’s sarcoma involving the foot.

**Discussion**

The aim of the present trial was to maintain the very high local control rate achieved with IF radiation in patients with stage I–II low-grade lymphoma, and to reduce the risk of out-of-field relapse by the addition of combination chemotherapy. Our results suggest this has been a successful strategy. Only three patients have developed localized recurrence within the irradiated field. At ten years the projected overall survival was 82%, and RFS rate was 73%. There were no deaths during treatment and tolerance of the program was excellent.

These results with combined modality therapy appear superior to reported results with IF radiation only in patients with clinical stage I–II low-grade lymphoma. In more than 650 patients treated with IF radiation only, the reported actuarial probability of remaining free of progressive disease has ranged from 40% to 65% at five years, and from 45% to 62% at ten years [3, 4, 13–21, 27, 28]. The two largest studies, of 105 and 285 patients, from Stanford [13] and the Princess Margaret Hospital [4], respectively, illustrate optimal results with standard IF radiation. The Stanford group [13] reported actuarial RFS rates at five and ten years of 62% and 54%, respectively. Gospodarowicz et al. from the Princess Margaret Hospital [3, 4] described similar results in 285 patients, with 52% and 48% remaining free of relapse at 10 and 15 years, respectively.

The sites and timing of disease relapse have also been remarkably similar in reported IF radiation series. Approximately 75% of all relapses occur within the first five years of treatment [3, 4, 13, 17, 27], and 80% to 90% of those relapses have been located outside the areas of initial disease involvement [3, 4, 13–21, 27, 28]. In studies of large series of patients followed for ten to 25 years, 80% to 85% of patients continuously free of disease at five years will never develop a relapse [3, 4, 13, 27]. Therefore, the doses of 30 to 40 Gy of radiation administered are adequate to achieve excellent durable local disease control, and initially occult disease remains the major clinical problem.

Based on the fact that many patients with clinically staged I–II low-grade lymphoma have occult abdominal disease at laparotomy [8, 9], we chose to investigate the addition of chemotherapy to IF radiation. We selected COP/CHOP-Bleo because of our favorable prior experience with this combination, its relative simplicity of administration and low toxicity [16]. It is uncertain whether other chemotherapy regimens with similar efficacy in the treatment of low-grade lymphomas, for example those incorporating fludarabine [29], may be similarly useful in combined modality programs. It has been established, however, that six months treatment with single agent oral chlorambucil does not dramatically improve patient outcome following IF radiation [22].

The role of more extensive radiation fields in the treatment of patients with stage I–II low-grade lymphoma is unresolved. Paryani et al. [13] reported that extended fields, perhaps better defined as regional fields, were no more effective than IF. This group [13] also suggested that total lymphoid irradiation could yield improved RFS. However, this conclusion was based on the outcome of a cohort that contained a high proportion of patients with laparotomy-staged disease, whose outcome is inherently more favorable than that of patients with clinically-staged disease. In their ongoing randomized trial of IF compared to total lymphoid irradiation utilizing laparotomy-staging, Paryani et al. [13] had not observed any significant differences in RFS or overall survival at the time of their most recent report. Clearly this issue would need to be
addressed in patients with clinically-staged disease in a larger controlled clinical trial.

In previous studies of IF radiation alone in patients with early stage low-grade lymphoma, the following parameters were found to predict an increased risk of relapse: extranodal disease [16], an elevated serum LDH level [16], bulky disease [4], follicular mixed histology [4], diffuse small lymphocytic histology [27], age above 40 [12] or 45 years [27], stage II disease [27, 28], and 'discontiguous' sites of involvement [3, 4]. Similarly, independent predictors of a lower survival rate following IF radiation alone included stage II disease, increasing age, follicular mixed histology, B-symptoms, and bulky disease [4]. In the current study only advanced age had a marginal correlation with an inferior RFS and overall survival. No other patient or disease features were identified that predicted an inferior outcome. Thus, the addition of risk-adapted combination chemotherapy may have been of particular benefit to patients with adverse risk factors.

The outcome for the 22 patients with no evidence of disease at the initiation of therapy was somewhat surprising. Although these patients may have been anticipated to have the most favorable outlook, their outcome was not different from those patients with residual clinically evident disease after diagnostic biopsy. Therefore, the inclusion of these patients cannot account for the favorable overall outcome of the entire cohort. Further, our results emphasize that patients who have no evidence of disease following the diagnostic biopsy should be treated identically to other patients with low-grade stage I–II disease.

Does the addition of chemotherapy to IF radiation merely delay relapse, or does it truly improve long-term disease-free survival? There are three published studies of combined modality therapy involving 95 patients with follow-up well beyond five years [15, 17, 22]. In the studies of Gomez et al. [15] and Richards et al. [17] patients were fully staged and followed for up to 13 (median ten) years, and ten (median five) years, respectively. In neither study were any relapses observed beyond five years. The larger study of Kelsey et al. [22] did not utilize CT-scanning or lymphangiography in staging. Despite the consequent probability of understaging a fraction of patients, no evidence of an increased incidence of late relapses was seen in the combined modality treatment arm; 78% of those patients relapse-free at five years remained so at ten years, with a very mature median follow-up of 12 years (maximum 18 years). Thus the available data suggest that the relapse pattern following combined modality therapy is similar to that observed following IF radiation therapy alone. Our current report, with a median follow-up of five years, has RFS results that are concordant with our preliminary report [23]. Currently thirty-three of our patients have been followed for more than five years in ongoing first CR and thus are beyond the period of anticipated highest risk of relapse. Continued observation of this cohort of patients will be important to determine conclusively the percentage of patients ultimately cured with combined modality treatment, as well as to define any late sequelae of therapy.

The observed plateau in RFS of between 40% and 50% in numerous reports of treatment with IF radiation alone strongly suggests that patients with stage I–II low-grade lymphoma can be cured. With the risk-adapted program of COP-Bleo or CHOP-Bleo chemotherapy and IF radiation described in this report, the fraction of patients in long-term remission is above 70%. We are hopeful that the integration of IF radiation with this relatively modest and well tolerated chemotherapy program may lead to an improvement over the 40%–50% cure rate that can be achieved with IF radiation alone.

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163


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