

differentiation, suggesting that the induction of the differentiation is related with the expression of the RANKL gene in ATLL cells. Cell differentiation was suppressed by osteoprotegerin/Fc, an inhibitor of RANKL, suggesting that such differentiation occurred through the RANK-RANKL pathway. In addition, direct contact between ATLL cells and hematopoietic precursor cells was essential for the differentiation, suggesting that membrane-bound RANKL rather than the soluble form plays a role in this process. The authors claimed that ATLL cells induce the differentiation of hematopoietic precursor cells to osteoclasts through RANKL expressed on their surface, in cooperation with macrophage colony-stimulating factor, and that they ultimately cause hypercalcemia. The etiology of hypercalcemia in ATLL is likely to be multifactorial and in individual patients is probably due to some combination of the factors just described.

Elevated serum levels of soluble interleukin-2 receptor in patients with ATLL, especially in those with the acute or lymphoma subtype, have been noted in several studies.<sup>65</sup> The serum level of soluble interleukin-2 receptor is suggested to be one of the useful markers for evaluating the clinical aggressiveness of the disease and for monitoring the response to therapy in patients with ATLL.

### Histopathology

The circulating cells in the peripheral blood have markedly polylobed nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm—the so-called flower cells that are characteristic of ATLL (Fig. 114-3).<sup>55</sup> A considerable diversity of morphology among ATLL cells has been recognized, however. Tsukasaki and associates<sup>66</sup> investigated the morphology of ATLL cells in 36 acute cases and 14 chronic cases. Chronic lymphocytic leukemia-like morphology with round nuclei was more frequent in the chronic type than in the acute type. In contrast, unusual morphology (lymphoblastic, vacuolated, granular pleomorphic, or large cells) was more frequent in the acute type than in the chronic type.

The swollen lymph nodes in patients with ATLL show diffuse infiltration of various histologic subtypes, including pleomorphic, large cell, mixed cell, or medium-sized cell types.<sup>67,68</sup> Figure 114-4 shows the histology of a biopsied swollen lymph node from a patient with lymphoma-type ATLL. The pleomorphic pattern (i.e., mixture of various-sized lymphoma cells from small cells to giant cells) and nuclear polymorphism are recognized. Lymph nodes from some patients in the incipient or early neoplastic phase of ATLL histologically resemble those that are found in Hodgkin's lymphoma.<sup>69-71</sup>

ATLL cells frequently involve the skin. Generalized nodular or subcutaneous eruptions, as shown in Figure 114-5A, are common; however, tumorous lesions are also recognized in some patients. Symptomatic plaque formation and sometimes nodular tumors are other cutaneous manifestations.<sup>71,72</sup> Histologically, diffuse or patchy infiltration of atypical lymphoid cells—usually small or medium in size with polymorphic nuclear contours in the upper dermis, sometimes with an intraepidermal infiltration—is noted (Fig. 114-5B). Large nuclear cells with highly irregular or cerebriform features are intermingled in some cases.

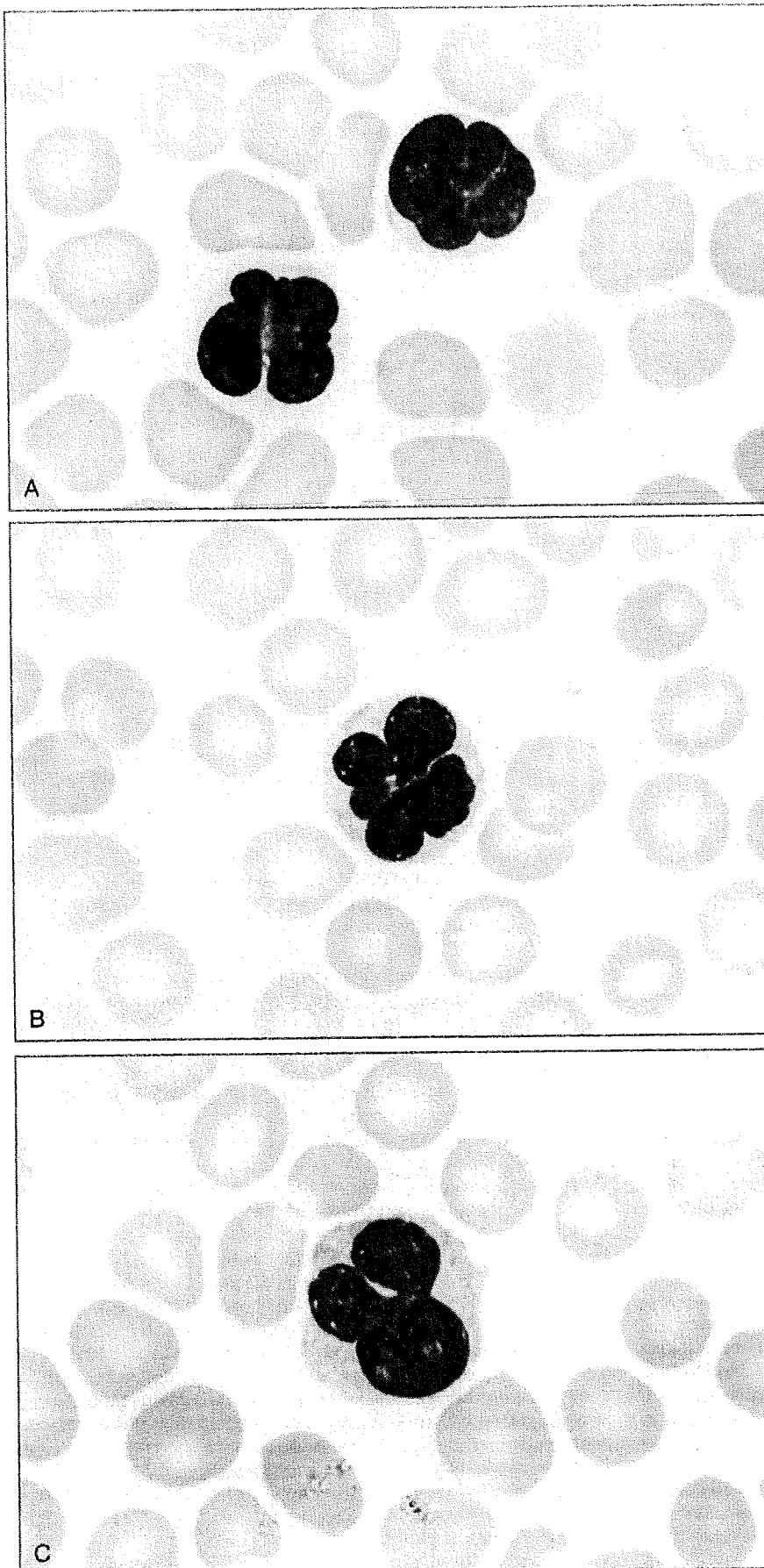
One of the difficult issues in the diagnosis of ATLL is its relationship with other peripheral T-cell malignancies that are not associated with HTLV-I. The clinical diagnosis of ATLL is suspected by the unique combination of its clinical and pathologic features. One of the T-cell malignancies that is likely to be confused with ATLL is mycosis fungoides/Sézary syndrome (MF/SS). Because cutaneous involvement is frequent in ATLL, the differentiation of smoldering-type ATLL from MF/SS is often difficult on the basis of the clinical manifestations alone. In the differential diagnosis of ATLL and other peripheral T-cell malignancies, HTLV-I serology and the molecular detection of the monoclonal integration of HTLV-I proviral DNA

are important. Various kinds of serologic assays have been used, including the immunofluorescence assay, the particle agglutination assay, the enzyme-linked immunosorbent assay (ELISA), and the Western blot assay. In general, a particle agglutination assay or ELISA is useful as a screening test, and Western blotting is used for the confirmation of the presence of serum antibody to HTLV-I. As shown in Figure 114-6, the demonstration of the monoclonal integration of HTLV-I proviral DNA by Southern blot analysis can lead to a definite diagnosis of ATLL.

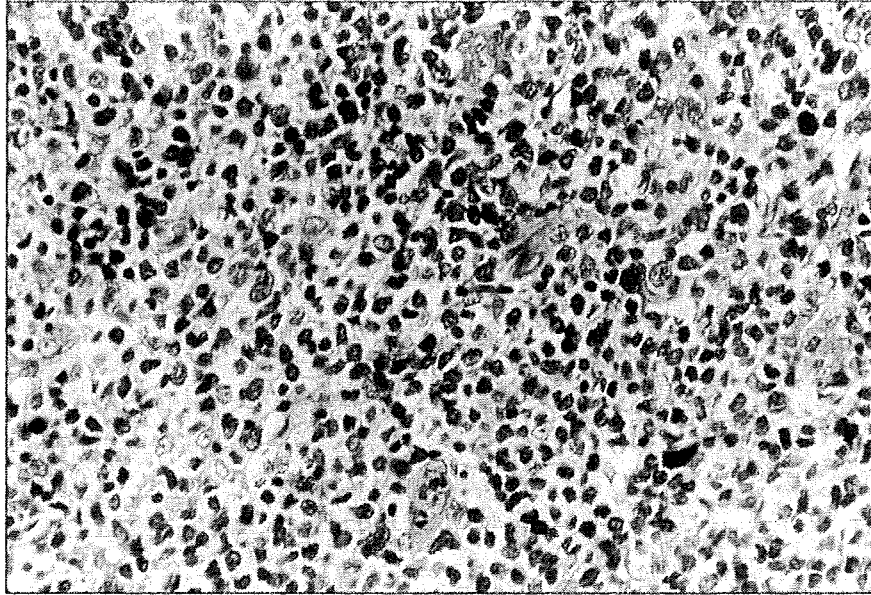
Several studies have reported the presence of seronegative HTLV-I carriers, and some HTLV-I carriers have been reported to be negative for serum anti-HTLV-I antibodies against viral structural proteins on screening examinations.<sup>73</sup> Kinoshita and associates<sup>74</sup> examined peripheral blood mononuclear cells from 209 healthy subjects living in an HTLV-I-endemic district in Japan for HTLV-I provirus, using PCR. A total of 76 subjects were positive for the provirus and 133 were negative, showing a close correlation with the results of the previously mentioned assays for anti-HTLV-I serum antibodies. None of the seronegative subjects reacted positively in PCR analysis. Infrequent HTLV-I infection among seronegative subjects in Japan was also suggested by the finding that the screening of blood donors for serum HTLV-I antibodies by the PA assay has reduced markedly the risk of HTLV-I transmission by blood transfusions.<sup>75</sup> Furthermore, by using PCR analysis, the absence of seronegative HTLV-I carriers among blood donors and healthy junior high school students in Japan was confirmed.<sup>76</sup> These observations suggest that seronegative HTLV-I carriers are extremely rare, although the possibility of their existence remains.

In Western countries, it has been reported that the HTLV-I viral genome was detected in the genomic DNA from patients with MF/SS, and a causal relation between HTLV-I and MF/SS was proposed.<sup>77,78</sup> An opposite conclusion was reached in a Japanese study; using PCR with four sets of primers (including *gag*, *pol*, *env*, and *pX* regions of HTLV-I), Kikuchi and colleagues<sup>79</sup> investigated both fresh and cultured T cells (128 specimens) derived from 50 Japanese patients with CTCL. In their study, none of the 128 DNA samples revealed positive results for HTLV-I. They concluded that CTCL, which does not include HTLV-I, is present in Japan. The absence of a correlation between HTLV-I and CTCL was confirmed by an international cooperative study reported by Bazarbachi and coworkers.<sup>80</sup> These researchers analyzed 128 patients (85 with MF, 28 with SS, 5 with Sézary cell leukemia, 4 with lymphomatoid papulosis, and 5 with unspecified CTCL) originating from Europe (France, Spain, United Kingdom, or Portugal) or from the United States (California) for the presence of HTLV-I infection markers, using a serologic analysis for antibody to HTLV-I, a reverse transcriptase assay, and a molecular analysis with PCR-amplified specimens. The results of this international study suggest that MF and SS are not associated with HTLV-I infection.

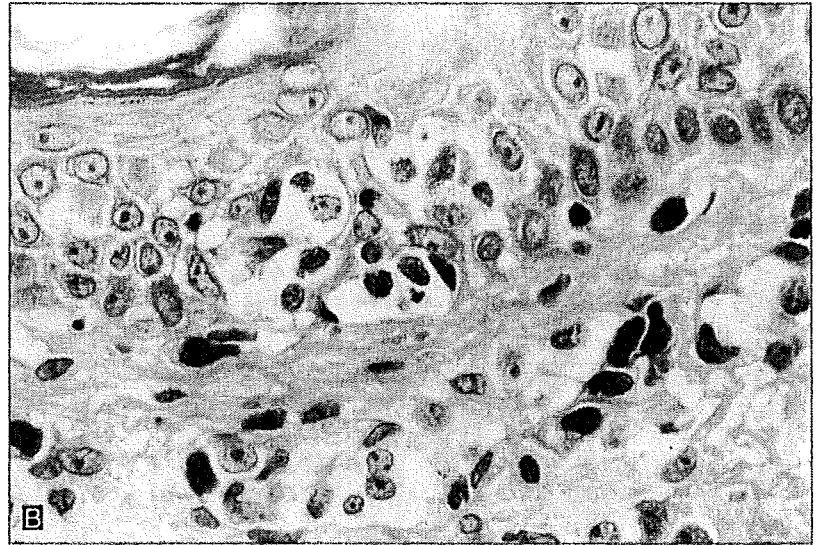
HTLV-I can infect lymphoid cells of different cell lineages in vitro, but the neoplastic cells in the great majority of ATLL cases exhibit the phenotype of mature CD4-positive T cells.<sup>81</sup> Malignant cells from the peripheral blood or from involved lymph nodes express CD2, CD3, CD4, CD5, the  $\alpha\beta$ -chains of the TCR, CD25 (IL-2R $\alpha$ ), CD45, CD29, and HLA-DR.<sup>82,83</sup> It is known that the expression of the CD3/TCR complex is decreased in ATLL cells.<sup>84</sup> Most ATLL cells lack CD7. Considerable phenotypic heterogeneity has been found in the neoplastic cells of ATLL. Although the most common phenotype is CD4-positive/CD8-negative, some patients with ATLL exhibit a CD4-positive/CD8-positive, CD4-negative/CD8-positive, or CD4-negative/CD8-negative phenotype. In addition, some patients with ATLL show phenotypic changes throughout the course of their disease. As regulatory T cells (Treg cells) express CD4-positive and CD25-positive molecules and possess potent immune response suppressive activity, several investigators analyzed a possible link between ATLL cells and Treg cells and found that forkhead/winged helix transcription factor (FoxP3), a



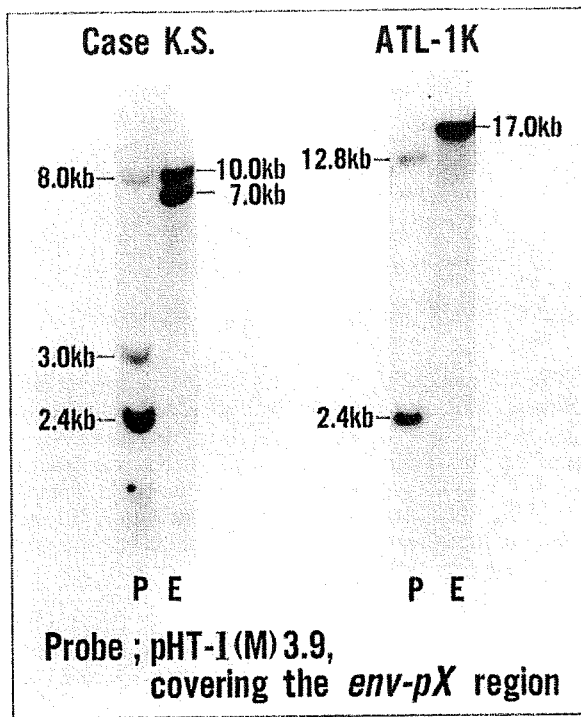
**Figure 114-3** • A-C, Leukemic cells (the so-called flower cells) showing characteristic polymorphic nuclei in a peripheral blood smear from a patient with acute-type ATLL.



**Figure 114-4** • Histology of a swollen lymph node from a patient with lymphoma-type ATLL, showing diffuse non-Hodgkin's lymphoma of the pleomorphic type. Lymphoma cells of various sizes—small cells, medium-size cells, large cells, and giant cells—are present. Nuclear polymorphism is present in most lymphoma cells.



**Figure 114-5** • Skin involvement of ATLL. **A**, Photograph of skin lesions in a patient with acute-type ATLL. **B**, Histology of skin infiltration of ATLL cells in the same patient; infiltrating leukemic cells are present in the epidermis.



**Figure 114-6** • Southern blot analysis of HTLV-I proviral DNA in peripheral blood mononuclear cells from an ATLL patient. The genomic probe, pHT-I (M) 3.9, covering the *env-pX* region, was used. ATL-1K, a cultured cell line from ATLL, was used as a positive control. The restriction enzymes Pst I (P) and EcoRI (E) were used. In the cellular DNA from this patient, two bands are present in the EcoRI digest, indicating the monoclonal integration of HTLV-I proviral DNA.

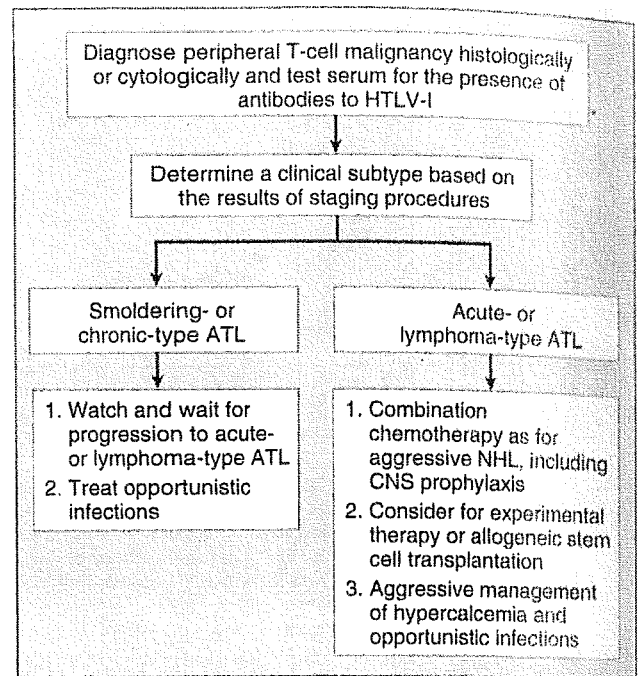
specific marker that is important for the function of Treg, on most ATLL cells. These results suggest the origin of ATLL cells to be derived from Treg.<sup>85-87</sup>

One of the remarkable features of ATLL cells (and of most HTLV-I-infected cells) is the expression of IL-2R. Both the  $\alpha$ - and  $\beta$ -chains of IL-2R are expressed on the surface of ATLL cells. It is postulated that IL-2 and IL-2R are implicated in the pathogenesis of ATLL. IL-2R is expected to be an excellent target for monoclonal antibody therapy.<sup>88</sup>

## CLINICAL COURSE AND TREATMENT

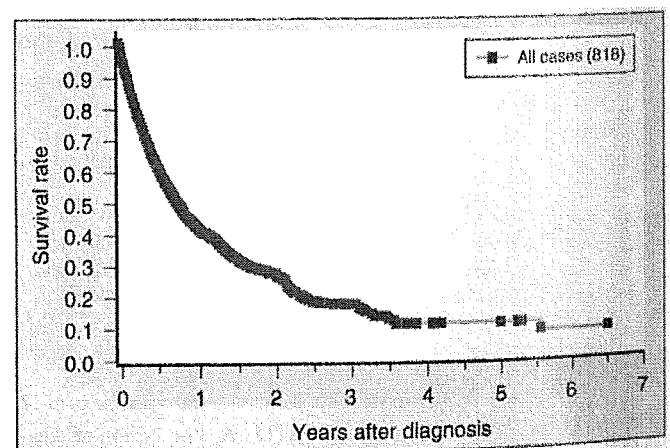
ATLL most often pursues the prototypic acute course; however, approximately one fourth of patients show a more indolent course (chronic and smoldering types), with disease limited predominantly to the peripheral blood and/or skin. These patients might experience multiple infections but can remain free of disease progression for many years.<sup>55</sup> These indolent diseases frequently progress to full-blown acute or lymphomatous ATLL, an event that is sometimes called the crisis. Some studies have reported that various kinds of infectious episodes might predispose to the transformation from an indolent to an aggressive disease course. At present, however, it is impossible to identify patients at the highest risk of transformation (Fig. 114-7).

Most patients with ATLL are not curable with current treatment modalities, even at the early stage of disease. In addition, no treatment has been shown to prevent progression to a more aggressive disease. Patients with chronic- or smoldering-type ATLL should be watched carefully for the development of infectious complications and for signs of progression to acute or lymphomatous ATLL.

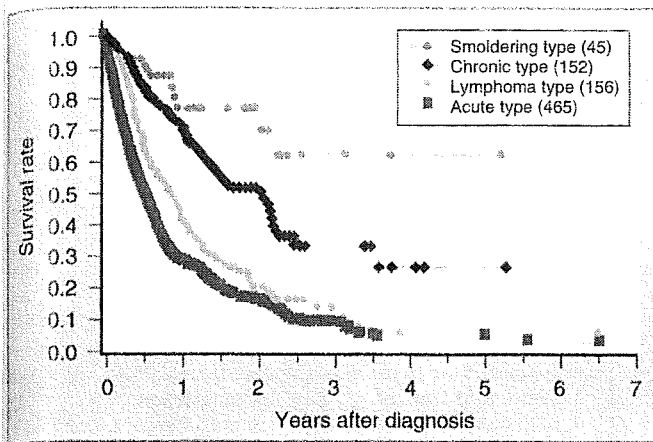


**Figure 114-7** • Approach to the patient with adult T-cell leukemia-lymphoma.

Without treatment, most previously untreated patients with aggressive forms (acute or lymphoma type) of ATLL die within weeks or months of diagnosis. The treatment of patients with acute or lymphomatous ATLL has not been very successful. Figure 114-8 shows the overall survival (OS) of 818 patients with ATLL regardless of disease subtype, and Figure 114-9 presents their survival curves according to the four clinical subtypes.<sup>55</sup> Some 85% of the patients received chemotherapy with one of a variety of different regimens. Most of the patients with smoldering-type ATLL lived well without chemotherapy for a long period. Approximately two thirds of the chronic-type patients died within about 2.5 years of diagnosis. Patients with lymphoma-type ATLL had poor prognoses, with an MST of 10.2 months. The most aggressive type of ATLL was the



**Figure 114-8** • Survival curves of 818 patients with ATLL. Number in parentheses indicates number of patients. (From Shimoyama M, and members of the Lymphoma Study Group, 1984-1987: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. *Br J Haematol* 1991;79:428.)



**Figure 114-9** • Survival curves of 818 patients with ATLL according to four clinical subtypes defined by the diagnostic criteria. Numbers in parentheses indicate number of patients. (From Shimoyama M and members of the Lymphoma Study Group, 1984–1987: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. *Br J Haematol* 1991;79:428.)

acute type, with an MST of 6.2 months. The projected 4-year survival rates of patients with the lymphoma and acute types were only 5%. The clinical subtype clearly determines the prognosis of each patient, suggesting that it can be used as a prognostic indicator for patients with ATLL.<sup>55</sup>

The Lymphoma Study Group (LSG) in Japan has analyzed prognostic factors for each subtype of ATLL.<sup>89–91</sup> In all patients with ATLL, advanced age (40 years or greater), poor performance status, high serum LDH, hypercalcemia, and four or more involved lesions were unfavorable factors. For patients with chronic-type ATLL, the major prognostic factors were the serum LDH, albumin, and blood urea nitrogen. Patients with chronic-type ATLL and normal values for the three factors (30% of patients with chronic type disease) showed a prognosis as good as that of patients with smoldering-type ATLL. Thus, patients with the favorable chronic type with normal LDH, albumin, and blood urea nitrogen values need not be treated immediately and can be placed on follow-up without treatment, whereas patients with the unfavorable chronic type who have an abnormal value in at least one of the three factors are candidates for cytotoxic chemotherapy<sup>91</sup> (Box 114-1).

### Clinical Trials by the Japan Clinical Oncology Group

Six consecutive chemotherapy trials focusing on ATLL have been conducted by the Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) since 1978.<sup>92–99</sup> The first trial, called LSG1 protocol (1978 to 1980), utilized VEPA therapy, which consisted of vincristine (VCR), cyclophosphamide (CPA), prednisolone (PSL), and doxorubicin (DOX). In this study, patients with NHL (including ATLL) at an advanced stage were enrolled. The complete remission (CR) rate was lowest (18%) for ATLL, intermediate (36%) for peripheral non-ATLL T-lymphoma (PNTL), and highest (64%) for B-cell lymphoma.<sup>92,93</sup> Between 1981 and 1983, the JCOG-LSG conducted a phase III trial using LSG1-VEPA versus LSG2-VEPA-M (VEPA + methotrexate) against advanced NHL, including ATLL.<sup>94,95</sup> Patients' sera were examined for anti-HTLV-I antibody to distinguish ATLL from PNTL.<sup>100</sup> The CR rate for patients who were given LSG2-VEPA-M for ATLL (37%) was higher than that for patients who were given LSG1-VEPA (17%;  $P = 0.09$ ). In the LSG1/LSG2 trial, however, the CR rate was significantly lower for ATLL than for B-cell lymphoma and PNTL ( $P < 0.001$ ). The MST of the 54 patients with ATLL treated with LSG1/LSG2 was 6 months, and the estimated 4-year survival rate was only 8%.<sup>94,95</sup>

These results suggest that CHOP-like chemotherapy of the first generation was not very effective against ATLL.

Between 1987 and 1991, the JCOG-LSG conducted a combination phase II study (JCOG8701) of a second-generation combination chemotherapy against advanced aggressive NHL (including ATLL). This combination chemotherapy, called LSG4, consisted of three different regimens:

1. VEPA-B-VCR, CPA, PSL, DOX, and bleomycin (BLM)
2. M-FEPA-methotrexate (MTX), vindesine (VDS), CPA, PSL, and DOX
3. VEPP-B-VCR, etoposide (ETP), procarbazine (PCZ), PSL, and BLM<sup>96</sup>

The CR rate (72%) for the LSG4 protocol among patients with aggressive NHL was significantly higher than that for the LSG1/LSG2 trial (57%;  $P < 0.05$ ). The CR rate for ATLL was improved from 28% (LSG1/LSG2) to 43% (LSG4). On the other hand, the CR rate for LSG4 was significantly lower for ATLL than for B lymphoma and PNTL ( $P < 0.01$ ). The patients with ATLL still showed a poor prognosis, with an MST of 8 months and a 4-year survival rate of 12%; however, the continued CR rate was increased to 12% (5 of 43) compared with 4% (2 of 54) in the LSG1/LSG2 trial. A multivariate analysis of the 267 patients with advanced aggressive NHL who were treated with the LSG4 demonstrated that the clinical diagnosis of ATLL was the most significant unfavorable prognostic factor (relative risk: 3.185;  $P = 0.0001$ ) for aggressive NHL patients in Japan.<sup>96</sup>

The disappointing results with conventional chemotherapies have led to the search for new active agents. 2'-Deoxycoformycin (DCF;

### Box 114-1. MANAGEMENT STRATEGY FOR PATIENTS WITH ADULT T-CELL LEUKEMIA-LYMPHOMA

When oncologists diagnose patients who are suspected of lymphoid malignancy, it is important to consider the possibility of ATLL. A routine check for serum HTLV-I antibody is recommended at initial diagnosis. The following three points are essential for the diagnosis of ATLL:

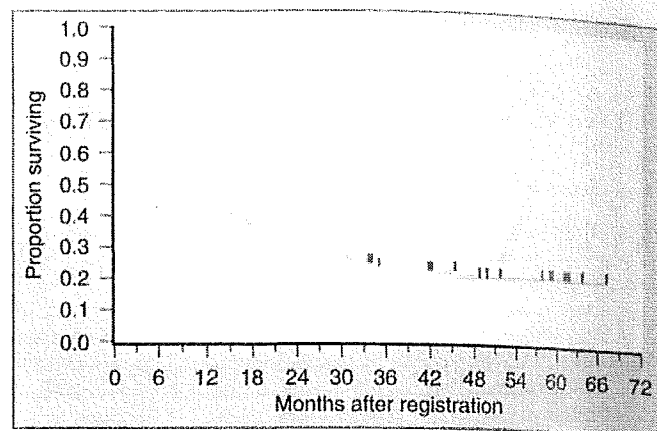
1. Cytologically or histologically proven lymphoid malignancy
2. Mature T-cell phenotype, mostly CD4-positive, determined by flow cytometry or immunohistochemistry
3. Positive for anti-HTLV-I antibody

When a patient is diagnosed with ATLL, it is important to determine the clinical subtype for the sake of optimizing treatment strategy. For patients with smoldering- or chronic-type ATLL, close observation is recommended. Careful monitoring for opportunistic infections—including bacterial, fungal, or *Pneumocystis carinii* infection—is also needed. For patients with acute- or lymphoma-type ATLL, the serum calcium level should be checked immediately. For those with complications of hypercalcemia, prompt management includes fluid therapy, bisphosphonate, and chemotherapy. Patients with acute- or lymphoma-type ATLL that requires therapy should be enrolled in clinical trials if these are available. When there is no active clinical trial or if a patient is ineligible for the trial, chemotherapy for aggressive NHL should be considered. For such patients, we usually give the LSG15 regimen, a multiagent dose-intensified regimen,<sup>98</sup> or CHOP therapy with prophylactic intrathecal administration of MTX. Because most patients with ATLL are not curable with current chemotherapy regimens, it is reasonable to consider the applicability of allogeneic stem cell transplantation for patients who have responded to chemotherapy. For relapsed or refractory patients, consider allogeneic stem cell transplantation or enrollment in a clinical trial of a new chemotherapeutic agent.

pentostatin), an irreversible inhibitor of adenosine deaminase, has been shown to be effective in a number of lymphoid malignancies. On the basis of the promising results of some single-institute studies of DCF, multicenter phase I and phase II studies of DCF were conducted against ATLL in Japan.<sup>91,101</sup> The phase II study of DCF revealed a response rate of 32% (10 of 31) in relapsed or refractory ATLL, using the weekly intravenous administration of 5 mg/m<sup>2</sup>. Two patients achieved CR, and eight patients achieved partial response (PR).<sup>91</sup> These encouraging results prompted the Japanese investigators to conduct a DCF-containing combination phase II trial (JCOG9109; LSG11) as initial chemotherapy for ATLL.<sup>97</sup> Sixty-two previously untreated patients with ATLL (34 patients with acute, 21 with lymphoma, and 7 with chronic subtypes) were enrolled. VCR (1 mg/m<sup>2</sup> intravenously on days 1 and 8), DOX (40 mg/m<sup>2</sup> intravenously on day 1), ETP (100 mg/m<sup>2</sup> intravenously on days 1 through 3), PSL (40 mg/m<sup>2</sup> orally on days 1 and 2), and DCF (5 mg/m<sup>2</sup> intravenously on days 8, 15, and 22) were administered every 28 days for 10 cycles unless disease progression or toxic complications occurred. Among the 61 patients who were evaluable for toxicity, 4 patients (7%) died of fatal infections (2 of sepsis and 2 of cytomegalovirus pneumonia). No other fatal nonhematologic toxicities occurred. In the 60 eligible patients, 17 (28%; 95% CI: 19% to 41%) achieved CR, while 14 achieved PR (response rate: 52%; 95% CI: 39% to 64%). After a median observation time of 27 months, the MST was 7.4 months, and the estimated 2-year survival rate was 17%, findings that were identical to those for the 43 patients with ATL who were treated with the previous LSG4 (JCOG8701).<sup>96,97</sup> Two conclusions were reached on the basis of the JCOG9109 study. First, patients with ATLL who were treated with a DCF-containing five-drug regimen (the LSG11) showed survival comparable with that of patients who were treated with a nine-drug regimen (the LSG4). Second, the prognosis of the patients with ATLL remained poor even though they were treated with a DCF-containing combination chemotherapy.

In 1994, JCOG-LSG initiated a new multiagent combination phase II study (JCOG9303; LSG15): a nine-drug regimen consisting of VCR, CPA, DOX, PSL, nimustine (MCNU), VDS, ETP, and carboplatin (CBDCA) with the intrathecal administration of MTX and PSL, for untreated patients with ATLL.<sup>98</sup> In this study, the elevation of relative dose intensity was attempted with the prophylactic use of granulocyte colony-stimulating factor. In addition, non-cross-resistant agents such as MCNU and CBDCA were incorporated into the regimens. Ninety-six previously untreated patients with aggressive ATLL were enrolled: 58 with acute type, 28 with lymphoma type, and 10 with unfavorable chronic type. Of the 93 eligible patients, 81% responded (75 of 93), 33 patients (35%) achieving CR and 42 (45%) achieving PR. Patients with lymphoma-type ATLL showed a better CR rate (67%, 18 of 27) than patients with acute-type ATLL (20%, 11 of 56) and patients with unfavorable chronic-type ATLL (40%, 4 of 10). The OS rate of 93 eligible patients at 2 years was 31% (Fig. 114-10). The MST was 13 months, and the median follow-up duration of the 20 surviving patients was 4.2 years. A trend toward better survival for patients with lymphoma-type ATLL (MST, 20 months) compared with patients with acute-type ATLL (MST: 11 months) was recognized (hazard ratio: 1.65). Grade 4 hematologic toxicities of neutropenia and thrombocytopenia were observed in 65% and 53% of the patients, respectively, but grade 4 nonhematologic toxicity was observed in only one patient. It was concluded that the LSG15 was feasible with mild nonhematologic toxicity and that it improved the clinical outcome of patients with ATLL.

To confirm whether the LSG15 is a new standard for the treatment of aggressive ATLL, JCOG-LSG conducted a phase III study comparing the LSG15 and biweekly CHOP (CPA, DOX, VCR, and PSL). Previously untreated patients with aggressive ATLL were randomized to receive either six courses of the LSG15 every 4 weeks or eight courses of biweekly CHOP. Both regimens were supported with



**Figure 114-10** • Kaplan-Meier estimate of the overall survival (OS) for the 93 eligible patients with aggressive ATLL. OS was defined as the time from registration until death from any cause or until the last follow-up evaluation for patients who were still alive (20 patients). (From Yamada Y, Tomonaga M, Fukuda H, et al: A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukemia-lymphoma [ATLL]: Japan Clinical Oncology Group (JCOG) Study 9303. *Br J Haematol* 2001; 113:375.)

granulocyte colony-stimulating factor and intrathecal prophylaxis. One hundred and eighteen patients were randomized. Seventy-two percent of the patients responded, with 23 patients achieving CR (40%) and 18 achieving PR (32%) in the LSG15. The ORR was 66%, with 15 patients achieving CR (25%) and 25 achieving PR (41%) in biweekly CHOP. The median progression-free survival (PFS) time and PFS at 1-year in the former were 7.0 months and 28%, respectively, whereas 5.4 months and 16% in the latter ( $P = 0.10$ ). The MST and OS at 3 years in the former were 12.7 months and 24%, respectively, whereas 10.9 months and 13% in the latter ( $P = 0.085$ ). After adjustment of patients' characteristics by Cox regression, the  $P$  value for OS became 0.029 because of unbalanced prognostic factors such as bulky lesion. In the LSG15 versus biweekly CHOP, percentage of grade 4 neutropenia, percentage of grade 4 thrombocytopenia, and percentage of grade 3 to 4 infection were 98% versus 83%, 74% versus 17%, and 32% versus 15%, respectively. Three toxic deaths were reported in the former. These results demonstrate that the LSG15 yields longer OS time than biweekly CHOP but with higher toxicity profiles that are acceptable and suggest that the LSG15 should be the new standard therapy for aggressive ATLL.<sup>99</sup>

### Development of New Agents for Therapy of Adult T-Cell Leukemia-Lymphoma

In addition to DCF, several types of new agents against ATLL have been investigated.

#### Irinotecan Hydrochloride

Irinotecan hydrochloride (CPT-11) is a semisynthetic camptothecin with inhibitory activity against topoisomerase I. Preclinical studies of CPT-11 have suggested a lack of cross-resistance between topoisomerase I inhibitors and other anticancer agents. Multicenter phase II studies of CPT-11 have been conducted against relapsed or refractory NHL in Japan.<sup>102,103</sup> In this study, 9 patients achieved CR, and 17 patients achieved PR (response rate 38%; 26 of 69), using a weekly intravenous administration of 40 mg/m<sup>2</sup>/day for 3 consecutive days. Within this group, 5 of 13 patients with ATLL (38%) responded to CPT-11 (1 patient achieving CR and 4 achieving PR).<sup>103,104</sup> The major toxicities of CPT-11 were leukopenia, diarrhea, and nausea and/or vomiting. Subsequently, to develop a new effective chemo-

therapy regimen against NHL and ATLL, two kinds of phase I/II studies of CPT-11 in combination with CBDCA or ETP were conducted for relapsed or refractory NHL.<sup>105,106</sup> In both studies, however, dose escalation was halted because of hematologic toxicity (in combination with CBDCA) and hepatotoxicity (in combination with ETP).

### Interferon- $\alpha$

On the basis of preliminary documentation of the efficacy of interferon- $\alpha$  against ATLL, two kinds of phase II trials of high-dose interferon- $\alpha$  have been conducted; however, the results have not been impressive. In 1995, Gill and associates<sup>107</sup> reported that 11 of 19 patients with acute- or lymphoma-type ATLL achieved major responses (5 CR and 6 PR) by the combination therapy of interferon- $\alpha$  and zidovudine. The efficacy of this combination was also observed in a French study; major objective responses were obtained in all five patients with ATLL (four with acute type and one with smoldering type).<sup>108</sup> Although the results of this combination are encouraging, the OS of previously untreated patients with ATLL was relatively short (4.8 months) compared with the survival of those in the chemotherapy trials conducted by the JCOG-LSG (7 to 8 months). Furthermore, the CR rate that was associated with the use of interferon- $\alpha$  and zidovudine among previously untreated patients (25%; 3 of 12) was not superior to the CR rates among those who were treated with the JCOG-LSG chemotherapy protocols (28% to 42%).<sup>109</sup> In 2001, White and colleagues<sup>110</sup> reported the results of this combination used for 18 patients with ATLL; only three patients (17%) showed objective responses (one CR and two PRs). Seventeen patients died with an MST after initiation of therapy of 6 months. To evaluate the role of this combination in ATLL, further studies are needed.

### Cladribine

Cladribine (2-chlorodeoxyadenosine) is a chlorinated purine analog that resists degradation by adenosine deaminase. Cladribine has been found to be effective against various B-cell malignancies such as hairy cell leukemia, B-cell chronic lymphoid leukemia, and indolent B-cell NHL. It is known that deoxycytidine kinase is rich in T cells, and an *in vitro* study showed the sensitivity of T-lymphoblastoid cell lines to cladribine. In addition, cladribine was reported to be effective against CTCL. With the aim of establishing an effective treatment against ATLL, clinical trials of cladribine were conducted in Japan. In the Japanese phase I study of cladribine, one relapsed patient with ATLL achieved PR.<sup>111</sup> On the basis of this encouraging result, a multicenter phase II study of cladribine against ATLL was conducted in Japan.<sup>112</sup> Cladribine was administered as 0.09 mg/kg/day by 7-day continuous intravenous infusion every 28 days up to six courses. When the planned interim analysis revealed that only 1 of the 15 eligible patients showed PR (response rate: 7%; 90% CI: 0% to 28%), however, patient entry into the phase II study was terminated.

### Monoclonal Antibodies

Because most ATLL cells express the  $\alpha$ -chain of IL-2R (CD25), Waldmann and colleagues have treated patients with ATLL with monoclonal antibodies to CD25.<sup>88</sup> Anti-Tac (anti-CD25) is a murine monoclonal IgG2a antibody that does not fix human complement, nor does it mediate antibody-dependent cell-mediated cytotoxicity. Anti-Tac has been shown to prevent the growth of certain cell lines *in vitro*, however, even in the absence of complement, by blocking IL-2 from gaining access to its receptor. Six of 19 patients (32%) who were treated with anti-Tac showed PR (4 patients) or CR (2 patients) lasting from 9 weeks to more than 3 years.<sup>113</sup> One of the significant impediments to this approach is that a quantity of soluble IL-2R is shed by the tumor cells into the circulation. The soluble IL-2R can bind to anti-Tac and inhibit binding to the tumor cell.

Other strategies using IL-2R as a target for the treatment of ATLL are conjugation with an immunotoxin (*Pseudomonas* exotoxin) or radioisotope (yttrium-90).<sup>114,115</sup> Anti-Tac coupled with *Pseudomonas* exotoxin, which inhibits protein synthesis, has been administered to patients with ATLL.<sup>114</sup> The action of immunotoxins depends on the expression of the target antigen on all malignant cells and on the cell's ability to internalize the antigen-antibody-complex that contains the toxin. To circumvent findings that not all malignant cells express the target antigen and that not all cells internalize bound substances, radiolabeled monoclonal antibodies (radioimmunoconjugates) were developed. Radioimmunoconjugates have the advantage of killing adjacent antigen-negative neoplastic cells or cells that fail to internalize the antigen-antibody complex. Waldmann and associates<sup>115</sup> have developed a stable conjugate of anti-Tac with yttrium-90. They have treated 18 patients with ATLL using this radioimmunoconjugate. Among the 16 patients who received 5- to 15-mCi doses, 9 (56%) showed objective responses (2 CR and 7 PR). The duration of response was longer than the previous results with unconjugated anti-Tac. Grade 3 or greater toxicities were limited largely to hematologic toxicities. The researchers claim that yttrium-90-labeled anti-Tac might provide a useful approach for the treatment of ATLL.

Prolonged circulation of radioimmunoconjugate irradiates normal tissues and radiosensitive bone marrow, producing DLTs (including myelosuppression), which limit the radiation dose that can be administered safely. In addition, the large size of the antibodies yields only slow access to tumor cells in bulky masses, precluding the use of short-lived radionuclides. In the pretargeting system, antibody and radionuclides are administered separately, and radioactivity rapidly and selectively accumulates in tumors, with a parallel reduction of radioactivity in normal tissues. Several molecular pairs with a high binding affinity, such as avidin and biotin, can be utilized for this purpose. Pretargeting is a novel technique in radioimmunotherapy that might offer means to deliver higher doses of radioimmunoconjugates in a way that significantly reduces exposure to normal tissues.<sup>116</sup>

Ishida and coworkers conducted immunostaining analysis for anti-CC chemokine receptor 4 (CCR4) expression in ATLL cells obtained from 103 patients with ATLL, and the clinical parameters and OS of the CCR4-positive and CCR4-negative patients were compared. Ninety-one (88%) of the 103 cases were positive for CCR4 staining. Multivariate analysis revealed that CCR4 expression was an independent prognostic factor ( $P < 0.05$ ).<sup>117</sup> A novel humanized CCR4 monoclonal antibody has been developed, the Fc region of which is defucosylated to enhance antibody-dependent cellular cytotoxicity by increasing its binding affinity to Fc receptor on effector cells. A phase I study of this anti-CCR4 mAb in patients with CCR4-positive T-cell malignancy including ATLL has been initiated in Japan.<sup>118</sup>

One of the potentially promising strategies for developing a new treatment against ATLL is to overcome drug resistance.<sup>119,120</sup> Kuwazuru and colleagues<sup>119</sup> analyzed the expression of p-glycoprotein (P-gp) in samples from 25 patients with ATLL by immunoblotting with a monoclonal antibody against P-gp. All six patients at relapsed were P-gp positive. More important, neoplastic cells from 8 of 20 patients with ATLL expressed P-gp at initial presentation. These results suggest that the expression of multidrug-resistant (mdr1) P-gp might correlate with the refractory nature of ATLL cells to cytotoxic chemotherapy. Subsequently, Lau and coworkers<sup>120</sup> reported the results of their investigation of the presence of an active multidrug-resistance phenotype in freshly isolated peripheral blood mononuclear cells from asymptomatic HTLV-I carriers, patients with TSP/HAM, and patients with ATLL. Significant P-gp-mediated efflux activity and enhanced mdr1 mRNA expression were observed in CD3-positive T-cell populations from 9 of 10 subjects. Furthermore, it was found that mdr1 gene promoter is transcriptionally activated by the HTLV-I Tax protein. These observations suggest the possibility of new

chemotherapeutic strategies against ATLL through the use of P-gp inhibitors.

### Arsenic Trioxide

Arsenic trioxide ( $As_2O_3$ ) is an effective agent for acute promyelocytic leukemia. Ishitsuka and associates<sup>121</sup> examined the suppressing effect of  $As_2O_3$  on in vitro growth of HTLV-I-infected T-cell lines and fresh ATLL cells. Proliferation of four HTLV-I-infected T-cell lines was reduced significantly by  $As_2O_3$ . The authors claimed that  $As_2O_3$  has therapeutic potential for the treatment of ATLL. Bazarbachi and colleagues<sup>122</sup> tested the effects of the combination of  $As_2O_3$  and interferon- $\alpha$  on cell proliferation, cell cycle phase distribution, and apoptosis in ATLL-derived T-cell lines; they found a synergistic effect between both.

### Allogeneic Hematopoietic Stem Cell Transplantation

The results of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for ATLL were reported by Japanese investigators.<sup>123,124</sup> In the report by Utsunomiya and associates,<sup>123</sup> 10 patients tolerated well the conditioning regimens, including total body irradiation. The median disease-free survival (DFS) after allo-HSCT was more than 17.5 months. Four patients died during the study period from acute graft-versus-host disease (grade IV), pneumonitis, gastrointestinal bleeding, or renal insufficiency. Two of 10 patients with no symptoms of graft-versus-host disease relapsed. In the more recent report by Fukushima and associates,<sup>124</sup> the authors analyzed 40 patients with acute and lymphoma types of ATLL who were treated with allo-HSCT in Japan between 1997 and 2002. All evaluable patients achieved CR after allo-HSCT, and the median survival time was 9.6 months. The estimated 3-year OS, DFS, and disease relapse rates were 45%, 34%, and 39%, respectively. Among 10 patients with relapsed ATLL after allo-HSCT, 5 patients achieved CR again: 3 by the reduction or cessation of immunosuppressive agents, which suggested a graft-versus-ATLL effect. These results suggested that allo-HSCT was effective for some patients with aggressive ATLL. In addition to the conventional allo-HSCT, Okamura and associates reported the results of a multicenter feasibility study of reduced-intensity allo-HSCT against ATLL.<sup>125</sup> Sixteen patients, all over 50 years of age, underwent allo-HSCT from human leukocyte antigen-matched sibling donors after a reduced-intensity allo-HSCT consisting of fludarabine (180 mg/m<sup>2</sup>), busulfan (8 mg/kg), and rabbit antithymocyte globulin (5 mg/kg). The observed regimen-related

toxicities and nonhematologic toxicities were acceptable. Disease relapse was the main cause of treatment failure. Three patients who had a relapse subsequently responded to a rapid discontinuation of the immunosuppressive agent and thereafter achieved another remission. After reduced-intensity allo-HSCT, the HTLV-1 proviral load became undetectable in eight patients. Reduced-intensity allo-HSCT is thus considered to be a feasible treatment for ATLL, warranting further investigations.

### Treatment of Complications

Hypercalcemia, which eventually occurs in most patients with ATLL, usually can be controlled with antitumor therapy and the appropriate use of other calcium-lowering agents.

Another major obstacle for the successful treatment of ATLL is T-cell immunodeficiency. Patients with ATLL often have infectious complications at diagnosis. As is shown in Table 114-2, 26% had infections at initial presentation, more than half of which were fungal, protozoal, and viral infections.<sup>55</sup> This finding could be due to a profound T-cell immunodeficiency. Other frequently encountered opportunistic infections include *Pneumocystis jirovecii* infection, tuberculosis, cytomegalovirus infection, and adenovirus infection.

Subclinical immunodeficiency was also evident among healthy carriers of HTLV-I. Strongyloidiasis is frequently associated with smoldering-type ATLL and an intermediate state between the healthy carrier state and smoldering-type ATLL. HTLV-I is known to induce the suppression or alteration of T-cell function. Yasunaga and coworkers,<sup>126</sup> in a study of peripheral blood mononuclear cells from HTLV-I-infected individuals, found a decrease in naive T cells and decreased levels of TCR gene rearrangement excision circles (generated by DNA recombination during early T lymphopoiesis) and an increase in Epstein-Barr virus DNA. It was suggested that the low number of naive T cells was due to suppressed production of T cells in the thymus, which might account for immunodeficiency in HTLV-I-infected individuals. Patients with ATLL require some supportive or preventive therapies for fungal, protozoal, and viral infections. A low dose of cotrimoxazole and an oral antifungal agent are recommended for use, together with cytotoxic chemotherapy.

There are case reports of B-cell NHL associated with Epstein-Barr virus and of Kaposi's sarcoma in patients with ATLL.<sup>127,128</sup> The profound immunodeficient state in patients with ATLL might allow the emergence of such opportunistic tumors.

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# よくわかる 悪性リンパ腫のすべて

編集

飛内賢正



永井書店

## ●はじめに

悪性リンパ腫は、腫瘍組織の形態学的特徴や腫瘍細胞の細胞表面マーカーや免疫遺伝子の発現などから推定される細胞の分化段階により、細かく分類されている。現在広く用いられている組織学的分類が World Health Organization (WHO) 分類であるが、この分類は、悪性リンパ腫を純粹に分子生物学的基盤に基づいた表現型により区別したものであり、悪性リンパ腫を専門とする者以外には極めて複雑な分類ともいえる。WHO 分類以前の悪性リンパ腫の分類は、Working Formulation 分類が広く用いられていた。この分類は 1982 年に公表されたものであり、B/T などの形質や細胞表面マーカーなどが考慮されていないため、今となつては、30 以上に区分されている WHO 分類に比べると腫瘍の性質を十分反映しているとは言い難いものである。しかし、臨床的な予後を考慮して作成された分類であったため、実地診療においては治療方針の決定に有用であった。Working Formulation 分類をもとにした NCI 分類は、非ホジキンリンパ腫を無治療の場合の疾患の進行が年単位である「低悪性度=indolent」、月単位である「中悪性度=aggressive」、週単位である「高悪性度=highly aggressive」という 3 つのカテゴリーに分類した。WHO 分類においてはこのような分類はなされていないが、治療方針を考慮するうえでの臨床的

表 1 WHO 分類における aggressive lymphoma

B cell Linage	T cell Linage
Mantle cell lymphoma	Peripheral T-cell lymphoma, unspecified
follicular, grade III	Angio-immunoblastic T-cell lymphoma
Diffuse large B-cell lymphoma	Enteropathy-type intestinal T-cell lymphoma
	Anaplastic large cell lymphoma

(文献 1) より改変)

表 2 本邦における悪性リンパ腫の病型別発生頻度

	%
Non Hodgkin lymphoma	94.7
Hodgkin lymphoma	4.4
B-cell neoplasms	68.5
T/NK-cell neoplasms	24.9
Mantle cell lymphoma	2.8
Follicular lymphoma	6.7
Diffuse large B-cell lymphoma	33.3
Peripheral T-cell lymphoma, unspecified	6.7
Angio-immunoblastic T-cell lymphoma	2.4
Enteropathy-type intestinal T-cell lymphoma	0.3
Anaplastic large cell lymphoma	1.5

(文献 2) より改変)

分類の有用性は現在でも変わっておらず、依然用いられている概念である。WHO 分類で、非ホジキンリンパ腫における中悪性度リンパ腫は、表 1<sup>1)</sup>に挙げたものとされている。このうち、びまん性大細胞型 B 細胞リンパ腫(diffuse large B-cell lymphoma ; DLBCL)は、全悪性リンパ腫の 30%強と、中悪性度リンパ腫の大半を占める最も発生頻度の高い病型である(表 2)<sup>2)</sup>。本稿では、日常診療において最も遭遇する頻度の高い DLBCL を中心に中悪性度リンパ腫の治療を解説する。

# 1 予後予測因子

## 1 International prognostic index (IPI)

中悪性度リンパ腫の予後予測因子として、international prognostic index (IPI)が広く知られている。IPI は、ドキシソルビシンを中心とした併用化学療法で治療された 2,031 例の中～高悪性度非ホジキンリンパ腫の予後因子の解析により提唱されたモデルである。年齢、LDH、臨床病期、節外病変数、performance status (PS)の 5 つの因子の数により、完全寛解割合や生存割合と相関関係を示す 4 つのリスクグループに分類される(表 3)<sup>3)</sup>。Low risk 群の 5 年生存率は 73%と良好であるが、low-intermediate risk 群は 51%、high-intermediate risk 群では 43%と決して良好な予後ではない。さらに、high risk 群の 5 年生存割合は 26%と不良である(図 1)。近年、DLBCL に対する中心的

表 3 IPI における 5 つの予後予測因子

因子
年齢 > 60 歳
血清 LDH 値 > 正常値
Performance status 2~4
臨床病期 III~IV 期
節外病変数 2 部位以上
因子 0~1 : low risk
2 : low-intermediate risk
3 : high-intermediate risk
4~5 : high risk

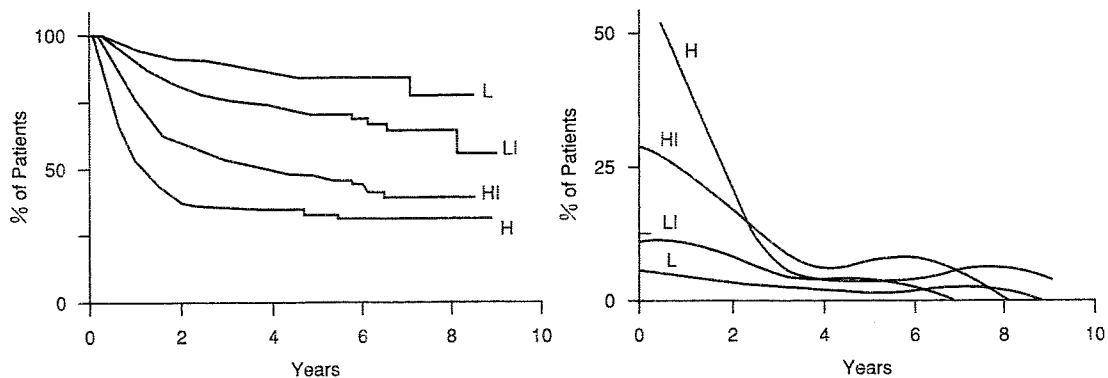


図 1 IPI によるリスク別の生存割合(左:全生存割合、右:死亡割合)  
L : low risk LI : low-intermediate risk HI : high-intermediate risk H : high risk

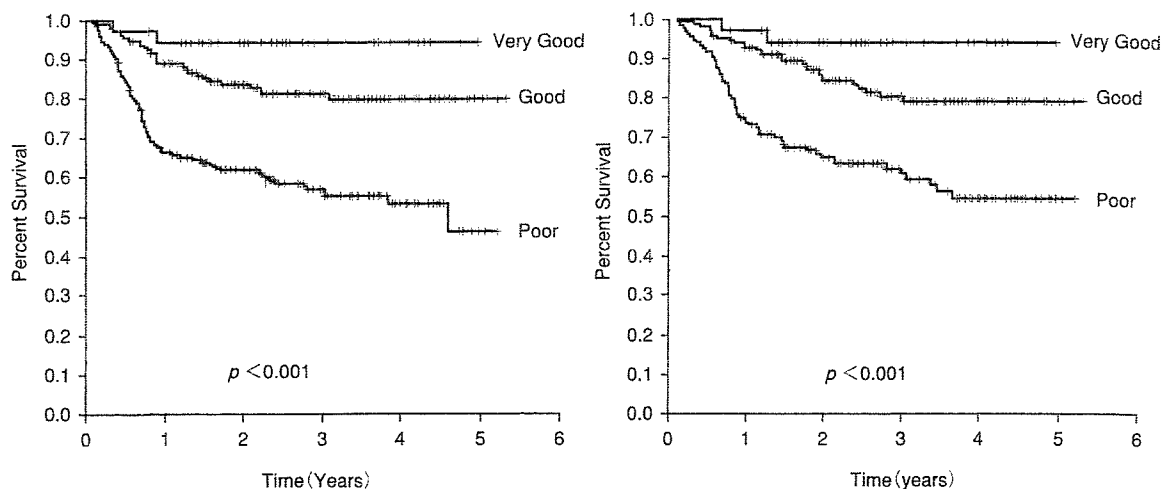


図 2 Revised IPI における生存曲線(左：無増悪生存割合、右：全生存割合)

な薬剤である rituximab を加えた治療による予後予測因子を検討したモデルとして revised IPI が提唱されており、4 年全生存割合が very good 群で 94%、good 群で 79%、poor 群で 54% と、rituximab 登場以前と比べて予後の改善が報告されている(図 2)<sup>4)</sup>。

## 2

### 限局期例の治療(図 3)

病変部位が 1 つのリンパ節領域に限局している、または病変部位は 2 つ以上のリンパ節領域に及んでいるが隣接しており、1 つの放射線照射野に収まるというような限局期中悪性度リンパ腫に対する治療は、かつては放射線単独療法が行われていた。しかし、大多数の例で再発が認められ、その後、放射線照射の後療法として化学療法が追加併用されるようになり、予後の改善が得られるようになった。現在の放射線と化学療法の併用療法としては、総コース数を減らした化学療法に照射野を限定した放射線照射を併用することが主流となっている。限局期例に対する放射線併用化学療法の有用性は、米国の Southwest Oncology Group (SWOG) で行われた大規模な比較試験の結果から報告された。臨床病期 I ~ II 期 (bulky mass を有する例は除く) の中悪性度リンパ腫患者 401 例を対象とした、8 コースの CHOP (cyclophosphamide、doxorubicin、vincristine、predonisone) 療法と、3 コースの CHOP 療法後に照射野を限局した放射線照射を追加する併用療法の比較試験で、5 年無増悪生存割合で 77% vs 64%、5 年全生存割合で 82% vs 72% と有意に併用療法群が上回っていた(図 4)<sup>5)</sup>。生命を脅かすような毒性や左室機能不全の発生頻度も併用療法群の方が少なく、この結果が公表された以降は、限局期中悪性度リンパ腫に対する標準的な治療は CHOP 療法 3 コース後に照射野を限局した放射線療法を追加

■ 15. 中悪性度リンパ腫の治療

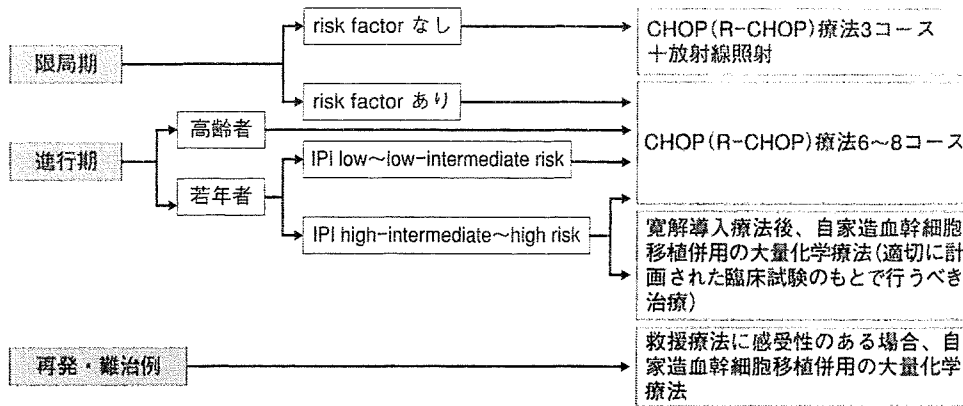


図 3 中悪性度リンパ腫に対する治療のフローチャート

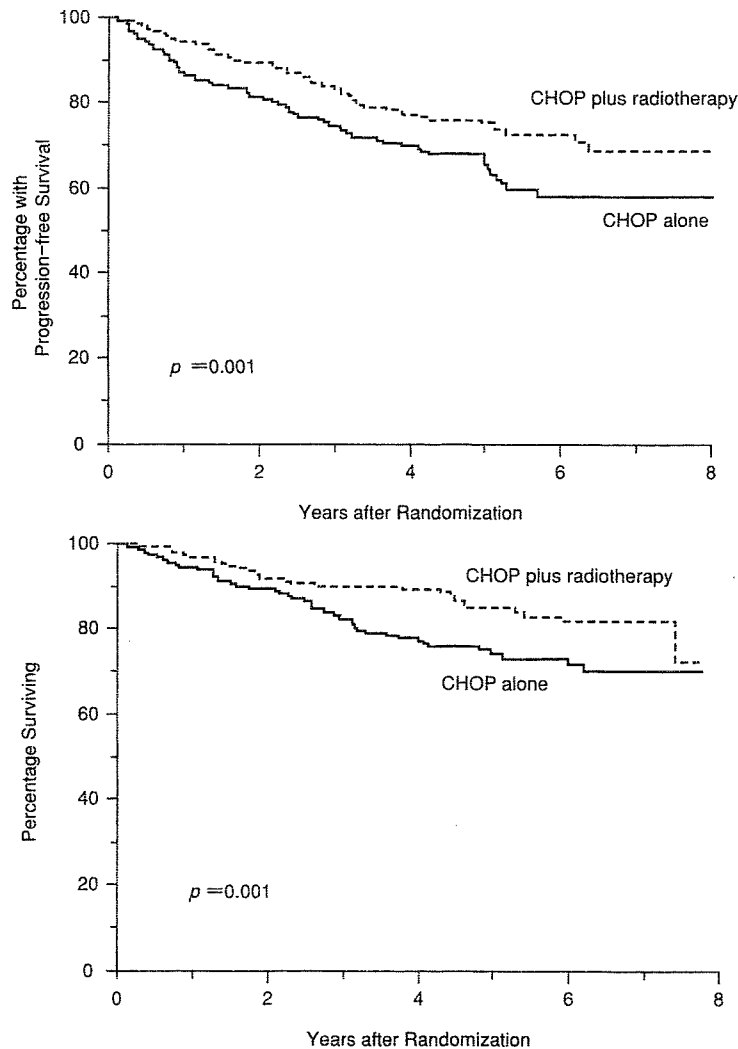


図 4 CHOP 療法 8 コースと CHOP 療法 3 コース+放射線併用療法の比較試験における生存曲線(上:無増悪生存割合、下:全生存割合)  
その後の報告では、長期経過観察により両群に差はなくなったとされている。



する併用療法とされた。しかし、その後の長期観察を経た報告では、両群に生存割合での違いはなくなっているとされている。また、化学療法と併用療法の比較試験において、併用療法の優位性が証明されなかった試験も複数存在する。米国の Eastern Cooperative Oncology Group (ECOG) で行われた比較試験では、CHOP 療法 8 コースの後に完全寛解となった例に対して局所放射線照射を追加するまたは無治療経過観察とするという比較で、6 年の無病生存割合で 69% vs 53% と追加照射群が上回っていたが、観察期間中央値 12 年における 15 年全生存割合は 60% vs 44% と、追加照射群が良好ながらも有意差はなかったと報告されている<sup>6)</sup>。フランスの Groupe d'Etudes des Lymphomes de l'Adulte (GELA) からは、ACVBP (dose-intensified doxorubicin, cyclophosphamide, vincristine, bleomycin, predonisone plus sequential consolidation) 療法と CHOP 療法 3 コースと放射線照射の併用療法の比較試験で、5 年無イベント生存割合で 82% vs 74%、5 年全生存割合で 90% vs 81% と、いずれも化学療法単独群が上回っていたと報告された<sup>7)</sup>。同グループからは、60 歳以上の高齢者を対象とした CHOP 療法単独 4 コースと、さらに放射線照射を併用した併用療法の比較試験が報告されているが、そこでも生存割合は両群

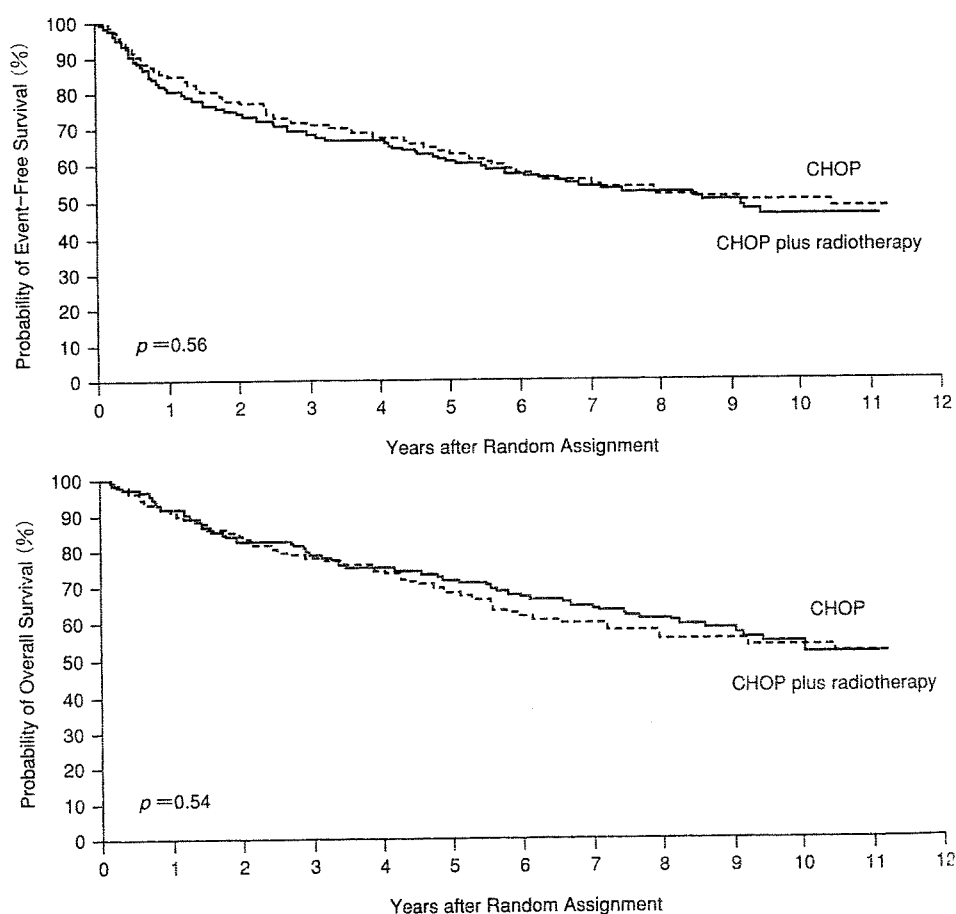


図 5 CHOP 療法 4 コースと CHOP 療法 4 コース+放射線併用療法の比較試験における生存曲線(上:無イベント生存割合、下:全生存割合)

とも同等であり(図5)<sup>8)</sup>、併用療法の有用性は証明されなかった。このように、限局期例に対する放射線併用化学療法の有用性は、かつてほど絶対的なものではないと現在は考えられている。長期的な観察で併用療法が化学療法単独に対して優位性を示すことができなかった理由として、放射線照射を併用することで局所の病変を制御することはできて、照射野以外の微小な病変に対してはコース数を減らした化学療法では十分でない可能性があることが考えられる。併用療法の利点は、局所制御を十分行うことのほかに、化学療法の総投与量を減らすことで二次発癌、不妊や心筋障害などの晩期合併症のリスクを減らすことにある。ECOG で行われた試験でも、IPI の risk factor (臨床病期の因子をⅢ～Ⅳ期→Ⅱ期へと変更したもの)を有さない例では長期の follow up でも変わらず良好な生存割合が認められており、再発の低リスク群や、若年者などの化学療法の総投与量を控えることが望ましい対象に対しては、併用療法は依然として有用な治療法である。

### 3 進行期例の治療(図3)

進行期中悪性度リンパ腫に対する治療の基本は、全身療法である化学療法である。化学療法高感受性である中悪性度リンパ腫に対して、交叉耐性を有さない薬剤を交互に使うこと、薬剤の用量強度を高めることで薬剤耐性を打破するという理論のもと、さまざまな薬剤の併用療法が考案されてきた。1970年代に開発された第一世代のCHOP療法に引き続いて、1980年代には methotrexate、bleomycin、etoposide、cytosine arabinoside、

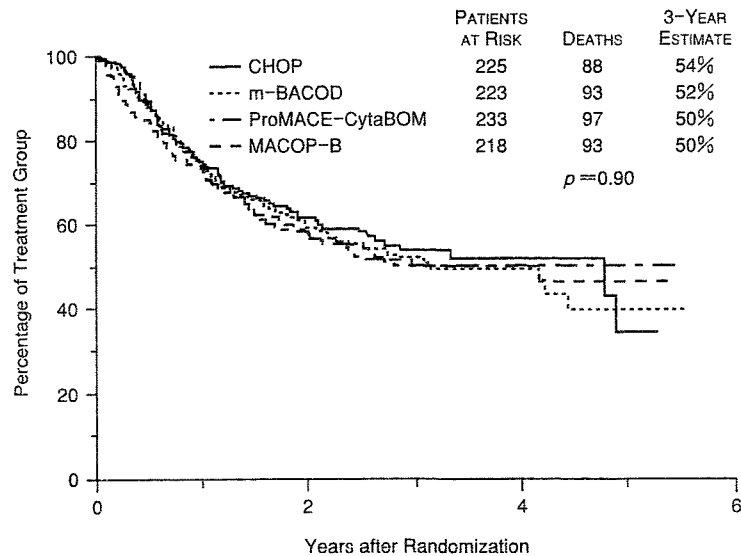


図6 CHOP療法と第三世代の化学療法の四群の比較試験における生存曲線(全生存割合)

procarbazine などの抗がん剤を追加した m-BACOD 療法、ProMACE-CytaBOM 療法、MACOP-B 療法など第二・第三世代と呼ばれる併用化学療法が開発され、主として単施設の第Ⅱ相試験の優れた成績として報告された。しかし、その後に米国で施行された、SWOG を中心とする intergroup での大規模な比較試験の結果、CHOP 療法を対照としてこれらの併用化学療法は有効性で CHOP 療法を凌駕しなかった(図 6)<sup>9)</sup>。また、毒性やコスト面では CHOP 療法が優れていることから、CHOP 療法が標準的な化学療法のレジメンであるとされた。これは、CHOP 療法が開発されてから 30 年以上経った現在でも、概ね変わらない事実として受け入れられている。1990 年代後半に入り、従来の抗腫瘍薬とはまったく異なる作用機序を有する薬剤の開発が進んだ。正常 B 細胞と B 細胞リンパ腫細胞の大半に発現しており、造血幹細胞や形質細胞を含むその他の血液細胞には発現していないという CD20 抗原に対して特異的に結合するマウス/ヒトキメラ抗体である rituximab は、その代表である。単剤でも B 細胞リンパ腫に対して高い奏効割合が認められ

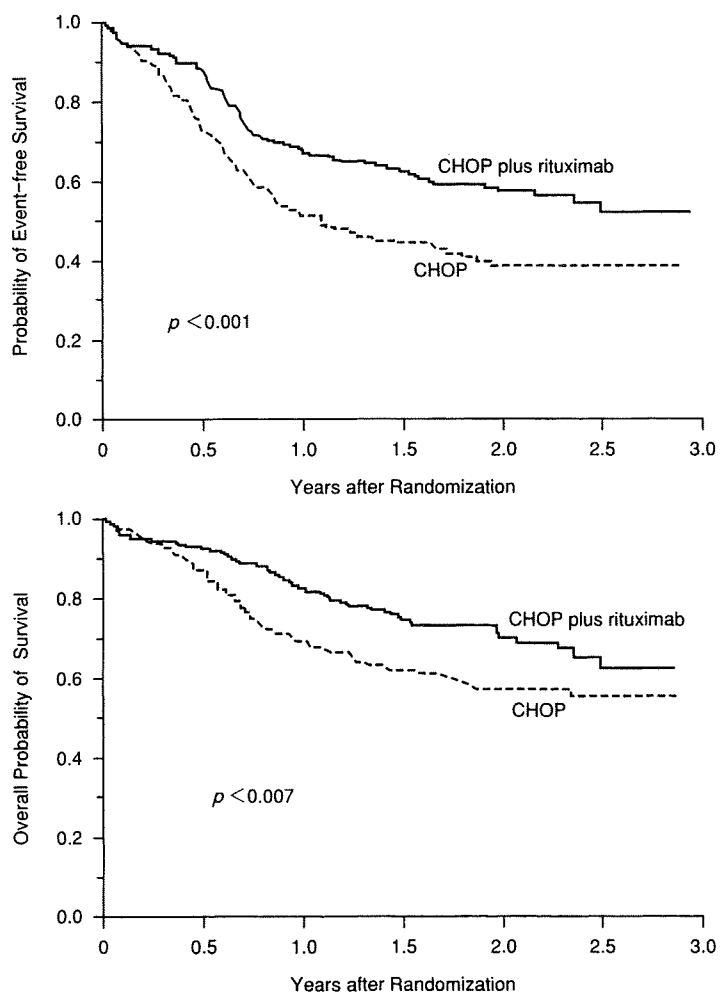


図 7 CHOP 療法と R-CHOP 療法の比較試験における生存曲線 (上：無イベント生存割合、下：全生存割合)

ていた rituximab は、当然従来の化学療法との併用法の開発も進められた。第Ⅱ相試験において、標準的な化学療法である CHOP 療法との併用でも 90%以上の奏効割合が認められ、毒性が増強することもなかったことから、CHOP 療法を超える治療法となることが期待された。GELA から、高齢者の未治療進行期 DLBCL 患者を対象とした CHOP 療法と rituximab 併用の CHOP 療法(R-CHOP 療法)の比較試験において、完全寛解割合のみでなく(76% vs 63%)、2年無イベント生存割合、2年全生存割合(70% vs 57%)のいずれも R-CHOP 群が勝っていたと報告された(図7)<sup>10)</sup>。サブグループ解析でも、IPI の低リスク群のみでなく高リスク群でも R-CHOP 療法が生存において CHOP 療法群を上回っていた。その後の follow up でも、IPI のリスク別を含めたすべての生存において R-CHOP 群が上回っており、rituximab を併用することの有用性は間違いないものとされている。そのほかに rituximab 併用の有無を検討した比較試験に、欧米を中心に行われた国際的な共同試験(MInT trial)と ECOG で行われたものがある。前者は若年者の IPI で low risk の患者を対象としたもので、CHOP 療法類似レジメンで rituximab の併用の有無を比較したところ3年の無イベント生存割合が79% vs 59%、3年の全生存割合が

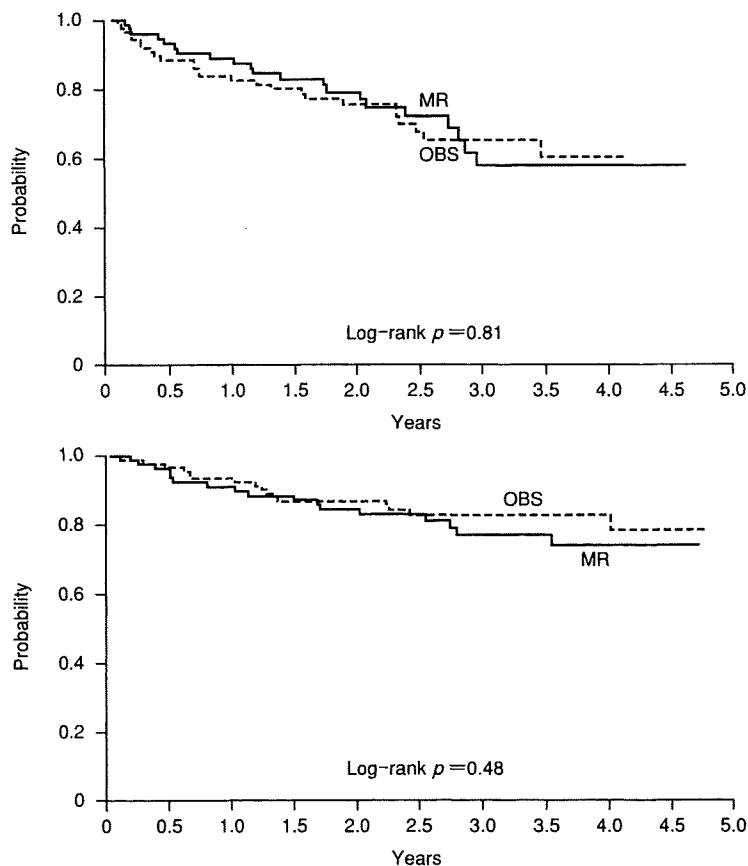


図 8 R-CHOP 療法後の rituximab による維持療法の有無における生存曲線(上：無イベント生存割合、下：全生存割合)  
OBS : observation MR : maintenance rituximab