damage in IVLBCL. However, the characteristics of extranodal expansion in IVLBCL may influence the ability of FDG-PET to detect disease involvement accurately [5–7]. Previous reports have revealed that FDG-PET is useful for the diagnosis of IVLBCL when this type of lymphoma is clinically suspected [8–11]. Unfortunately, these reports did not mention the accuracy of FDG-PET in detecting involvement of organs such as bone marrow, skin, liver, spleen or kidney, in which most cases of IVLBCL are diagnosed [12–14]. Whether FDG-PET is useful for initial assessment of disease involvement in IVLBCL is thus unclear.

To evaluate the accuracy of FDG-PET in detecting disease involvement of IVLBCL, we compared FDG-PET images with the results of pathological findings in four consecutive IVLBCL patients evaluated using FDG-PET before treatment.

2 Design and methods

2.1 Study design

To evaluate the role of FDG-PET in IVLBCL, we conducted a retrospective analysis of four consecutive patients (2 men, 2 women) with IVLBCL treated at Ogaki Municipal Hospital between May 2006 and November 2007. IVLBCL was diagnosed according to the WHO classification. Patients underwent FDG-PET and various organ biopsies for evaluation before the beginning of treatment. The accuracy of FDG-PET for detecting various organ involvements was analyzed by comparing the results of pathological findings.

2.2 Patients

Patient characteristics are shown in Table 1. Median age of patients at diagnosis was 62 years (range 54–76 years). In all patients, lymphoma displayed aggressive clinical behavior including high fever. Blood examination revealed high levels of serum lactate dehydrogenase (LDH), soluble interleukin-2 receptor (sIL-2R) and C-reactive protein (CRP).

2.3 FDG-PET

All patients underwent FDG-PET before beginning treatment. FDG-PET studies were acquired using two PET tomographs: a SET-3000 B/L (Shimadzu Corp., Kyoto, Japan) and an ADVANCE NXi Imaging System (General Electric Yokogawa Medical Systems, Tokyo, Japan). Patients had fasted ≥8 h and had no history of diabetes mellitus or blood glucose abnormalities at the time of

Table 1 Patient characteristics at FDG-PET study

Case	Age/sex	WBC (μl^{-1})	PLT ($\times 10^4\ \mu l^{-1}$)	LDH (IU/l)	CRP (mg/dl)	Ferritin (ng/ml)	sIL-2R (U/l)	Disease site confirmed by pathological specimen	Positive imaging by FDG-PET	Therapy	Survival (day)
1	69/Female	970	4.4	2,118	16.11	NE	28,600	Bone marrow, skin, kidney	Spleen, stomach	PSL	11
2	54/Female	5,920	26.8	4,528	16.73	457	6,000	Kidney	Sternum, sacrum bone, left iliac bone, left femur	R-CHOP	301+
3	76/Male	9,120	7.8	1,382	11.37	975	12,100	Bone marrow, skin	Diffuse bone	PSL, CPA + Dex	14
4	55/Male	3,980	6.5	607	13.68	564	5,880	Bone marrow	Diffuse bone, spleen	R-CHOP	62+

FDG-PET ^{18}F-fluorodeoxyglucose positron emission tomography, *WBC* white blood cell count, *PLT* platelet count, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *sIL-2R* soluble interleukin-2 receptor, *HPS* hemophagocytic syndrome, *PSL* prednisolone, *CPA* cyclophosphamide, *Dex* dexamethasone, *R-CHOP* rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone, *NE* not evaluated

FDG-PET. No patients had received any kind of hematopoietic growth factors or steroid therapies before diagnosis. The scan was started 60 min after administration of FDG (dose range 163–232 MBq) and performed from the proximal femur to the skull base. FDG-PET images were interpreted by two radiologists at Kizawa Memorial Hospital, Minokamo, Japan.

2.4 Pathological diagnosis

All patients received random skin and bone marrow biopsies. Skin biopsies were performed from three apparently healthy abdominal and femoral skin sites by dermatologists at Ogaki Municipal Hospital. Bone marrow biopsies were obtained from iliac bone. Renal biopsy was performed for two of the four patients. One patient (Patient 1) received biopsies including stomach according to the findings of FDG-PET. The other patients received biopsies before receiving FDG-PET. Tumor cells were confirmed by CD20 and/or CD79a immunohistochemical staining in organ biopsy specimens. Diagnoses were made by consensus agreement of three expert pathologists (Y.I., S.S. and S.N.) at Ogaki Municipal Hospital and Nagoya University Hospital.

3 Results

3.1 FDG-PET

All patients revealed various patterns on FDG-PET. Accumulation of FDG in the bone was observed in three of four patients (Fig. 1a), as patchy accumulation in one patient and diffuse accumulation two patients. The remaining patient without bone accumulation displayed spleen and stomach accumulation (Fig. 1b). No patient revealed renal or skin accumulation. The highest standardized uptake value (SUV) reached 8–14 in diffuse bone accumulation.

3.2 Site of pathological diagnosis of IVLBCL

Bone marrow and skin involvements were detected in three and two patients, respectively. Both patients who received renal biopsy displayed disease in the pathological specimens. No disease was detected in the gastric biopsy specimen.

3.3 Accuracy of disease detection by FDG-PET

FDG-PET images were further evaluated for accuracy of detecting various organ involvements by comparing results with various organ biopsies. These results are summarized in Table 2. In two of the four patients, concordant results were obtained with respect to bone marrow involvement (Fig. 1c). In the remaining two patients, the results of pathological diagnosis and FDG-PET were discordant (Fig. 1d). False-negative and false-positive findings were observed in one patient each. One patient with a false-negative FDG-PET result showed fewer lymphoma cells in the bone marrow specimen than patients with concordant FDG-PET results (Fig. 1c, d). We were unable to detect renal or skin involvement by FDG-PET, despite positive pathological findings (Fig. 1e, f).

4 Discussion

In the assessment of IVLBCL, caution must be exercised when interpreting the results of FDG-PET. In our study, FDG-PET was able to detect only two of seven pathologically confirmed lesions (29%). Usefulness of FDG-PET in the initial assessment of IVLBCL and the evaluation of therapeutic effects may be limited.

In patients with nodal DLBCL, FDG-PET has been shown to detect at least one lesion 100% of the time [6, 7, 15]. Several reasons contribute to these extremely contrasting findings. First, FDG uptake may be lower in IVLBCL cells than in DLBCL cells. However, this seems unlikely given that IVLBCL is a subtype of DLBCL, and IVLBCL and DLBCL are histopathologically and genetically similar [3, 4, 12]. Furthermore, in our patients, the results of tests on the initial visit, such as markedly high LDH and rapidly progressing clinical course indicated rapidly proliferating IVLBCL cells, which would be associated with rapid sugar consumption due to high IVLBCL cell turnover. These findings suggest that FDG uptake of IVLBCL cells is no lower than DLBCL. Second, the difference may be due to the kinetics of FDG in the body. FDG accumulates in the brain, kidney and bladder, so lesions in these organs are difficult to identify [16]. In fact, renal lesions could not be detected in our study. In certain organs where FDG naturally accumulates, lymphoma infiltration may be underestimated. Third, differences may exist in the localization of tumor cells between DLBCL and IVLBCL. The biggest difference with nodal DLBCL is that tumor cells invade extranodal vessels in IVLBCL. Tumor cells invade diffusely in IVLBCL and compared to DLBCL, which comprises solid tumor, the volume of regional tumor is lower. In fact, in the present study, when FDG-PET and biopsy findings matched, the number of tumor cells tended to be higher. Moreover, even with DLBCL, FDG-PET is less reliable for extranodal cases, particularly marrow infiltration [7]. This indicates that the number of tumor cells per volume is lower for marrow infiltration than for nodal lesions, supporting our deduction.

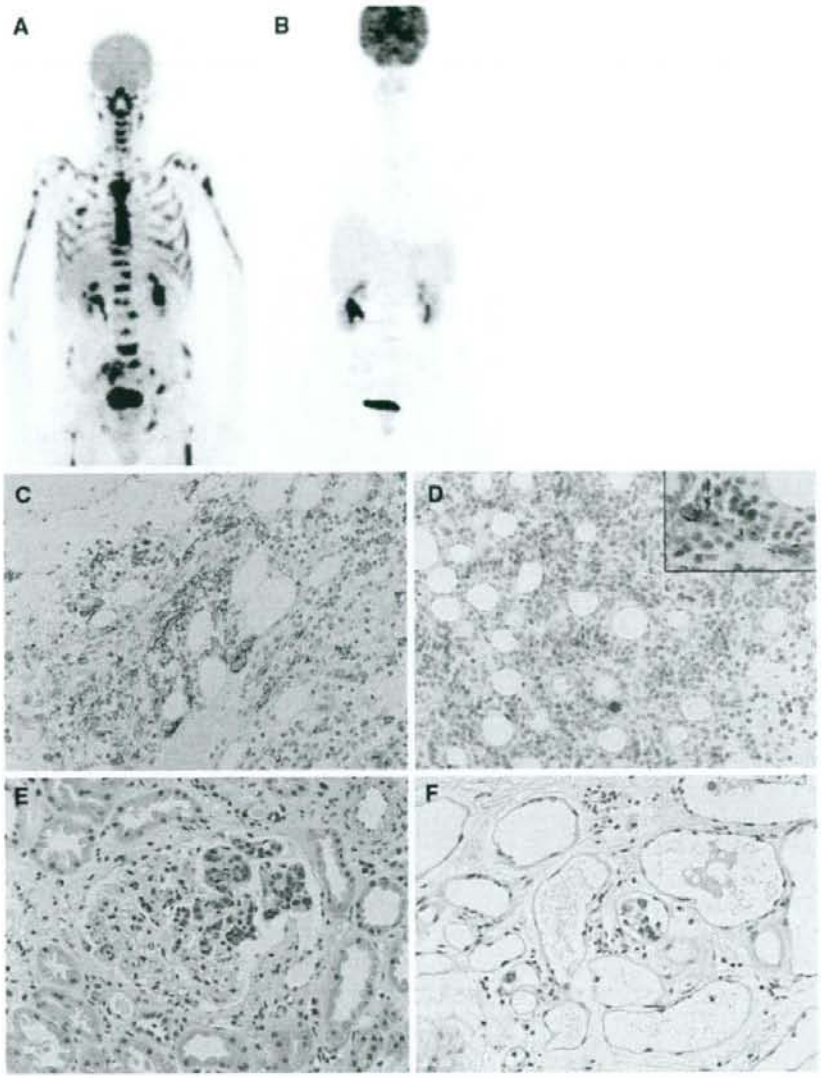

Fig. 1 FDG-PET image and pathological findings of organ biopsies. **a** FDG-PET for Patient 3. Diffuse accumulation of FDG was observed in systemic bone. Maximum SUV reached 8 to 14. **b** FDG-PET for Patient 1. Accumulation of FDG was observed in the stomach and spleen, but not in bone. **c** Concordant results for bone marrow. Bone marrow aspiration revealed a number of CD20+ lymphoma cells with diffuse and intrasinusoidal pattern. Lymphoma cells were uniformly distributed in the specimen (CD20 immunostain ×200). **d** Discordant (false-negative) results in bone marrow. Bone marrow aspiration revealed few CD20+ lymphoma cells with an intrasinusoidal pattern. Lymphoma cells were focally distributed in the specimen (CD20 immunostain ×200, *inset* ×400). **e** Discordant (false-negative) results in the kidney. Renal biopsy revealed lymphoma cells in glomerular capillaries (H&E ×200). **f** Discordant (false-negative) results in the skin. Skin biopsy revealed lymphoma cell in small vessels of the dermis (H&E ×200)

Table 2 Diagnostic accuracy of FDG-PET by anatomical site

Diagnostic site	Concordant		Discordant		Total
	Positive	Negative	FDG-PET-positive, biopsy-negative	FDG-PET-negative, biopsy-positive	
Bone marrow	2	0	1	1	4
Kidney	0	0	0	2	2
Skin	0	2	0	2	4
Stomach	0	0	1	0	1

All the numerical data indicate the number of patients

In the present study, although diagnostic accuracy was lower compared to nodal DLBCL, FDG-PET was useful in identifying IVLBCL in several regards. First, PET gathers useful information that cannot be obtained by conventional diagnostic methods. As no solid lesions are present with IVLBCL, CT cannot detect lesions. Biopsy thus offers the only other diagnostic method, but determining where to perform biopsy is often difficult. With PET, accurate diagnosis may be made sooner by examining areas with FDG accumulation. In fact, when affected areas could not be identified in patients exhibiting clinical symptoms associated with IVLBCL, FDG-PET was performed and accurate diagnoses were made by taking biopsy samples

from areas with FDG accumulation [9, 10]. Second, the use of FDG-PET may improve the safety of therapy for IVLBCL. Recently, we have reported the usefulness of rituximab-containing chemotherapies for IVLBCL [17], but about 30% of IVLBCL patients display respiratory symptoms [12, 17], and rituximab infusion can reportedly cause severe respiratory complications [18]. If FDG-PET shows a pulmonary lesion, premedication may avoid complications. In the future, investigation of the significance of PET in rituximab therapy will be necessary.

The present study revealed characteristic FDG-PET findings for IVLBCL. In the future, a study focusing on the usefulness of FDG-PET in IVLBCL is needed.

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Case Study

Sustained Remission after Rituximab-containing Chemotherapy for Intravascular Large B-cell Lymphoma

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Intravascular large B-cell lymphoma (IVL) is rare aggressive disseminated lymphoma associated with poor outcomes. Rituximab is a novel molecular agent that can reportedly improve outcomes for patients with diffuse large B-cell lymphoma. However, the safety and efficacy of rituximab in patients with IVL are unclear. A 76-year-old woman was hospitalized due to altered consciousness, fever and respiratory abnormalities. Definitive diagnosis of IVL was obtained following repeated biopsies of bone marrow. The patient received chemotherapy consisting of cyclophosphamide, vincristine, doxorubicin, prednisolone, and rituximab (R-CHOP), and achieved complete remission after 3 courses of treatment. She has remained in complete remission for over 3 years after diagnosis. This report suggests that rituximab-containing regimens could be safe and effective for elderly patients with IVL. [*J Clin Exp Hematopathol 48(1) : 25-28, 2008*]

Keywords: intravascular large B-cell lymphoma, rituximab, combination chemotherapy

INTRODUCTION

Intravascular large B-cell lymphoma (IVL) is a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL), as classified by the World Health Organization.[1] IVL is a rapidly aggressive disseminated disease, characterized by the presence of lymphoma cells only in the lumina of small vessels of the central nervous system, skin, lungs, kidneys, and bone marrow, without marked lymphadenopathy. The absence of IVL in traditional sites of lymphoma presentation makes accurate and timely diagnosis difficult. In previous reports, around half of patients have been diagnosed post mortem,[2] and repeated biopsies of skin, kidney, and bone marrow are often necessary for the diagnosis of this type of lymphoma.[3,4]

Left untreated, IVL is uniformly fatal. Steroids generally provided only transient improvement.[2] Most therapeutic regimens were ineffective, with a median survival of several months from the date of clinical presentation.[4,5] Recently, anthracycline-containing chemotherapy has been reported to improve clinical outcomes of patients with IVL. Ferreri *et al.* reported an overall 3-year survival rate of 33% and a response rate of 59% in the patients who received anthracycline-containing chemotherapy.[6] Murase *et al.* reported a median survival duration for IVL patients receiving anthracycline-based chemotherapy of 13 months.[7] Considering that most IVL patients are categorized in the high-risk group according to the International Prognostic Index,[7] the survival of IVL patients is probably comparable to that of patients with DLBCL.[8] Thus anthracycline-containing chemotherapies appear to be useful, and that the poor prognosis of IVL[9] might be attributable to delayed initiation of chemotherapy.

Rituximab is a novel monoclonal antibody against CD20 B-cell antigen. The addition of rituximab to the CHOP regimen has been found to improve treatment outcomes in patients with DLBCL.[10] Recent reports suggest the efficacy of rituximab for the treatment of IVL,[11,12] however, the scale of these studies was small and the long term outcomes remain unclear.

CASE REPORT

A 76-year-old woman with no past medical history of note was admitted to Ogaki Municipal Hospital in July 2003 with a one-week history of continuous malaise, headache, and leth-

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argy. After admission, she developed neurological signs including disorientation and unresponsiveness, in addition to a persistent fever. Blood examination revealed : white blood cell count, 6,280/μL ; red blood cell count, 380 x 10^4/μL ; hemoglobin, 11.3 g/dL ; and platelet count, 25.3 x 10^4/μL. Laboratory studies showed : aspartate aminotransferase, 90 IU/L ; alanine aminotransferase, 79 IU/L ; C-reactive protein, 10.2 mg/dL ; lactate dehydrogenase (LDH), 2249 IU/L (normal range : 130-450 IU/L) ; and ferritin, 846.5 ng/mL. Soluble IL-2 receptor (sIL-2R) was elevated to 7955 U/L. Physical examination showed no systemic lymphadenopathy, splenomegaly or focal neurological deficits. Arterial blood gas analysis demonstrated respiratory insufficiency with a partial pressure of arterial oxygen (PaO_2) of 48.5 mmHg without hypercapnia. Computed tomography (CT) of the abdomen revealed mild splenomegaly without lymphadenopathy or hepatomegaly. Transbronchial lung biopsy revealed no evidence of malignancy. CT of the brain showed no marked abnormalities. Bone marrow aspiration revealed hemophagocytic syndrome, but no evidence of malignancy.

In addition, skin and renal biopsies were negative. However, repeat bone marrow examination revealed CD20-positive lymphoma cells in the lumen of vessels (Fig. 1). These lymphoma cells were immunohistochemically negative for CD3, CD10, MUM-1, and Bcl-6. IVL was subsequently diagnosed on the basis of the CD20-positive intraluminal lymphoma cells in October 2003.

The patients respiratory failure and neurological manifestations resolved spontaneously following her first admission within 4 weeks. The patient was then discharged from the hospital without the definitive diagnosis of IVL. Three months later, she developed fever with elevated sIL-2R and

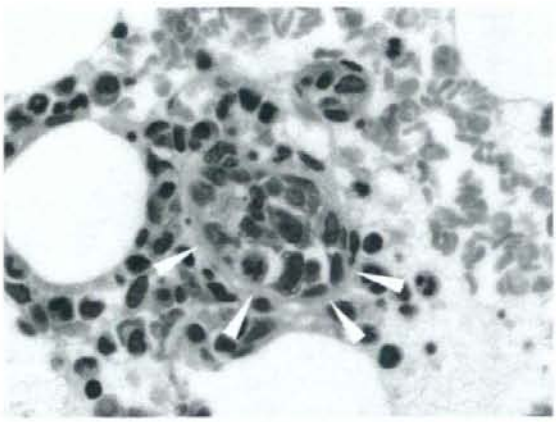

Fig. 1. Hematoxylin and eosin staining in bone marrow clot. *The white arrows* indicate tumor cells present in lumens of small vessels. These cells were highlighted by staining for CD20. Original magnification x400.

chemotherapy was initiated. Initially she was treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) alone as a first course. Subsequently, rituximab was added to CHOP regimen at the time of her second course of chemotherapy (R-CHOP). The patient received acetaminophen and diphenhydramine as premedication for rituximab. No infusion reaction occurred with any of the administrations. Her fever improved after starting chemotherapy, and sIL-2R and LDH levels normalized. The patient did not require any delay in administration or dose reduction and achieved complete remission after 3 cycles of R-CHOP with resolution of clinical symptoms, and normalization of clinical laboratory tests and bone marrow findings. As of the time of writing, the patient remains alive and in complete remission over 3 years after diagnosis.

DISCUSSION

The present report describes a sustained 3 year remission following a R-CHOP regimen for the treatment of IVL in an elderly patient. Our result is consistent with previous reports about rituximab therapy for IVL patients.[11,12] These reports, in addition to ours, suggest that rituximab-containing regimens improve clinical outcomes for patients with IVL, as well as in patients with DLBCL.[10]

A recent report using cDNA microarrays has revealed that DLBCL can be divided into subgroups ; germinal center B-cell (GCB) type and activated B-cell (ABC) type.[13] Hans *et al.* found that these subtypes could be accurately identified according to immunohistochemical expression patterns of CD10, bcl-6, and MUM-1.[14] In our patient, lymphoma cells were regarded as non-germinal center B-cell (non-GCB) type due to an immunoexpression profile negative for CD10, bcl-6, and MUM-1 staining. Murase *et al.* revealed that most IVL cells belong to the non-GCB type.[7] Recent reports indicate that non-GCB type DLBCL benefits from the addition of rituximab to CHOP, whereas the GCB type does not.[15,16] Our experience suggests that this classification is useful for predicting treatment responses in IVL. However, further large-scale studies are warranted.

Patients possessing a high number of tumor cells in their peripheral blood have been reported to develop severe infusion reactions induced by rituximab.[17] IVL patients with a high tumor burden in their vessels possibly are at risk for infusion reactions. In addition, respiratory distress syndrome following rituximab infusion has been reported.[18] In our patient, respiratory insufficiency with a low PaO_2 was observed at the time of her first admission. Thus, we omitted the addition of rituximab over concern of infusion reaction in the first course of chemotherapy. Due to our therapeutic strategies against infusion reactions, no infusion reactions occurred in the clinical course of our patient. The addition of rituximab during second course or later of chemotherapy was

safe, without adverse events of rituximab.

Several reports have revealed long-term survival after autologous hematopoietic stem cell transplantation for IVL, not only in patients who achieved complete remission but also in patients with relapsed disease.[19-21] However, transplantation is not a feasible option for most IVL patients of advanced age. Our patient was too elderly to receive autologous hematopoietic stem cell transplantation. Conversely, the R-CHOP regimen is reportedly feasible for elderly patients.[10] Actually, the present patient completed 8 courses of R-CHOP regimen without any marked adverse effects. Considering the high median age for IVL (67 years), R-CHOP might be feasible for most IVL patients.[6] The safety and efficacy of an R-CHOP regimen for elderly IVL patients should be investigated in further studies.

Several cases of central nervous system relapse were recently reported.[22,23] Although our patient has maintained complete remission without intrathecal infusion, intrathecal chemotherapy as a precaution against central nervous system relapse may be worth investigating in future studies.

In summary, we report an elderly patient with IVL who achieved sustained remission after receiving R-CHOP without requiring steroids and antibiotics. Due to this atypical clinical course, further careful follow-up of this patient is needed.

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≪悪性リンパ腫を極める：各病理組織型に基づく治療法≫
Hodgkin リンパ腫

大間知　謙*

要旨

- 放射線療法や化学療法の進歩により，Hodgkin リンパ腫は約 80%の例で長期生存が見込めるようになっている．
- 適切な治療を行うためには予後因子に基づいた疾患の層別化が必須であり，限局期・予後良好群，限局期・予後不良群，進行期の 3 群に分けて治療戦略を考える必要がある．
- それぞれの病態に応じて，放射線療法，化学療法，化学療法と放射線療法の併用を使い分ける必要がある．

はじめに

放射線療法や化学療法の進歩により，Hodgkin リンパ腫は約 80% の例で長期生存が見込めるようになっている[1]．しかし，良好な転帰を得るためには適切な治療が必要であり，そのためには予後因子に基づいた疾患の層別化が必須である．Hodgkin リンパ腫の予後因子としては，臨床病期，浸潤リンパ節領域数，巨大病変の有無，B 症状，赤沈などがあげられている．その中でも臨床病期はもっとも重要な予後因子であり，病期に加えて他の予後因子の数などにより層別化がなされているのが現状である．

層別化は，① 限局期・予後良好群，② 限局期・予後不良群，③ 進行期，の 3 群に分けられている．予後因子の扱いが研究グループにより若干異なっているため国際的な共通の基準は存在しないが，おおむね，限局期・予後良好群は予後不良因子を有さないⅠ～Ⅱ期，限局期・予後不良群は予後不良因子を有するⅠ～ⅡA 期，進行期はⅡB 期，Ⅲ～Ⅳ期とされている．Hodgkin リンパ腫に対する治療形態は，放射線療法，化学療法，化学療法と放射線療法の併用（combined modality treatment：CMT）療法がある．いずれの方法を用いるかは，病期や予後因子を加味した先述の 3 群に分けて考える必要がある．

Hodgkin リンパ腫は，治療による長期生存が高率に望める疾患群であり，長期的にはリンパ腫の予後よりも晩期毒性による合併症が問題となる．よって現在の課題は，① 放射線の照射野や照射量を減らすことの可能性，② 化学療法単独療法の検討，③ より短期間，より毒性の少ない化学療法の探求，それに併用する放射線療法の適正量の検討，となっている．

本稿では，各病期別に対するエビデンス，それらから考えられる現在の標準療法について解説する．

限局期・予後良好群

1．放射線単独療法

放射線照射量に関する比較試験は，German Hodgkin Study Group（GHSG）より報告されている．限局期・予後良好群の患者を，40 Gy の

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extended field radiotherapy (EF-RT) 群と，30 Gy の EF-RT に加え，それに続く 10 Gy の involved field radiotherapy (IF-RT) 群にランダム化して治療を行ったところ，5 年の freedom from treatment failure にて EF-RT 群で 70%，EF-RT＋IF-RT 群で 81% と，放射線量を減量したほうが上回っており，限局期の Hodgkin リンパ腫に対する放射線単独療法は 30 Gy で十分である可能性が示唆された[2]．

予後因子が考慮されていなかった時代の放射線療法では，上半身に対する広範囲な照射である mantle 照射であっても，長期の観察において約 5 割という高率な再発が認められていた．これは，限局期といえども約 20% に腹部リンパ節への浸潤が隠れていることに起因している．予後因子を考慮した照射野の範囲に関しては，The European Organization for Research and Treatment of Cancer (EORTC) で行われた，mantle 照射単独と mantle 照射と予防的腹部リンパ節への照射の併用の比較試験がある．腹腔鏡で腹部リンパ節浸潤陰性の限局期・予後良好群の患者のランダム化比較試験で，6 年無再発生存率が単独照射群 vs 拡大照射群で 74% vs 72% と，差は認められなかった[3]．retrospective な検討でも，予後因子を考慮した場合の mantle 照射の有効性は複数報告されており，現在でも放射線単独療法は，有力な治療オプションであると考えられる．

2．化学療法と放射線療法の併用

限局期・予後良好群は，放射線単独療法でも高率に治癒が期待できる．そのためこの疾患群では，長期的にみると原疾患そのものよりも発育障害，甲状腺機能低下，二次発癌などの放射線療法による晩期毒性が問題となることがしばしばある．そこで，毒性を減らした化学療法と限局した放射線療法の組み合わせにより，十分な局所制御と病変と隣接したリンパ節領域に対する予防的な治療を同時に行うことを目的とした，CMT が考案された．

EF-RT と CMT (EF-RT＋化学療法) の比較試験であるが，GHSG による ⅠA～ⅡB 期の患者を対象とした EF-RT と EF-RT＋ABVD 療法 (doxorubicin, bleomycin, vinblastine, dacarbazine) 2 コースの比較では，7 年の freedom from treatment failure で CMT が優っていた (67% vs 88%)[4] と報告されている．照射野を EF-RT から IF-RT へ縮小した CMT に関する比較試験がイタリアのグループから報告されているが，4 コースの ABVD 療法後に EF-ET，または IF-RT を行ったところ，12 年の freedom from progression rate でそれぞれ 93% vs 94% と，治療法により差がなかったとされている[5]．

以上を踏まえ，限局期・予後良好群に対する標準療法は，放射線照射に IF-RT を併用した CMT であり，化学療法の適応とならない場合の治療オプションとしては，EF-RT であると考えられている．

限局期・予後不良群○

過去の放射線療法の試験で再発したものから予後因子が抽出されており，放射線単独療法は治療の選択肢とはならない．

化学療法と CMT の比較試験が Grupo Argentino de Tratamiento de la Leucemia Aguda より報告されているが，Ⅰ，Ⅱ期の患者を対象に CVPP 療法 (cyclophosphamide, vinblastine, procarbazine, predonisone) 6 コースと，CVPP 療法 6 コース＋IF-RT 30 Gy を行ったところ，予後良好群では両群に差はなかったが，予後不良群では無再発生存率で 34% vs 75%，全生存率で 66% vs 84% と，CVPP 群のほうが下回っており[6]，この結果もあって，現状では化学療法単独よりも CMT 中心に治療開発が進められてきている．

CMT に用いられる化学療法のレジメンであるが，これは後述の進行期例に対する化学療法の変遷とともに変化してきており，現時点での標準は ABVD 療法と考えられている．CMT における化学療法のコース数，放射線の照射野に関しては，二つの大規模な比較試験の結果が参考になる．

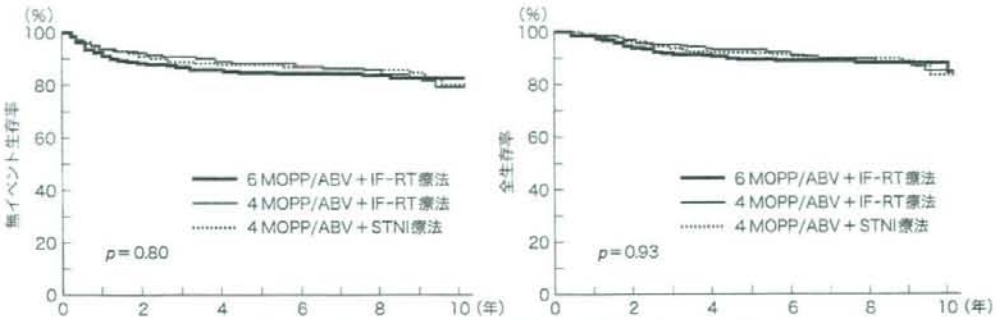

Fig. 1. 限局期・予後不良群に対する CMT 療法の生存曲線

GHSG により，COPP 療法(cyclophosphamide, vincristine, procarbazine, predonisone)＋ABVD 療法 4 コースと EF-RT 30 Gy または IF-RT の比較試験が行われ，5 年の freedom from treatment failure でそれぞれ 85.8% vs 84.2%，全生存率で 90.8% vs 92.4% と，差がなかったと報告された[7]．またこの報告では，照射野を小さくすることで急性毒性の頻度を減らすことができるのみでなく，二次発癌のリスクも減らすことができたとされている．

EORTC と Groupe d'Etude des Lymphomes de l'Adulte により行われた intergroup study において，MOPP/ABV 療法(nitrogen mustard, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine)6 コース＋IF-RT，MOPP/ABV 療法 4 コース＋IF-RT，MOPP/ABV 療法 4 コース＋EF-RT の比較試験では，5 年の無イベント生存率で 84% vs 88% vs 87%，10 年の全生存率で 88% vs 85% vs 84% と，3 群に差は認められなかった[8](Fig. 1)．

これらの結果を踏まえ，現時点での限局期・予後不良群に対する標準療法は，ABVD 療法 4 コースと IF-RT 併用の CMT とされている．

進　行　期

1．標準的な化学療法

第一世代の化学療法とされる MOPP 療法は，約 80% という高い完全寛解率の割に長期生存は約 50% しか得られないこと，アルキル化薬を中心とした併用療法は不妊や二次性白血病のリスクを上昇させることなどから，第二世代の化学療法として，交差耐性や単剤での高い効果が考慮されて組み合わされた ABVD 療法が開発された．さらに第三世代の化学療法として，腫瘍細胞が耐性を獲得することを回避するために寛解導入の早期に多剤を用いるべきという Goldie-Coldman の理論，およびそれぞれの毒性が重複しなかったという事実に基づき，MOPP 療法と ABVD 療法を組み合わせた MOPP/ABVD(ハイブリッド)療法が開発された．この治療は高い効果が認められていたが，急性毒性や二次発癌などの晩期毒性も，従来の化学療法よりも高い傾向にあった．

これらのレジメンを比較した試験が，Cancer And Leukemia Group B により報告されている．進行期の患者を MOPP 療法 6〜8 コース，MOPP/ABVD 療法 12 コース，ABVD 療法 6〜8 コースの 3 群にランダム化して治療を行ったところ，完全寛解率がそれぞれ 67% vs 83% vs 82%，5 年の failure free survival で 50% vs 65% vs 61% と，MOPP 療法よりほかの二つのレジメンより有意に上回っていた[9](Fig. 2)．ほかにも ABVD 療法とハイブリッド療法を比較した試験がいくつかあるが，いずれの結果においても，有効性に関してはほぼ同等だが毒性に関してはハイブリッド療法

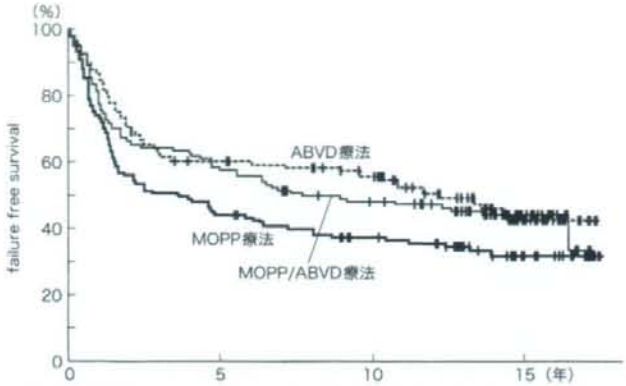

Fig. 2. MOPP vs ABVD vs MOPP/ABVD 療法における failure free survival
長期観察においても，ABVD および MOPP/ABVD 療法の優位性は変わらなかった．

が有意に多いとされており，これらの結果から，ABVD 療法はハイブリッド療法と同等の効果を有しながら毒性が少ないことが示され，進行期 Hodgkin リンパ腫に対する標準療法であると考えられている．

2．bulky mass に対する地固め療法としての放射線療法

悪性リンパ腫に対する日常診療では，治療開始時に bulky mass を有した例で，地固め療法としての放射線療法が行われることがしばしばあったが，その有用性を検討した比較試験がある．GHSG により，COPP/ABVD 療法 3 コースで完全寛解が得られたのちに IF-RT 20 Gy を行う群と，もう 1 コースの化学療法を行う群とでのランダム化が行われたが，無増悪生存率，全生存率のいずれも両群で差は認められなかったと報告された[10]．

EORTC からは，MOPP/ABV 療法 6〜8 コースで寛解が得られたのちに IF-RT を行う群と，無治療経過観察する群を比較した試験が報告されたが，5 年の無イベント生存率で 79% vs 84%，全生存率で 85% vs 91% と，ここでも治療により差はなかったとされた[11]．

これらのことから現在では，たとえ初発時に bulky mass を有したとしても，完全寛解後に放射線療法を加えることの意義は否定的と考えられている．

3．治療強度を高めた化学療法

化学療法の強度が弱いと治療効果も下がることは古くから指摘されていたことであるが，治療強度を強めることで治療効果が上がるのかという疑問に対する明確な答えは存在しない．化学療法の治療強度を高めた治療の代表的な例が，自家造血幹細胞移植併用の大量化学療法であるが，Hodgkin リンパ腫に対する地固め療法としての大量化学療法の意義を検討した比較試験が，European Bone Marrow Transplant Registry を中心に，intergroup study として行われた．

進行期患者を対象に ABVD 療法，または類似レジメンを 4 コース行ったのちに，部分寛解以上の効果が得られた患者を自家造血幹細胞移植併用の大量化学療法を行う群と，さらに 4 コースの化学療法を行う群にランダム化して治療を行ったところ，5 年の failure free survival で 75% vs 82%，全生存率で 88% vs 88%，無再発生存率で 88% vs 94% と，両群に差は認められず，地固め療法とし

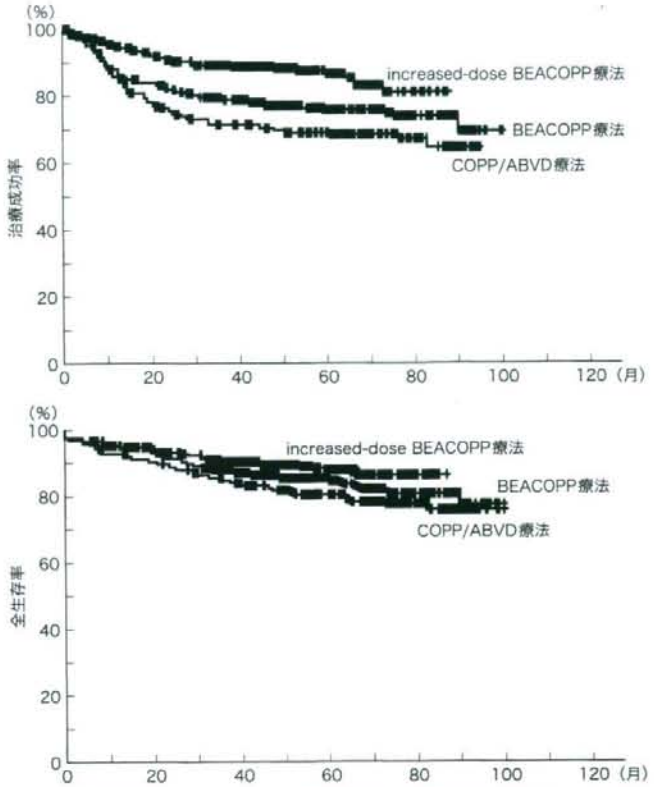

Fig. 3. 進行期 Hodgkin リンパ腫に対する COPP/ABVD 療法 vs BEACOPP 療法 vs increased-dose BEACOPP 療法の生存曲線
中間解析の時点で，COPP/ABVD 療法群が劣っていることが判明したため，途中から登録中止となっている．

ての大量化学療法を行う意義は証明されなかった[12]．

GHSG からは，通常の化学療法の治療強度を強めた比較試験が報告されているが，そこでは進行期例を対象に COPP/ABVD 療法と BEACOPP 療法 (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)，increased-dose BEACOPP 療法の比較を行ったところ，5 年の freedom from treatment failure で 69% vs 76% vs 87%，全生存率で 83% vs 88% vs 91% と，有意に強度を高めた治療法である increased-dose BEACOPP 療法が上回っていたという結果であった[13] (Fig. 3)．しかし，血液毒性を含めて，毒性は 3 群に差はなかったが，increased-dose BEACOPP 療法で治療が行われた 9 例に急性骨髄性白血病・骨髄異形性症候群が認められており，この結果をそのまま日常診療に適応させるには注意が必要である．

そのほかにもさまざまな研究グループにより，治療期間の短縮，治療強度の向上，毒性の軽減な

Fig. 4. Hodgkin リンパ腫に対する治療のフローチャート
CS：clinical stage，EF-RT：extended field irradiation，IF-RT：involved field irradiation，
RF：risk factor(巨大縦隔腫瘤，年齢，赤沈亢進，複数の浸潤リンパ節領域など)．

どを目的とした，第四世代のレジメンが報告されているが，それらのものがABVD療法に代わる治療レジメンとなるかは，現在検証中である．

今後の展望●

以上，現在のHodgkinリンパ腫治療におけるエビデンスについて述べてきた．これらをフローチャートにすると，Fig. 4のようになる．

しかしこれは現在検討中の新しい世代のレジメンを用いた比較試験の結果により，大きく変わっていくことも期待されている．また近年，悪性リンパ腫の診療に positron emission tomography (PET)が用いられるようになり，それを用いた治療戦略の可能性も検討されている．

Hodgkinリンパ腫は，PETがとくに有用である病型の一つであり，治療開始前の病期診断のみならず，治療の効果判定にも有用とされている．2コースの化学療法後にPETを行い，その時点でPET上完全寛解となっていた例と寛解となっていなかった例とに分けて予後をみたところ，寛解となっていた例のほうが有意に無増悪生存率および全生存率が良好であったことが報告されており[14]，今後はこれまで報告されてきたような予後因子以外に，治療の反応性に応じて早期に治療を完了したり，より強力な治療法を考慮するというような層別化がなされるようになるかもしれない．

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表紙体裁

表題*　執筆者名**

脚注：英文タイトル, 発表学会名, ローマ字綴り執筆者名, 役職名, 所属(病院の場合は郵便番号, 住所を入れる)

本　文

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1. X線フィルム, スライドは紙焼きし, 大きさは手札以上とする.
2. 写真中に必要な文字, 矢印などはトレーシングペーパーの上に記入する.
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