compensatory VEGF production and that autocrine/paracrine VEGF signaling is not involved in AS proliferation. To investigate other growth signaling pathway in angiosarcoma, we performed receptor tyrosine kinase (RTK) signaling array analysis. Among receptor tyrosine kinase signaling, this array demonstrated HAMON expressed Src stronger than HMVEC did (Supplementary Fig. 3).

4. Discussion

Our novel human AS cell line HAMON expresses endothelial marker CD31 and VEGFR2. HAMON has the potential to generate immature vessel-like structures. In addition, subcutaneous implantation of HAMON cells on NOD/*Scid* mice generated tumors identical to human AS. In comparison to previously reported AS cell lines [5,6], HAMON is considered a preferable cell line for the following reasons: (1) *in vivo* tumorigenecity was demonstrated and (2) HAMON proliferates stably in a commercially available medium (EBM-2).

As an *in vivo* experimental model of human AS, implanted human AS tissue has been maintained as serially xenotransplanted tumors. A similar *in vivo* model was reported by Masuzawa et al. [17], who had demonstrated the inhibitory effect of recombinant IL-2 immunotherapy against AS a decade before. However, it has been recognized that IL-2 monotherapy is not effective enough to control AS [18]. Furthermore, an *in vivo* model of heterotransplanted tumor tissue has been considered a more accurate preclinical model than cell-line-derived tumor models or genetically engineered tumor models [19,20]. Therefore, our serially heterotransplanted AS tumor can be regarded as an adequate *in vivo* experimental model of human AS. As far as we checked, AS metastatic lesion has not been identified in this model. With this xenografted model, *in vivo* therapeutic experiments were performed.

Recently, it has been well recognized that VEGF plays a crucial role in promoting tumor angiogenesis [21]. Therefore, as a promising treatment for tumors, several novel agents targeting VEGF signaling have been developed, such as an anti-VEGF antibody (bevacizumab) and receptor tyrosine kinase (RTK) inhibitors (*e.g.*, sorafenib, sunitinib). These reagents have shown anti-tumor effect against some advanced-stage tumors, such as those of colon cancer and renal cell carcinoma [8].

Bevacizumab, a recombinant anti-human VEGF antibody, is an initial drug targeting tumor angiogenesis, and this agent has been utilized supplementarily to other anti-cancer agents [22]. Several reports have also demonstrated the efficacy of bevacizumab monotherapy against solid tumors [12]. AS have been considered as tumors that depend on VEGF signaling in their biology; therefore, the inhibition by bevacizumab might lead to tumor suppression. We performed receptor tyrosine kinase signaling antibody array in order to check which signal pathway is activated in HAMON. Among receptor tyrosine kinase signaling, it demonstrated that only Src was upregulated in HAMON in comparison to in HMVEC (Supplementary Fig. 3). However, our experiment revealed that bevacizumab monotherapy is not effective enough to control AS *in vitro* and *in vivo*.

Sunitinib is an orally administered, small-molecular tyrosine kinase inhibitor that exhibits potent antiangiogenic and antitumor activity [23]. Targeted RTK receptors inhibited by sunitinib include VEGFR1 and VEGFR2, PDGFRs, c-kit and Flt1. Of these, the signal transduction initiated by VEGFR2 activation has been regarded as having the highest angiogenic potency [7]; therefore, it was speculated that VEGFR2 blocking by sunitinib might lead to the inhibition of AS growth. However, in our *in vitro* experiments, even 1 μM sunitinib did not induce suppression of cell proliferation of HAMON. Furthermore, in *in vivo* experiment, neither 40 mg/kg/day sunitinib nor 120 mg/kg/day sunitinib led to tumor regression or growth inhibition.

In the clinical field, RTK inhibitors have been administered against several tumors. On the other hand, some investigations with animal models have revealed that these inhibitors accelerate tumor invasion or metastasis [14,24]. This discrepancy suggests that the effects of angiogenesis inhibitors on tumors are not as theoretically simple as expected. In the case of AS, several reports have noted that agents targeting VEGF signal transduction should be promising against AS [9,25]. In fact a few successful cases have been also reported [26], however the outcomes in other clinical studies have not been as good as expected [27,28]. In addition, clinical trials of bevacizumab or other receptor tyrosine kinase inhibitors such as pazopanib in treating patients with angiosarcoma have been conducted, but the outcome remains unclear. To date, there have been very few preclinical and clinical trials of sunitinib against AS. Antonescu et al. reported that AS with *VEGFR2* mutation showed overexpression of VEGFR2 protein, and they suggested that such cases might be targeted by sunitinib [25]. In our novel cell line HAMON and serially transplanted AS tumor, *VEGFR2* mutation was not found (data not shown). It is possible that AS cases with *VEGFR2* mutation might respond better to sunitinib than HAMON and our xenotransplanted tumor did.

A few reports have shown that VEGF and VEGFRs are expressed in AS [10,11]. According to such expression profiling, the existence of an autocrine or paracrine loop of VEGF signaling in AS has been suspected. It has been revealed that endothelial cells secrete VEGF by themselves and that the VEGF autocrine pathway is also functional in endothelial cells [16]. Lee et al. demonstrated, in their study on VEGF signaling for vascular homeostasis, that consistent phosphorylation of VEGFR2 in human endothelial cells was achieved even without exogenous VEGF stimulation [16]. Additionally, Antonescu et al. reported that COS-7 cells transfected with *VEGFR2*-mutants showed autophosphorylation on tyrosine of VEGFR2 even under VEGF-free condition [25]. Furthermore, the phosphorylation level of VEGFR2 mutants was slightly decreased with recombinant human VEGF stimulation, and they regarded this reaction as a negative feedback loop. However, both studies were performed with cells other than AS; therefore, VEGF signaling on AS is not yet fully understood. Moreover, in therapeutic experiments with sunitinib against other tumors, no appreciable changes in VEGF and VEGFRs plasma levels were reported [15].

Our study demonstrates that, whereas exogenous VEGF accelerates HAMON proliferation, VEGF signaling in AS is not necessarily regulated by the autocrine and/or paracrine system, which is different from normal endothelial cells and genetically VEGFR2-activating cells. In addition, neither blocking of VEGF with bevacizumab nor blocking of the VEGFR2 with sunitinib led to the inhibition of AS growth. These data allow us to speculate that (1) VEGF signaling in AS is differently regulated than in endothelial cells and (2) different angiogenic/growth signaling also functions in AS. HAMON expressed Src stronger than HMVEC did. The Src pathway is highly active in sarcoma [29]. The small-molecule tyrosine kinase inhibitor dasatinib, which targets Src, decreased cell viability in chondrosarcoma cell lines [30]. In particular, Src has been known to cause metastatic sarcomas, hemorrhagic disease and hemangiosarcomas in chicken embryos [31]. Therefore, Src might be associated with AS biology and its growth signaling, although further investigation is required.

We conclude that, whereas VEGF-targeting therapy including anti-VEGF antibody and RTK inhibitors is promising for several tumors, VEGF signaling of AS might be regulated in a different fashion from tumor angiogenesis; therefore, monotherapy with anti-angiogenic agents should be administered to AS with careful consideration until the AS pathomechanism has been clearly clarified.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2013.02.008.

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薬疹を疑う臨床症状，検査成績の診かたと考え方

Katayama Ichiro
片山　一朗

はじめに

薬疹は日常臨床で他科からの依頼が多い代表的な皮膚疾患であるが，確定診断にいたらず，中毒疹という診断名で終わることも多い．中毒疹は教科書的にはほぼ薬疹と同義に扱われている（原因が特定出来ない場合）が訴訟時代の今日，原因を特定出来ない場合あえて薬疹と診断せず中毒疹としておいた方が良いという意見もみられる．臨床的にはウイルス感染症，接触皮膚炎（汎発性），膠原病，内臓悪性腫瘍なども原因病原体や接触抗原，背景疾患が特定，診断できなければ中毒疹の定義を満たすかと考えられる．このことは薬疹（汎発性接触皮膚炎も含める），ウイルス感染症，デルマドロームなどの全身疾患では皮疹発現に共通の病態が存在し，最終的な皮膚での表現型が中毒疹としての汎発性，紅斑性の皮疹を呈すると考えることも可能である．薬疹を疑わせる臨床症状は多様であるが基本的に診断が問題となるのは中毒疹としての汎発性の発疹を診たときの考え方かと思われる．本講演では私の診断アルゴリズと自験例を供覧し診断のポイントを考えてみたい．

薬疹の定義・概念

薬疹は経口ないし経静脈的に投与された薬剤により汎発性に生じた皮疹を指す．経皮的に投与された場合でもその反応が全身性に生じた場合や，坐剤，吸入剤，膣剤，舌下錠などによるものも薬疹として扱う（表1）[1]．アレルギー性，薬剤の毒性反応・蓄積などによる非アレルギー性，薬理作用による機序などにより生じる（表2）．薬疹は薬剤の再投与で同一の症状が再現されるが薬剤性過敏症症候群（DIHS）などではウイルス感染の極期，再活性化の時期にのみ薬疹が誘発されることがある．

片山　一朗　Katayama Ichiro
大阪大学皮膚科
〒565-0871 大阪府吹田市山田丘2-2

薬疹を疑う症状と診断の注意点

薬疹は急性，全身性に発症することが多く，その原因薬剤，臨床型も多彩・多様である．特に近年分子標的薬やバイオロジックス製剤があいつい

表1　薬疹の定義・概念

薬疹は経口ないし経静脈的に投与された薬剤により汎発性に生じた皮疹を指す
経皮的に投与された場合でもその反応が全身性に生じた場合や，坐剤，吸入剤，膣剤，舌下錠などによるものも薬疹として扱う
アレルギー性の機序，薬剤の毒性反応・蓄積などによる非アレルギー性の機序，薬理作用による機序などにより生じる
薬疹は薬剤の再投与で同一の症状が再現される．
アンピシリン疹，DIHSなどではウイルス感染の極期，再活性化の時期にのみ薬疹が誘発されれることがある．

表2　薬疹の発症機序

1 薬理作用：ステロイド痤瘡，分子標的薬（ゲフィチニブ，イマチニブなど）
2 蓄積作用：銀，ミノマイシン，アンカロンなど
3 アレルギー：固定薬疹，紅斑丘疹型薬疹など
4 毒性反応：ヨード疹，日光疹（ケトプロフェンなど）
5 菌交代現象：抗生物質
6 複数の病因：DIHS（ウイルス感染症＋アレルギー）
7 免疫変調作用：自己免疫疾患の誘導(IFNなど) 逆説反応（生物製剤など）
8 病因不明：手足症候群（分子標的薬，抗ガン剤） BRONJ（ビスフォスフォネート関連顎骨壊死）

で登場し，新しいタイプの薬疹が報告されている[2]．またジェネリック薬品へのシフトにより，過去のアレルギー歴があるにも拘わらず，同一成分の薬剤が投与されている例の増加や成分の違いによる薬剤テストの偽陽性，偽陰性の問題などが指摘されており[3]，アレルギーカードの発行や患者への服薬指導が重要と考えられる．病型に応じ迅速に診断，治療方針を決め，時期を逸さず対応する必要がある（表3，4）．

薬疹と中毒疹

小児ではパルボウイルスB19が感染するといわゆるリンゴ病と呼ばれる典型的な顔面の紅斑や四肢に網状の紅斑を呈する．小児皮膚筋炎でも伝染性紅斑や全身性エリテマトーデスと鑑別が困難な顔面の紅斑を診ることがあるか，これはその発症機序に何らかの共通性があるのかもしれない．成人では，パルボウイルスB19感染女性患者で，より汎発性で重篤な紅斑性の病変を認め，関節リウマチを疑わせる関節痛や発熱と顔面の浮腫など強い症状が見られる[4, 5]．このことは単に女性が小児に接することが多いことの反映なのか，膠原病が女性に多いことと関連するのか興味がもたれる．また特定のHLAを持つ患者にカルバマゼピンによるスチーブンス・ジョンソン症候群などの重症薬疹が発症しやすいこと[6]，分子標的薬などのバイオロジックス製剤が特定の臨床症状を呈しやすいことなどが報告され[7]，中毒疹・薬疹のあらた

表3　薬疹を疑う症状，所見

1）全身性に発疹が見られた場合
2）問診にて過去に同様のエピソードがある場合
3）患者の問診で薬剤との因果関係が明らかな場合
4）膠原病や自己免疫疾患においてその症状，臨床検査成績などが非定型的である場合
5）固定薬疹や皮膚粘膜眼症候群型など皮疹の性状より診断可能な場合
6）臨床検査にて末梢血好酸球増多，肝機能異常などが見られる場合
＊感染症との鑑別，肝，腎，肺など全身臓器の病変の有無を確認する．薬剤の内服　時期，既往，合併症などを家族を含め詳細に聞く事

表4　薬疹の診断の注意点

1）皮膚症状の評価：
　薬疹のタイプ，分布，性状，粘膜疹の有無の検討
　薬剤摂取歴の十分な問診(特に過去1ヶ月間の服薬歴)
　原因薬剤の絞り込み
2）薬剤歴の聴取：
　栄養剤や健康食品，漢方薬，坐剤などの使用歴
　多剤を内服している患者には薬剤日記を付けて貰う
　高齢者の場合家人から問診する必要がある
3）不安傾向の強い場合,アレルギーなどの思い込みが見られることがある（特に歯科麻酔など）

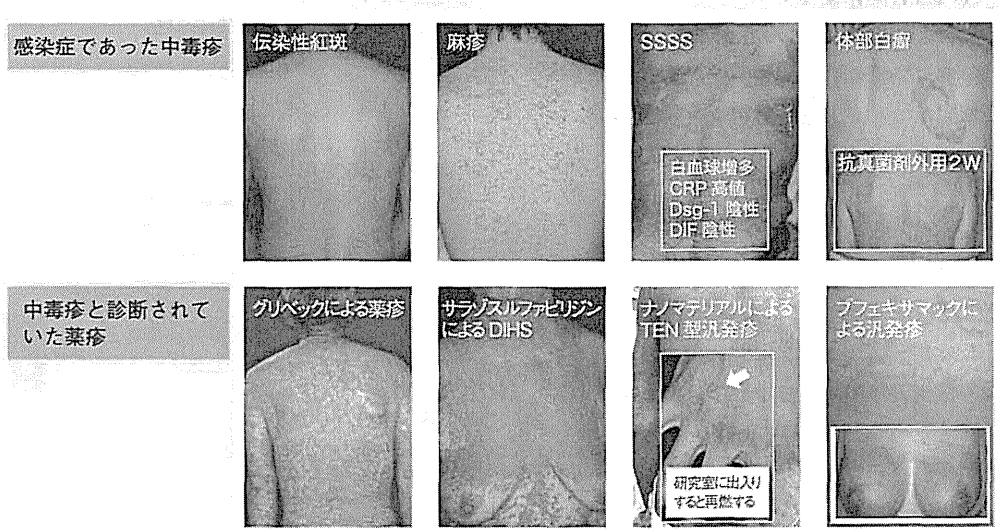

図1　感染症であった中毒疹，中毒疹と診断されていた薬疹

な発症機序や病因が明らかになってきた．図1に筆者の経験した薬疹，中毒疹の臨床像を示す．

臨床検査の進め方

皮膚科的検査：判定，手技ともに専門医に相談するのが望ましい．

●スクラッチ・プリック試験(IgE抗体を証明する)：薬剤溶液を一滴前腕に滴下し，皮内針，プリックランセッターにて穿刺し，20分後の膨疹形成を調べる．対照として正常人にも施行する必要がある．蕁麻疹型，アナフィラキシー型で陽性となる．

●皮内テスト（IgE抗体，IgG抗体を証明する）．IgE抗体では0.02ml，IgG抗体では0.1mlを皮内注射し20分後の膨疹および6，12，24時間後の紅斑形成を証明する．上記に加え，紫斑，血管炎型で陽性となることが多い．

●パッチテスト（感作T細胞を証明する）：薬剤を30%濃度でワセリンの希釈し，48時間のパッチテストを行う．紅斑丘疹型，多型紅斑型，苔癬型で陽性となることが多い．光線過敏型薬疹の場合，光パッチテストを行う，固定薬疹では皮疹部で行う．

●打ち消し試験：多数の薬剤を内服している場合，可能性の高い薬剤から漸次内服を中止し，症状の推移を見る．

●誘発試験：皮膚テストが陰性の場合行うが，アナフィラキシー型やTEN型などの重症薬疹では通常施行しない．うがい法，口含み法，口なめ法などを行い，陰性であれば常用量の1/100，1/10位から開始する．

●他の検査：肝機能検査，好酸球の増加の有無，ウイルス感染症の否定（EB, HHV6 IgG,IgM抗体をペア血清で測定するなど）などを行う．薬剤RAST，ヒスタミン遊離試験，リンパ球刺激試験（感作Tリンパ球の証明）は薬剤により陽性率は様々である．近年スチーブンス・ジョンソン症候群やTENなどの重症薬疹でGranulysinなどの血中レベルが上昇することが報告されており[8]，その意義についての検討が必要である．長崎大学で施行した検査所見では好酸球増多，肝機能障害，抗核抗体陽性などの異常が見られた（表5）が，これらはウイルス感染症などでも見られることより皮膚症状，粘膜症状などにも注意して診断する必要がある．我々の研究室では最近蛍光色素であるCFSUとBrDUを用いたFACSによる解析により，薬剤特異的なT細胞の動態を検討しており，制御性T細胞の誘導によるアレルギー反応の可能性を報告している[9] 図2に検査の進め方を示す．

あらたな薬疹の病因論

近年のバイオテクノロジーの急速な発展に伴い，人や動物の細胞や組織に由来する生物活性物質を遺伝子工学的手法により創り，医薬品・医療用具に応用する，いわゆるバイオロジックス，分子標的薬の開発が著しく進展している．この範疇に入る治療薬としては従来から使用されているヒト型ホルモンやヒト血漿蛋白などに加え，サイトカイ

表5　異常検査値のまとめ（長崎大学での検討）

好酸球の上昇（5%以上）	13／20（65.0%）
抗核抗体陽性（40倍以上）	7／12（58.3%）
LDHの上昇	7／12（36.8%）
GOTの上昇	7／19（30.0%）
GPTの上昇	6／20（25.0%）
IgEの上昇	2／14（14.3%）
組織中の好酸球浸潤	5／12（41.2%）
（好酸球上昇を伴う症例）	5／5
蛍光抗体直接法陽性	2／12（16.7%）

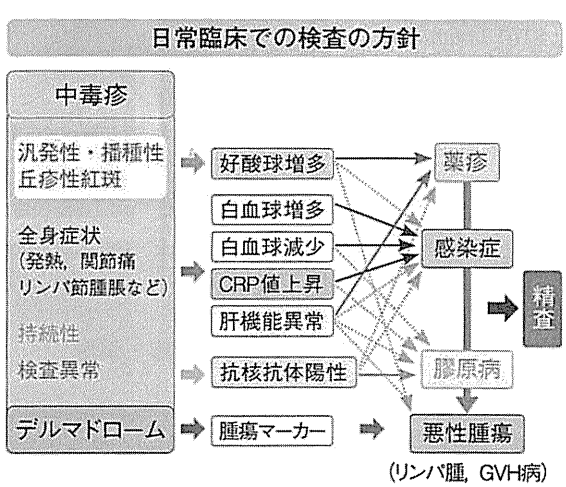

図2　薬疹を疑う時の検査の進め方

ン，成長因子，モノクローナル抗体，ウイルス・細菌ワクチン成長因子阻害薬などが挙げられるが，使用の機会が増加する過程で，その副作用としての皮膚障害も報告が増えている．従来の薬疹としての皮膚症状に加え，バイオロジックス本来の生物作用としての皮膚への影響も考慮して診断，治療を行って行く必要がある．

また最近図3に示すようなInflammasomeとよばれる細胞内シグナル転写因子群による炎症反応の誘導機構が注目されている[10]．本来アレルギー感作性を持たない物質がInflammasome活性化状態で誘導されるIL1などの存在下で感作性を示すことが報告され，薬疹発症の新しい機序として今後検討して行く必要がある[11]．

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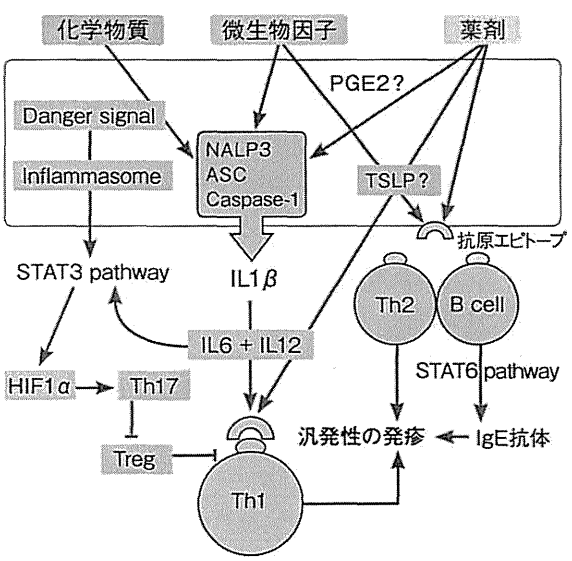

図3　Inflammasomeと中毒疹・薬疹

Eur J Dermatol 2012; 22(6): 1-3

CORRESPONDENCE

Toxic epidermal necrolysis complicated by sepsis, haemophagocytic syndrome, and severe liver dysfunction associated with elevated interleukin-10 production

Toxic epidermal necrolysis (TEN) is a condition of blistering and widespread purpuric macules involving more than 30% [1] of the total skin surface area. It is a life-threatening condition associated with a mortality rate of 20-70%, which is attributed to sepsis (33%) or other causes [1]. In more than 90% of cases, TEN is characterised as an adverse reaction to an administered drug [1]. Severe liver dysfunction is not typical during TEN as it affects 10% of cases.

Here, we report a case of TEN complicated by haemophagocytic syndrome (HPS) and severe liver dysfunction, in which increased interleukin (IL)-10 levels were detected in the patient's serum.

A 76-year-old Japanese woman, who was treated for 2 weeks with etodolac for cervical spondylosis, developed a cough and sore throat similar to a common cold 4 days after treatment began. On examination, severe liver dysfunction was found (serum levels of 1,166 IU/l aspartate aminotransferase and 1,302 IU/L alanine aminotransferase) accompanied for 3 days by extensive skin eruption. After these findings, etodolac administration was discontinued, and the patient was transferred to our hospital.

In addition to skin symptoms, extensive bulla formation and erosions were found in the oral and vulva mucous membrane. An abdominal lesional skin biopsy showed full-thickness epidermal necrosis and eosinophil infiltration. A drug lymphocyte stimulation test was etodolac-negative. Results of paired serological tests for mycoplasma, Epstein-Barr virus, herpes simplex virus, and cytomegalovirus were all negative. Moreover, no serum anti-hepatitis A, -hepatitis B surface antigen, or -hepatitis C virus antibody was found. Antinuclear antibody was negative. Despite steroid pulse therapy (1 g/day for 3 days), plasma exchange (total of five times), intravenous immune globulin administration (0.4 g/kg/day for 5 days), and antibiotic therapy during hospitalisation, the severe liver dysfunction and progression of epidermal detachment (approximately 60% of the body surface area) was prolonged, and the patient died due to sepsis.

Serum levels of IL-10 and other indicator molecules were monitored over the course of hospitalisation of the patient (summarized in *figure 1A*). In this case of TEN with HPS complication, increased IL-10 production appears to be a marker of poor prognosis. The elevated IL-10 is proposed to be a mediator of ongoing advanced liver degeneration during immunoenhancement, in an hypothesis we propose to explain our observations (*figure 1B*).

In cases of TEN, attention to sepsis followed by erosions is critical. The complicating HPS observed is a rare but frequently fatal disorder of immune regulation, characterized by pancytopenia, hepatosplenomegaly, and increased proliferation and activation of macrophages [2]. Clinical symptoms of HPS are not specific, and therefore diagnosis is frequently delayed or found at autopsy [3]. From our observations, we hypothesise that HPS may have begun at a period during sepsis when additional elevation of IL-10 was observed.

IL-10 is a central and critical anti-inflammatory cytokine produced by various cell populations including $Foxp3^+$ regulatory T cells, Th1, Th2, Th17, B-cells, and dendritic cells [4]. Serum concentration of IL-10 is significantly higher in fulminant versus severe acute hepatitis [5]. It has been observed that serum IL-10 is elevated in patients with both sepsis and HPS and proposed to be a prognostic factor [3, 6]. In this case report, serum IL-10 levels were apparently elevated after plasma exchange during progression of epidermal detachment. We propose that while modest increases in IL-10 levels may have a positive effect, a massive anti-inflammatory response may in fact lead to a poor prognosis.

In conclusion, this report is the first to show that a case of TEN complicated by sepsis, HPS, and severe liver dysfunction was accompanied by enhanced and prolonged

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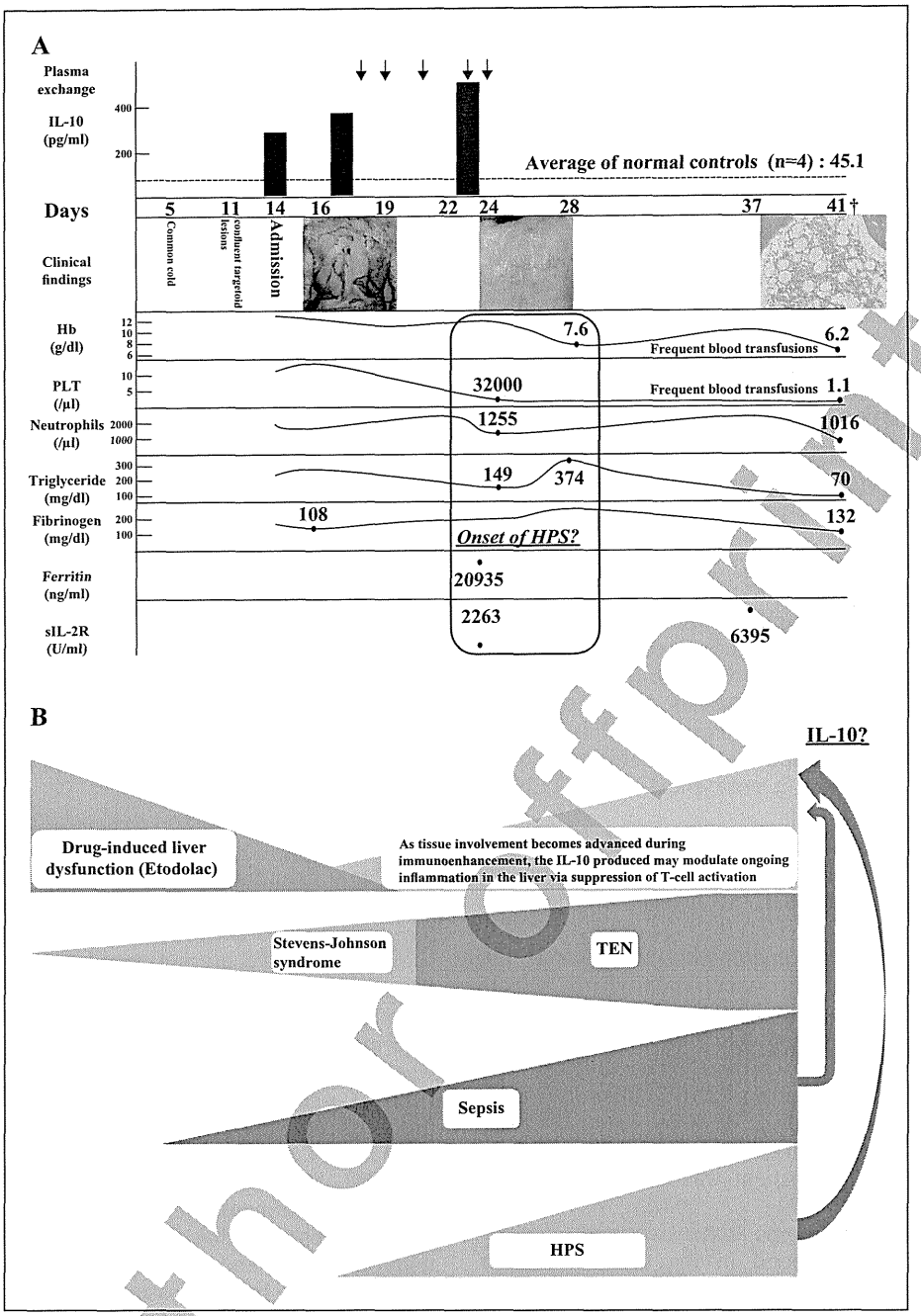

Figure 1. A) History, time course, and clinical findings of a patient with toxic epidermal necrolysis. Serum levels of IL-10 (measured by ELISA; Becton-Dickinson) and other indicators over the course of hospitalisation are shown. The average levels of IL-10 in normal control subjects are indicated by the broken line. The small inserts show the extensive skin involvement in the patient, and a photomicrograph of a section of involved skin indicates epidermal necrosis and eosinophil infiltration. Serum IL-10 levels were apparently further elevated after plasma exchange (indicated by arrows at the top of the figure). The proposed period of onset of haemophagocytic syndrome is indicated by the central boxed region. Abbreviations and symbols used: Hb, haemoglobin; PLT, platelet count; sIL-2R, soluble IL-2 receptor; HPS, haemophagocytic syndrome; †, death of the patient. **B)** Hypothesis relating prolonged elevated serum IL-10 levels to progression of liver dysfunction. Although drug-induced liver damage may improve after discontinuation of nonsteroidal immunosuppressant treatment, the elevated IL-10 production caused by sepsis and haemophagocytic syndrome is proposed to modulate ongoing liver inflammation via suppression of T-cell activation.

elevation of IL-10 production. Our observations are consistent with IL-10 being a key regulating factor in TEN progression. ■

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[1] Department of Dermatology,
[2] Department of Traumatology and Acute Critical Medicine,
[3] Department of Pathology,
Osaka University Graduate School of Medicine,
2-2 Yamadaoka, Suita,
Osaka 565-0871 Osaka, Japan
<yamaoka@derma.med.osaka-u.ac.jp>

Toshifumi YAMAOKA[1]
Hiroaki AZUKIZAWA[1]
Atsushi TANEMURA[1]
Hiroyuki MUROTA[1]
Tomoya HIROSE[2]
Koichi HAYAKAWA[2]
Takeshi SHIMAZU[2]
Naoki WADA[3]
Eiichi MORII[3]
Ichiro KATAYAMA[1]

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GUIDELINE

Guidelines for the management of cutaneous lymphomas (2011): A consensus statement by the Japanese Skin Cancer Society – Lymphoma Study Group

Makoto SUGAYA,[1] Toshihisa HAMADA,[2] Kazuhiro KAWAI,[3] Kentaro YONEKURA,[4] Mikio OHTSUKA,[5] Takatoshi SHIMAUCHI,[6] Yoshiki TOKURA,[6] Koji NOZAKI,[7] Koji IZUTSU,[8] Ritsuro SUZUKI,[9] Mitsuru SETOYAMA,[10] Tetsuo NAGATANI,[11] Hiroshi KOGA,[12] Mamori TANI,[13] Keiji IWATSUKI[2]

[1]*Department of Dermatology, Faculty of Medicine, University of Tokyo, Tokyo,* [2]*Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama,* [3]*Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences,* [4]*Department of Dermatology, Imamura Bun-in Hospital, Kagoshima,* [5]*Department of Dermatology, Fukushima Medical University School of Medicine, Fukushima,* [6]*Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu,* [7]*Department of Gastrointestinal, Breast and Endocrine Surgery, The University of Tokyo Hospital,* [8]*Department of Hematology, Toranomon Hostapital, Tokyo,* [9]*Department of Hematopoietic Stem Cell Transplantation Data Management/Biostatistics, Nagoya University Graduate School of Medicine, Nagoya,* [10]*Department of Dermatology, Faculty of Medicine, University of Miyazaki, Miyazaki,* [11]*Department of Dermatology, Tokyo Medical University Hachioji Medical Center, Tokyo,* [12]*Department of Dermatology, School of Medicine, Shinshu University, Matsumoto, and* [13]*Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan*

ABSTRACT

In 2010, the first Japanese edition of guidelines for the management of cutaneous lymphoma was published jointly by the Japanese Dermatological Association (JDA) and the Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group. Because the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: (i) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as mycosis fungoides/Sézary syndrome; and (ii) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal natural killer/T-cell lymphoma, nasal type. References that provide scientific evidence for these guidelines have been selected by the JSCS – Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system.

Key words: adult T-cell leukemia/lymphoma, cutaneous lymphoma, guideline, mycosis fungoides, Sézary syndrome.

INTRODUCTION

A number of guidelines on the management of cutaneous lymphoma have already been published in Europe and North America. However, the prevalence and clinical types of cutaneous lymphoma vary among different ethnic groups, and medical systems vary from country to country. As a result, the unmodified European/US guidelines may not be well-suited for use in Japan. We wanted to provide a "best treatment" consensus on clinical practice guidelines for cutaneous lymphoma, based on the actual situation in Japan.

In these guidelines, the diagnosis of cutaneous lymphoma is based on classifications from the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer, Cutaneous Lymphomas Task Force (EORTC),[1] and on the 4th edition of the WHO classification published in 2008.[2] The staging and classification of mycosis fungoides (MF)/Sézary syndrome (SS) are based on the tumor

Correspondence: Keiji Iwatsuki, M.D., Ph.D., Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmoceutical Sciences, Okayama, 700-8558, Japan. Email: keijiiwa@cc.okayama-u.ac.jp

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–node–metastasis (TNM) staging from the International Society for Cutaneous Lymphomas (ISCL) group.[3] For cutaneous lymphomas other than MF/SS, we decided to use the TNM staging system proposed by the ISCL[4] rather than the conventional Ann Arbor classification system.

The British group,[5] EORTC[6] and European Society for Medical Oncology (ESMO)[7] each issued treatment guidelines for MF/SS. In 2009, using published work and overseas guidelines for references, we published the first edition of guidelines based on the actual situation of cutaneous lymphoma in Japan.[8] Because the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: (i) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as MF/SS; and (ii) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal natural killer (NK)/T-cell lymphoma (ENKL), nasal type. References that provide scientific evidence for these guidelines have been selected by the Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system. The evidence level and degree of recommendation used for the current version are shown in Table 1.

BASIS FOR THE CURRENT GUIDELINES

The cutaneous lymphomas listed in the present guidelines are basically in accordance with the WHO–EORTC classification (2005),[1] but it is difficult to precisely define "primary cutaneous" lymphoma. Ordinarily, a condition is defined as "primary cutaneous" lymphoma if appropriate procedures show no extracutaneous lesions at the time of diagnosis. The present guidelines include lymphomas and hematopoietic malignancies with marked affinity for the skin (Fig. 1, Table 2). The diagnostic nomenclature follows the 4th edition of the WHO classification (2008).[2]

To describe the skin lesions of cutaneous lymphoma, typically MF/SS, uniform terminology is needed. Without consistent terminology, accurate disease staging is impossible, and inconsistencies may develop in prognostic analysis. The ISCL/EORTC group has defined terminology for MF/SS.[9] Those definitions are adopted in the present guidelines (Table S1), and representative clinicopathological findings of various types of cutaneous lymphoma are provided in supporting information (Figs S1–S7).

STAGING

Staging for MF/SS (ISCL/EORTC 2007, modified in 2011)

For the staging of MF/SS, we previously used the categories developed by Bunn *et al.*[10] and Sausville *et al.*[11] In 2007, a new staging system was proposed by the ISCL/EORTC group,[3] which was modified in 2011 (Tables S2 and S3).[12]

In the ISCL/EORTC staging system, peripheral blood findings are classified into three categories: B_0 (atypical lymphocytes accounting for $\leq 5\%$ of peripheral blood lymphocytes), B_1 (atypical lymphocytes accounting for >5% of peripheral blood lymphocytes, but <1000/μL), and B_2 (atypical lymphocyte

Table 1. Standards for the determination of evidence level and degree of recommendation

Classification of evidence level	
I	Systematic review and/or meta-analysis Staging/classification proposal and treatment recommendation or consensus paper from WHO, EORTC and ISCL
II	One or more randomized comparative studies
III	Non-randomized comparative studies
IV	Analytical epidemiology studies (cohort research and case–control studies) Case series studies (≥ 5 cases)
V	Descriptive studies (case reports and case series studies [<5 cases])
VI	Opinions of expert committee and individual specialists*
Degree of recommendation classification†	
A	Strongly recommended for implementation (efficacy shown by at least 1 report providing level I or high-quality level II evidence)
B	Recommended for implementation (efficacy shown by ≥ 1 reports providing low-quality level II, high-quality level III, or very high-quality level IV evidence)
B-C1	Recommended for implementation, but less strongly supported than B
C1	Implementation can be considered, but evidence‡ is insufficient (low-quality III–IV, high-quality multiple V, or committee-approved VI evidence)
C2	No evidence‡; cannot be recommended (no evidence of effectiveness, or evidence available of ineffectiveness)
D	Recommended not to implement (high-quality evidence of ineffectiveness or harmfulness)

*Data from basic research and theories derived from such data are placed at this level. †Some of the "degree of recommendation" statements in these guidelines are not in complete agreement with the above table. ‡"Evidence" refers to knowledge from clinical trials and epidemiological research. This is because these "degree of recommendation" grades were based on a consensus among the committee members, taking feasibility into account. This consensus was reached after due consideration of the shortage of evidence internationally on the treatment of skin cancer and the fact that the evidence from overseas is not directly applicable in Japan.

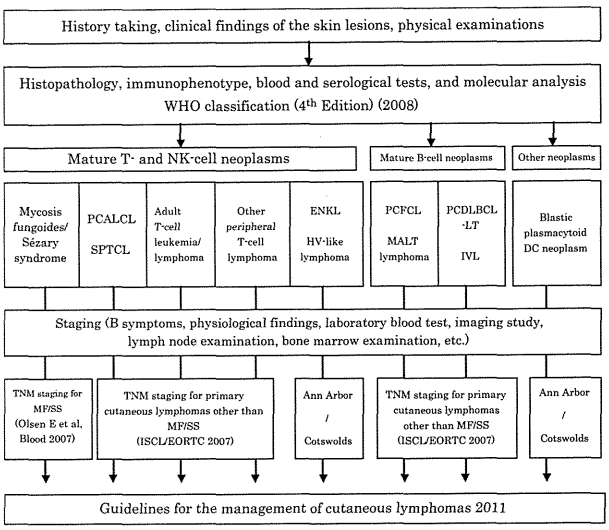

Figure 1. Diagnostic and staging algorithm for cutaneous lymphomas. DC, dendritic cell; ENKL, extranodal T/NK-cell lymphoma, nasal type; HV, hydroa vacciniforme; IVL, intravascular large B-cell lymphoma; MALT lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type; MF/SS, mycosis fungoides/Sézary syndrome; PCALCL, primary cutaneous anaplastic large cell lymphoma; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; PCFCL, primary cutaneous follicle center lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; TNM, tumor–node–metastasis; WHO, World Health Organization.

count of $\geq$1000/μL with a positive clone). Additional parameters that meet the B_2 criteria include the following: CD4/CD8 ratio of 10 or more, $CD4^+CD7^-$ of 40% or more, and $CD4^+CD26^-$ of 30% or more.[3,12,13] Cases with erythroderma who meet the B_2 criteria are defined as SS, or stage IVA_1 (Table S3 and Fig. S1). Erythrodermic MF of the B_0 or B_1 category is classified as stage IIIA or IIIB.

If lymphoma cells replace all or large portions of the lymph node structure, the condition is diagnosed as N_3 and is classified as stage IV_2 (Table S3). Even if the lymph node is infiltrated by atypical cells, a diagnosis of N_3 is not made as long as the foci are small and nodal architecture is preserved.[3,12]

TNM classification of cutaneous lymphoma other than MF/SS (ISCL/EORTC 2007)

No TNM classification appropriate for the evaluation of cutaneous lesions was available for primary cutaneous lymphoma categories other than MF/SS. In 2007, the ISCL and EORTC proposed a new TNM classification system (Table S4).[4] Although the TNM classification reflect the extent of lesions, an adequate staging system has not been established yet. Moreover, the classification does not indicate prognoses for some disease types.[14] The category of "non-MF/SS" covers many types of cutaneous lymphoma, and new staging systems are needed for each disease type, based on the collected clinical data and prognostic analysis.

Table 2. Classification of cutaneous lymphomas

Cutaneous T/NK cell lymphoma
Mycosis fungoides: MF
Variants
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome: SS
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Hydroa vacciniforme-like lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
Primary cutaneous $CD4^+$ small/medium T-cell lymphoma*
Peripheral T-cell lymphoma, not otherwise specified
Cutaneous B-cell lymphomas
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Hematological precursor cell neoplasm
Blastic plasmacytoid dendritic cell neoplasm

*Provisional. Representative clinicopathological features of MF/SS, anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, subcutaneous panniculitis-like T-cell lymphoma, extranodal NK/T cell lymphoma, hydroa vacciniforme-like lymphoma, blastic plasmacytoid dendritic cell neoplasm have been shown in Figs S1–S7.

Staging of other cutaneous lymphomas and hematopoietic malignancies

Shimoyama and colleagues have provided a widely-used classification of adult T-cell leukemia/lymphoma (ATLL): acute, lymphoma, chronic and smoldering types.[15] According to Shimoyama's criteria, ATLL patients with cutaneous lesions only are usually classified into the smoldering group. It is not appropriate to stage ATLL patients with the TNM system proposed by Kim *et al.*[4] because of the presence of minimal hematological disease. Furthermore, for other hematological malignancies such as ENKL, nasal type, and blastic plasmacytoid dendritic cell neoplasm, the Ann Arbor or Cotswolds staging (Table S5)[16] has been widely adopted in Japan because of hematological and extracutaneous spreading of the illness.

EPIDEMIOLOGY OF CUTANEOUS LYMPHOMA

In line with the WHO classification (3rd edn), the incidence of all types of lymphomas was reported by pathologists in Japan.[17] The data were distinct from those in Western countries and similar in several ways to other data from Asia, although the relatively high rate of ATLL was attributed to the geographical difference in the etiologic factor, human T-lymphotropic virus

type 1 (HTLV-1). The JSCS – Lymphoma Study Group has conducted a nationwide survey of cutaneous lymphoma annually since 2007 (www.okayama-hihuka.jp/pdf/kekka2010.pdf). MF/SS account for approximately 51% of all cutaneous lymphomas, followed by ALCL and ATLL at approximately 9–8% each. B-cell lymphoma accounts for approximately 15% of all cutaneous lymphoma in Japan, so it is less frequent than in Europe or North America. ENLK, nasal type, accounts for only approximately 2%, which is nearly always associated with Epstein–Barr virus (EBV) infection. The NK-cell type is dominant in Japan.

PROGNOSTIC ANALYSIS

Prognostic analyses of patients with cutaneous lymphoma are limited.[18–21] In the present guidelines, we have highlighted the prognoses of MF/SS, ATLL, and ENLK, nasal type, the latter two of which preferentially occur in Japan. For the other types of cutaneous lymphoma, we have used reports from other countries (Table 3).[22–26]

MF/SS

Previous researchers already contributed to disease staging and prognostic analysis for MF/SS.[27] Since the new staging was advocated in 2007, prognostic analyses have been reported from Japan and the UK (Table 3).[18,22] The survival rates of Japanese patients with MF/SS were similar to those shown in previous studies conducted in the USA and Europe. The prognoses of patients with skin tumor (stage IIB) and extracutaneous involvement (stage IV) were significantly worse than those of patients with early-stage disease (stages IA–IIA). Erythrodermic MF patients without blood involvement (stage IIIA) showed excellent survival. Independent prognostic factors in multivariate analyses were higher age and the presence of either skin tumor or extracutaneous disease.[18] Although findings in Japan showed the prognosis for stage IIIA to be quite favorable, a British analysis indicated that it was similar to the prognosis for stage IIb,[22] this may have occurred because the two reports did not use the same diagnostic criteria for erythrodermic lymphoma, resulting in differences in patient characteristics.

ATLL

A recent observation in Japan indicated that the patch and plaque types of ATLL were associated with better survival rates.[19] Multivariate analysis demonstrated that the hazard ratios of the erythrodermic and nodulotumoral types were significantly higher than that of the patch type, and that the eruption type is an independent prognostic factor for ATLL. The overall survival worsened as the T stage became more advanced: the multipapular type and T2 were comparable, and the purpuric type had a significantly poorer prognosis than T1 (Fig. S3).[19]

ENKL

Suzuki *et al.*[20] have reported the prognosis of a total 150 patients with ENKL, nasal type, consisting of 123 nasal and 27 extranasal (16 cutaneous, nine hepatosplenic, one intestinal and one nodal) lymphomas. We focused on patients with the cutaneous type of ENKL, and re-examined their prognoses. Patients with stage I disease (determined by the Ann Arbor staging system) showed a favorable prognosis in 5-year overall survival of 75%, but the prognoses deteriorated in the advanced stages (Table 3). Unlike a previous study on $CD56^+$ hematological neoplasms with or without EBV infection in Europe,[28] our data highlighted that ENKL is usually associated with EBV infection, and assessed the prognoses of "nasal" and "cutaneous" ENKL separately.

TREATMENT GUIDELINES

Treatment guidelines for MF/SS

Mycosis fungoides/Sézary syndrome is the oldest defined form of cutaneous lymphoma, and is more common than other primary cutaneous lymphomas (Tables 4–11). At present, no treatment based on high-level evidence is available for this condition. In many cases, the clinical course may extend for 10 years or more. Therefore, the success or failure of therapeutic intervention may be difficult to determine. Moreover, ethical issues may complicate the implementation of randomized placebo-controlled studies. Only four randomized studies have compared the effectiveness of different treatment methods[29–32] and only one randomized placebo-controlled study has been conducted.[33] These guidelines give substantial weight to consensus among the committee members. The "B" recommendation level has been given to first-line therapies for daily clinical practice.

An additional problem is that far fewer treatment options are available for MF/SS in Japan than in Western countries. In the present guidelines, we have included information on treatment modalities that have not been approved by the Japanese National Health Insurance system. Experimental therapies not yet approved overseas or in Japan have been omitted from these guidelines.

CQ1: Is monitoring the clinical course without treatment recommended for MF?
Degree of recommendation: C1 (stage IA only), C2 (other than stage IA).
Recommendation: In stage IA of MF, one acceptable option is to monitor the clinical course without treatment. For stages beyond IA, monitoring the clinical course without treatment is generally not recommended (Data S1).

CQ2: Are topical steroids recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Topical steroid therapy is recommended at all stages of MF/SS (Data S1).

CQ3: Is topical chemotherapy recommended for MF/SS?
Degree of recommendation: C1.
Recommendation: Mechlorethamine/nitrogen mustard (HN2) or carmustine (BCNU) topical chemotherapy is currently used in Europe and North America, and is recommended for early-stage MF (stage IA through IIA). These agents are not yet approved or available in Japan. Nimustine hydrochloride (ACNU) is currently used topically in some facilities in Japan,

Table 3. Survival rates of various cutaneous lymphomas and hematological neoplasms

Disease	Stage	5y-OS	5y-DSS	Median survival time (months)	References
MF/SS	IA	94–100	98–100	426	18, 22
	IB	84–89	89–95	258	
	IIA	78–87	87–89	190	
	IIB	47–73	56–88	56–78	
	IIIA	47–100	54–100	56	
	IIIB	40	48	41	
	IVA1	0–37	0–41	23–46	
	IVA2	18–33	23–50	25–46	
	IVB	0–18	0–18	13–17	
ATLL	T1	82.5	82.5	192.6*	19, 23
	T2	27.3	27.3	47.9	
	T3	0	0	17.3	
	T4	0	0	3	
	Multi-papular type	42.1	47.1		
	Purpuric type	40.0	40.0		
ALCL	T1	85	93		24
	T2	81	93		
	T3	63	77		
	Leg (–)	86	100		
	Leg (+)	53	67		
SPTCL	HPS (–)	91			25
	HPS (+)	45			
		Total 82			
Nasal ENKL	I	55 (4 years)		59.8	20
	II	33 (4 years)		11.2	
	III	31 (4 years)		33.1	
	IV	10 (4 years)		5.3	
		Total 36 (4 years)		Total 12.9	
Cutaneous extranasal ENKL	I	75 (2 years)		Not reached	20
	II	0 (2 years)		6.2	
	III	Not reached†		75.5†	
	IV	14 (2 years)		4	
		Total 33 (2 years)		Total 6.8	
BNKL	BM/blood (–)	0	25.3 (2 years)	17.1	21
	BM/blood (+)	19.6	46.4 (2 years)	20.4	
	Skin (–)	0	21 (2 years)	24.2	
	Skin (+)	20	48 (2 years)	22.2	
Extranodal MZL of MALT		94–97			26, 27
PCFCL		87–96			
PCDLBCL		37–73			

*Mean survival time. †One case. ALCL, anaplastic large cell lymphoma; ATLL, adult T cell leukemia/lymphoma; BM, bone marrow; BNKL, blastic NK-cell lymphoma; DSS, disease-specific survival; ENKL, extranodal NK/T-cell lymphoma; HPS, hemophagocytic syndrome; MF, mycosis fungoides; MZL of MALT, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; OS, overall survival; PCDLBCL, primary cutaneous diffuse large B-cell lymphoma; PCFCL, primary cutaneous follicle center lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; SS, Sezary syndrome.

and can be considered for small skin lesions or for short-term use (Data S1).

CQ4: Is ultraviolet (UV) light therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Oral psoralen plus UV-A therapy (PUVA) therapy or narrow-band UV-B therapy is recommended for early-stage MF (stage IA through IIA) (Data S1).

CQ5: Is PUVA therapy with concomitant retinoid or interferon (IFN) therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: PUVA with concomitant oral etretinate (RePUVA) or PUVA with concomitant IFN is recommended for MF/SS (Data S1).

CQ6: Is radiation therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Localized radiation therapy is recommended as a palliative treatment for skin lesions in MF, regardless of disease stage. Total skin electron beam therapy is recommended for MF (stage IB through IIA) (Data S1).

CQ7: Are oral retinoids recommended for MF/SS?
Degree of recommendation: B-C1.

Table 4. Summary of clinical questions and degree of recommendation for mycosis fungoides/Sézary syndrome

Clinical question	Degree of recommendation
CQ1: Is monitoring the clinical course without treatment recommended for mycosis fungoides?	C1 (stage IA) C2 (other than stage IA)
CQ2: Are topical steroids recommended for mycosis fungoides/Sézary syndrome?	B
CQ3: Is topical chemotherapy recommended for mycosis fungoides/Sézary syndrome?	C1
CQ4: Is ultraviolet light therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ5: Is psoralen plus ultraviolet A therapy with concomitant retinoid or interferon therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ6: Is radiation therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ7: Are oral retinoids recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ8: Is interferon therapy recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ9: Is extracorporeal photochemotherapy recommended for mycosis fungoides/Sézary syndrome?	B (erythroderma) C1 (non-erythroderma)
CQ10: Are molecular-targeted therapies recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ11: Is chemotherapy recommended for mycosis fungoides/Sézary syndrome?	B (refractory, extracutaneous lesions) D (early stage)
CQ12: Is hematopoietic stem cell transplantation recommended for mycosis fungoides/Sézary syndrome?	C1 (allogeneic) C2 (autologous)

Table 5. (MF/SS-1) Topical therapy of first choice recommended for stages I and IIA*

Treatment	Degree of recommendation	CQ
Monitoring the clinical course without treatment	C1 (stage IA only)/C2	CQ1
Topical steroid therapy†	B	CQ2
ACNU topical therapy‡	C1	CQ3
BB-UVB†	B	CQ4
NB-UVB	B	CQ4
PUVA	B	CQ4
Localized radiation therapy§	B	CQ6

*If the patient does not respond to the topical therapy selected for initial treatment, before proceeding to a second-line therapy recommended for stage I through IIA (Table 6 MFSS-2), consider the use of other first-line topical therapies. †Stage IA/IB. ‡Small area, short-term use. §Radical radiation therapy for "minimal" stage IA unilesional mycosis fungoides, or where multiple lesions are localized within the same radiation field or multiple field in close proximity, and palliative radiation for infiltrated plaques resistant to topical therapy other than radiation. ACNU, nimustine hydrochloride; BB, broad-band; NB, narrowband; PUVA, psoralen plus ultraviolet A therapy; UVB, ultraviolet B.

Table 6. (MF/SS-2) Second-line therapy recommended for stages I and IIA

Treatment	Degree of recommendation	CQ
TSEB*	B	CQ6
Etretinate†,‡	B-C1	CQ7
IFN-α†,§	B-C1	CQ8
IFN-γ†	B-C1	CQ8
RePUVA†	B	CQ5
IFN-α + PUVA †,§	B	CQ5
IFN-γ + PUVA †	B	CQ5
Chemotherapy¶	D/B¶	CQ11

*TSEB can be used as first-line therapy for stage IB/IIA (T2) with intense subjective symptoms accompanied by extensive highly infiltrated plaques and histopathological confirmation of folliculotropic mycosis fungoides or large cell transformation. †Can be a first-line treatment if systemic therapy is required (B1 or histopathological confirmation of folliculotropic mycosis fungoides or large cell transformation). BRM therapy (etretinate, IFN-α, IFN-γ) can be used as monotherapy or in concomitant administration with PUVA, and its concomitant use can also be investigated with topical therapies other than PUVA. ‡Duration of response to oral etretinate is usually short; consider for use as concomitant therapy. §IFN-α therapy has been used in only a few cases in Japan. ¶Third-line therapy for stage IB/IIA disease resistant to skin-targeted therapy and BRM therapy. BRM, biological response modifiers; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

Recommendation: Oral etretinate can be useful in the treatment of MF/SS (Data S1).

CQ8: Is IFN therapy recommended for MF/SS?
Degree of recommendation: B-C1.

Recommendation: IFN-α therapy is recommended in early-stage MF/SS (stage IA–IIA) if systemic therapy is required, and in advanced disease (stage IIB–IVA1). This treatment option has not yet been approved in Japan. IFN-γ, which has been used for the treatment of MF in Japan, is considered as effective as IFN-α, and may prove useful (Data S1).

CQ9: Is extracorporeal photochemotherapy (ECP) recommended for MF/SS?
Degree of recommendation: B (erythrodermic MF/SS), C1 (non-erythrodermic disease).

Recommendation: ECP/photopheresis is recommended for stage T4 erythrodermic MF and SS. It may also be considered in cases of refractory non-erythrodermic MF. ECP is

Table 7. (MF/SS-3) First-line therapy recommended for stage IIB*

Treatment	Degree of recommendation	CQ
Concomitant use of the following forms of BRM therapy and topical therapy		
BRM therapy		
Etretinate	B-C1	CQ5,7
IFN-α[†,‡]	B-C1	CQ5,8
IFN-γ[‡]	B-C1	CQ5,8
Topical therapy		
PUVA ± localized radiation therapy[§]	B	CQ4,5,6
Localized radiation therapy[§]	B	CQ6
TSEB[¶]	B	CQ6

*If the patient does not respond to initial treatment, before proceeding to a second-line therapy recommended for refractory stage IIB (Table 8 MFSS-4), consider other first-line topical therapies. [†]Concomitant therapy with IFN-α and PUVA: degree of recommendation = B. IFN-α therapy has been used in only a few cases in Japan. [‡]IFN-α monotherapy or IFN-γ monotherapy can be used as first-line therapy. [§]Palliative radiation for localized tumors. [¶]If lesions extend over <10% of body surface area, TSEB monotherapy can be used as first-line therapy. BRM, biological response modifiers; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

Table 8. (MF/SS-4) Treatment methods recommended for refractory stage IIB/III or stage IV mycosis fungoides

Treatment	Degree of recommendation	CQ
Chemotherapy*	B	CQ11

*Consider concomitant use of topical therapy appropriate for T classification.

Table 9. (MF/SS-5) First-line therapy recommended for stage III *

Treatment	Degree of recommendation	CQ
ECP ± IFN-α[†]	B	CQ9
TSEB + ECP[†,‡]	B	CQ6
Concomitant use of the following forms of BRM therapy and topical therapy		
BRM therapy		
Etretinate	B-C1	CQ5,7
IFN-α[†,§]	B-C1	CQ5,8
IFN-γ[§]	B-C1	CQ5,8
Topical therapy		
PUVA	B	CQ4,5
TSEB[§]	B	CQ6

*If the patient does not respond to initial therapy, before proceeding to a therapy recommended for refractory stage III (Table 8 MFSS-4), consider other first-line therapies. [†]ECP and IFN-α therapy have been used in only a few cases in Japan. [‡]TSEB monotherapy can be used as first-line therapy for stage IIIA disease. [§]IFN-α monotherapy or IFN-γ monotherapy can be used as first-line therapy. BRM, biological response modifiers; ECP, Extracorporeal photochemotherapy; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

Table 10. (MF/SS-6) Recommended therapy for Sézary syndrome (stage T4, IVA1-IVB)*

Treatment	Degree of recommendation	CQ
ECP ± IFN-α[†]	B	CQ9
TSEB + ECP[†]	B	CQ6
Chemotherapy ± IFN-α[†]	B	CQ11

*For stage IVA1 Sézary syndrome with a low Sézary cell count, initial therapy selection may be the same as for stage IIIB (Table 9 MF/SS-5). [†]ECP and IFN-α therapy have been used in only a few cases in Japan. ECP, extracorporeal photochemotherapy; IFN, interferon; TSEB, total skin electron beam.

Table 11. (MF/SS-7) Treatment to be considered for refractory stage IV disease

Treatment	Degree of recommendation	CQ
Allogeneic hematopoietic stem cell transplantation	C1	CQ12
Autologous hematopoietic stem cell transplantation	C2	CQ12

not yet approved by the Japanese National Health Insurance system, and currently almost no Japanese medical institutions perform the procedure (Data S1).

CQ10: Are molecular-targeted therapies recommended for MF/SS?
Degree of recommendation: B-C1.
Recommendation: Treatment with denileukin diftitox, vorinostat or romidepsin may be useful in recurrent or refractory MF/SS. Vorinostat is the only drug in this category that is approved for coverage by Japanese health insurance (Data S1).

CQ11: Is chemotherapy recommended for MF/SS?
Degree of recommendation: B (if disease is refractory or accompanied by extracutaneous lesions), D (early-stage MF).
Recommendation: Chemotherapy is not recommended as a first line of treatment in early-stage MF (stage IA–IIA). Chemotherapy is recommended for MF/SS stage IB–IIIB that is resistant to topical therapy or biological response modifier therapy, and for MF/SS stage IVA1–IVB accompanied by extracutaneous lesions (Data S1).

CQ12: Is hematopoietic stem cell transplantation recommended for MF/SS?
Degree of recommendation: C1 (allogeneic hematopoietic stem cell transplantation), C2 (autologous hematopoietic stem cell transplantation).
Recommendation: Autologous hematopoietic stem cell transplantation with concomitant high-dose chemotherapy is not generally recommended for MF/SS. In young patients with advanced disease, allogeneic hematopoietic stem cell transplantation may be considered in the context of a clinical study (Data S1).

Cutaneous T/NK-cell lymphoma other than MF/SS (non-MF/SS)

Cutaneous T/NK cell lymphomas other than MF/SS are classified by WHO–EORTC into two broad categories: relatively aggressive lymphomas with poor prognosis (aggressive group), and indolent lymphomas with favorable prognosis (indolent group) (Table 12).[1,34–39] In patients with aggressive lymphomas including primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma, primary cutaneous γδ T-cell lymphoma, and peripheral T-cell lymphoma, not otherwise specified, the 5-year survival rates are less than 20%. However, the clinical course is not uniform, and patients whose symptoms are limited to cutaneous lesions may live for much longer.

For patients who present with cutaneous lesions only, without general symptoms or notable laboratory test findings, skin-directed therapies used for MF/SS might be chosen as a first-line treatment. Systemic chemotherapy may be considered for patients with tumor infiltration into the lymph nodes or visceral organs. However, the best treatment option must be explored for each individual patient, based on that patient's conditions. Clinical questions (CQ) are not defined in this category because uniform guidelines are difficult to develop. In contrast, CQ have been defined in each lymphoma in the indolent group (primary cutaneous anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous $CD4^+$ small/medium T-cell lymphoma).

The MF/SS staging classifications are not applicable to cutaneous T/NK cell lymphomas other than MF/SS because of differences in disease progression. In 2007, the ISCL and EORTC jointly advocated the TNM classification system for cutaneous lymphomas other than MF/SS.[4] Because the prognostic impact of this classification system has not yet been validated, it might be premature to establish guidelines based on it. However, no other applicable classification systems are available at the present time. In order to obtain clinical information based on common criteria, we have adopted the TNM classification in the present guidelines.

Primary cutaneous anaplastic large cell lymphoma.

CQ13: Are localized therapies such as radiation therapy or surgical resection recommended for primary cutaneous anaplastic large cell lymphoma?
Degree of recommendation: B.
Recommendation: Remission can be induced by radiation therapy or surgical resection in many patients, so these methods are recommended where feasible (Data S1).

CQ14: Is chemotherapy recommended for primary cutaneous anaplastic large cell lymphoma?
Degree of recommendation: B (for lymph node lesions and visceral organ infiltration), C1 (symptoms limited to cutaneous lesions only).
Recommendation: For patients with cutaneous lesions only, if those lesions are resistant to topical treatment such as radiotherapy and surgical excision, or if they have multiple lesions, chemotherapy may be considered. Chemotherapy is recommended for lymph node lesions and for infiltration in the visceral organs (Data S1).

Subcutaneous panniculitis-like T-cell lymphoma.

CQ15: Is radiation therapy recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Radiation therapy can provide control of localized lesions within the irradiated area. Radiation can be considered as initial therapy for skin lesions within a localized area (T1, T2) without systemic symptoms (Data S1).

CQ16: Are oral steroids recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: B.
Recommendation: Steroid monotherapy has been reported to relieve systemic symptoms such as pyrexia and abnormal hepatic function and to induce remission in some cases; oral steroids are recommended for subcutaneous panniculitis-like T-cell lymphoma (Data S1).

Table 12. Summary of CQ and degree of recommendation for cutaneous T-/natural killer cell lymphoma (non-MF/SS)

Clinical question	Degree of recommendation
CQ13: Are localized therapies such as radiation therapy B or surgical resection recommended for primary cutaneous anaplastic large cell lymphoma?	B
CQ14: Is chemotherapy recommended for primary cutaneous anaplastic large cell lymphoma?	B (extracutaneous lesions) C1 (cutaneous lesions only)
CQ15: Is radiation therapy recommended for subcutaneous panniculitis-like T-cell lymphoma?	C1
CQ16: Are oral steroids recommended for subcutaneous panniculitis-like T-cell lymphoma?	B
CQ17: Is combination chemotherapy recommended for subcutaneous panniculitis-like T-cell lymphoma?	B-C1
CQ18: Is radiation therapy recommended for primary cutaneous $CD4^+$ small/medium T-cell lymphoma?	B
CQ19: Is chemotherapy recommended for primary cutaneous $CD4^+$ small/medium T-cell lymphoma?	C1

CQ17: Is combination chemotherapy recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: B-C1.
Recommendation: Combination chemotherapy may be considered if the condition is resistant to steroid therapy. Prognosis is poor for patients complicated by hemophagocytosis; combination chemotherapy is recommended in such cases (Data S1).

Primary cutaneous CD4$^+$ small/medium T-cell lymphoma.

CQ18: Is radiation therapy recommended for primary cutaneous CD4$^+$ small/medium T-cell lymphoma?
Degree of recommendation: B.
Recommendation: Radiation therapy can induce remission in many cases, and survival rates are relatively good. Radiation therapy is recommended for single and localized lesions (T1, T2) (Data S1).

CQ19: Is chemotherapy recommended for primary cutaneous CD4$^+$ small/medium T-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Chemotherapy can also be considered for primary cutaneous CD4$^+$ small/medium T-cell lymphoma with multiple lesions (Data S1).

ATLL (disease type limited to cutaneous lesions)

Adult T-cell leukemia/lymphoma is a form of T-cell lymphoma caused by HTLV-1 which occurs in a variety of organs (Table 13). Three major findings required for diagnosis: (i) appearance of morphologically abnormal T lymphocytes (typically CD4$^+$ and CD25$^+$); (ii) seropositivity for anti-HTLV-1 antibody; and (iii) Southern blot confirmation for monoclonal integration of HTLV-1 provirus into tumor cells.[15,40] For cutaneous symptoms to be diagnosed as eruptions specific to ATLL, histological confirmation is required for (i) and (iii). In particular, (iii) is required for a differential diagnosis to exclude other cutaneous lymphomas such as MF. The overall treatment guidelines for ATLL must involve cooperation and coordination with other departments, including departments of hematology and oncology. Thus, we limit these guidelines to instances in which only cutaneous lesions are detected. However, no uniform diagnostic criteria exist for the conventionally advocated concept of "cutaneous" ATLL.[40–43] The present guidelines cover ATLL cases, where systemic treatments such as chemotherapy and transplantation are not indicated.

Eruptions specific to ATLL are defined as cutaneous symptoms in cases seropositive for anti-HTLV-1 antibody and where cutaneous histology shows monoclonal integration of HTLV-1. In the present guidelines, we have provisionally considered "ATLL with cutaneous lesions only" to be "cases in which ATLL cells account for <5% of all peripheral blood cells, excluding the acute, lymphoma, and chronic types".[19,40]

Table 13. Summary of CQ and degree of recommendation for adult T-cell leukemia/lymphoma (ATLL) with cutaneous lesions only

Clinical question	Degree of recommendation
CQ20: Is ultraviolet light therapy recommended for ATLL with cutaneous lesions only?	B-C1
CQ21: Is radiation therapy recommended for ATLL with cutaneous lesions only?	B
CQ22: Are oral retinoids recommended for ATLL with cutaneous lesions only?	C1
CQ23: Is interferon therapy recommended for ATLL with cutaneous lesions only?	C1
CQ24: Is single-agent chemotherapy recommended for ATLL with cutaneous lesions only?	B-C1

CQ20: Is UV light therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B-C1.
Recommendation: PUVA therapy can induce remission in ATLL with cutaneous lesions only, and may be useful. Regardless of whether extracutaneous lesions are present, PUVA can be expected to relieve cutaneous symptoms. However, beneficial effects of PUVA on extracutaneous lesions or the prognosis of patients have not been confirmed (Data S1).

CQ21: Is radiation therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B.
Recommendation: Radiation therapy can be expected to provide symptomatic relief in ATLL with cutaneous lesions only, and is recommended. However, beneficial effects on the prognosis of patients have not been confirmed (Data S1).

CQ22: Are oral retinoids recommended for ATLL with cutaneous lesions only?
Degree of recommendation: C1.
Recommendation: Retinoids can induce remission in ATLL with cutaneous lesions only, and may be considered for use (Data S1).

CQ23: Is IFN therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: C1.
Recommendation: IFN-γ can relieve symptoms in ATLL with cutaneous lesions only, and may be considered for use. Beneficial effects on extracutaneous lesions or the prognosis of patients have not been confirmed (Data S1).

CQ24: Is single-agent chemotherapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B-C1.
Recommendation: Single-agent chemotherapy can be useful for disease refractory to skin-direct therapy in cases where combination chemotherapy is not indicated. However, beneficial effects on the prognosis of patients have not been confirmed (Data S1).

Other T/NK-cell lymphomas

In addition to ENKL, the WHO classification for hematopoietic malignancies, revised in 2008, has listed hydroa

vacciniforme-like lymphoma as an independent disease (Table 14).[2] This condition has been reported in Asia, including Japan, in Mexico, and in Peru. Hydroa vacciniforme-like lymphoma is a form of T-cell lymphoma that is associated with EBV. It occurs most frequently in children and adolescents, and is often accompanied by photosensitivity and hypersensitivity to insect bites. Prognosis, although varied, is poor if complicated by systemic conditions such as hemophagocytosis. There have been no reports of treatment for this condition alone, but a few reports are available on treatment of chronic active EBV infection and on EBV^+ T/NK-cell lymphoproliferative diseases. Treatment has been attempted with antiviral therapy using the antiviral agents acyclovir and ganciclovir, immunotherapy using agents such as IFN-α and interleukin 2, and chemotherapy using corticosteroids and etoposide.[44] However, the reports involve a very small number of cases, insufficient even for descriptive research, so findings cannot be considered conclusive.

Blastic plasmacytoid dendritic cell neoplasm is a rare disease formerly designated as $CD4^+/CD56^+$ hematodermic neoplasm.[45] Most patients usually respond to initial polychemotherapy, but the relapse rate is high. The prognosis is dismal, with a median overall survival of 12–14 months.

ENKL, nasal type.

CQ25: Is CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy recommended for ENKL, nasal type?

Degree of recommendation: C2.

Recommendation: ENKL, nasal type, generally responds poorly or only temporarily to CHOP therapy; this treatment is not recommended (Data S1).

CQ26: Is combination radiation therapy and chemotherapy recommended for ENKL, nasal type?

Degree of recommendation: B.

Recommendation: For localized lesions, radiation therapy with simultaneous or subsequent DeVIC (dexamethasone, VP16, ifosfamide, carboplatin) chemotherapy is recommended (Data S1).

Blastic plasmacytoid dendritic cell neoplasm.

CQ27: Is chemotherapy recommended for blastic plasmacytoid dendritic cell neoplasm?

Degree of recommendation: C1.

Recommendation: No standard treatment has been established for blastic plasmacytoid dendritic cell neoplasm. Multidrug chemotherapy may be considered. However, such treatment provides only temporary effectiveness, and almost all patients die within a few years (Data S1).

Hydroa vacciniforme-like lymphoma.

CQ28: Is allogenic hematopoietic stem cell transplantation recommended for hydroa vacciniforme-like lymphoma?

Degree of recommendation: B-C1.

Recommendation: Allogenic hematopoietic stem cell transplantation may be useful in the treatment of hydroa vacciniforme-like lymphoma (Data S1).

Cutaneous B-cell lymphoma

The WHO–EORTC classification of 2005 lists the following subtypes within the category of cutaneous B-cell lymphoma:[1] primary cutaneous marginal zone B-cell lymphoma (PCMZL); primary cutaneous follicle center cell lymphoma (PCFCL), primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, leg type); PCLBCL, other; and intravascular large B-cell lymphoma (IVL) (Table 15). In the 2008 revision of the WHO classification of hematopoietic malignancies, the nomenclature, the PCMZL was replaced by "extranodular marginal zone B-cell lymphoma (MALT lymphoma)".[2] The term, PCDLBCL, leg type, was entered as a subcategory of "diffuse large B-cell lymphoma, not otherwise specified". The term "primary cutaneous diffuse large B-cell lymphoma, other" was removed from the list. Disease type is an important prognostic factor for cutaneous B-cell lymphoma. Both PCFCL and PCMZL are indolent-type lymphomas with a favorable prognosis, while prognosis is poor in PCDLBCL and IVL. In the following discussion, cutaneous B-cell lymphoma is divided into two groups: the indolent group and diffuse large cell group.

No randomized clinical trials have been conducted in these disease groups, and research has been limited primarily to descriptive studies. However, in 2008, the EORTC and ISCL published guidelines for the treatments of cutaneous B-cell lymphoma, based on previous reports.[46] Most of the reported treatment methods for topical therapy involved radiation and/or surgical resection. Most of the methods for systemic therapy involved chemotherapy and the administration of rituximab. However, a few reports were found on topical administration of IFN-α and on the use of photodynamic therapy.

Table 14. Summary of CQ and degree of recommendation for other natural killer (NK)/T-cell lymphomas and related diseases

Clinical question	Degree of recommendation
CQ25: Is CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy recommended for extranodal NK/T-cell lymphoma, nasal type?	C2
CQ26: Is combination radiation therapy and chemotherapy recommended for extranodal NK/T-cell lymphoma, nasal type?	B
CQ27: Is chemotherapy recommended for blastic plasmacytoid dendritic cell neoplasm?	C1
CQ28: Is allogenic stem cell transplantation recommended for hydroa vacciniforme-like lymphoma?	B-C1

Table 15. Summary of CQ and degree of recommendation for primary cutaneous B-cell lymphoma (indolent type: primary cutaneous follicle center lymphoma and extranodal marginal zone lymphoma)

Clinical question	Degree of recommendation
CQ29: Is radiation therapy recommended for indolent-type primary cutaneous B-cell lymphoma?	B
CQ30: Is surgical resection recommended for indolent-type primary cutaneous B-cell lymphoma?	B
CQ31: Is rituximab monotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?	B-C1
CQ32: Is combination chemotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?	C1
CQ33: Is combination chemotherapy recommended for primary cutaneous diffuse large B-cell lymphoma?	B
CQ34: Is rituximab monotherapy recommended for primary cutaneous diffuse large B-cell lymphoma?	B
CQ35: Are surgical resection and radiation therapy recommended for diffuse large B-cell lymphoma?	C1

CQ29: Is radiation therapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B.
Recommendation: Radiotherapy is recommended for diseases in the indolent group (PCMZL and PCFCL) (Data S1).

CQ30: Is surgical resection recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B.
Recommendation: Surgical resection is recommended for resectable lesions of diseases in the indolent group (PCMZL and PCFCL) (Data S1).

CQ31: Is rituximab monotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B-C1.
Recommendation: Rituximab may be useful for the treatment of diseases in the indolent group (PCMZL and PCFCL), particularly in cases of multiple lesions (Data S1).

CQ32: Is combination chemotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Combination chemotherapy may be considered for diseases in the indolent group that are refractory to other treatment regimens, and for advanced extracutaneous disease (Data S1).

CQ33: Is combination chemotherapy recommended for PCDLBCL?
Degree of recommendation: B.
Recommendation: Combination chemotherapy, and particularly the concomitant use of rituximab, is recommended for PCDLBCL, leg type, and for IVL (Data S1).

CQ34: Is rituximab monotherapy recommended for PCDLBCL?
Degree of recommendation: B.
Recommendation: Rituximab monotherapy is recommended for the treatment of PCDLBCL in cases where combination therapy may be poorly tolerated, such as in the elderly and in patients with severe complications (Data S1).

CQ35 Are surgical resection and radiation therapy recommended for PCDLBCL?
Degree of recommendation: C1.
Recommendation: In patients who cannot tolerate rituximab combination chemotherapy, such as the elderly and patients with severe complications, surgical resection and radiation therapy may be considered (Data S1).

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