Ⅲ-11 肺高血圧症

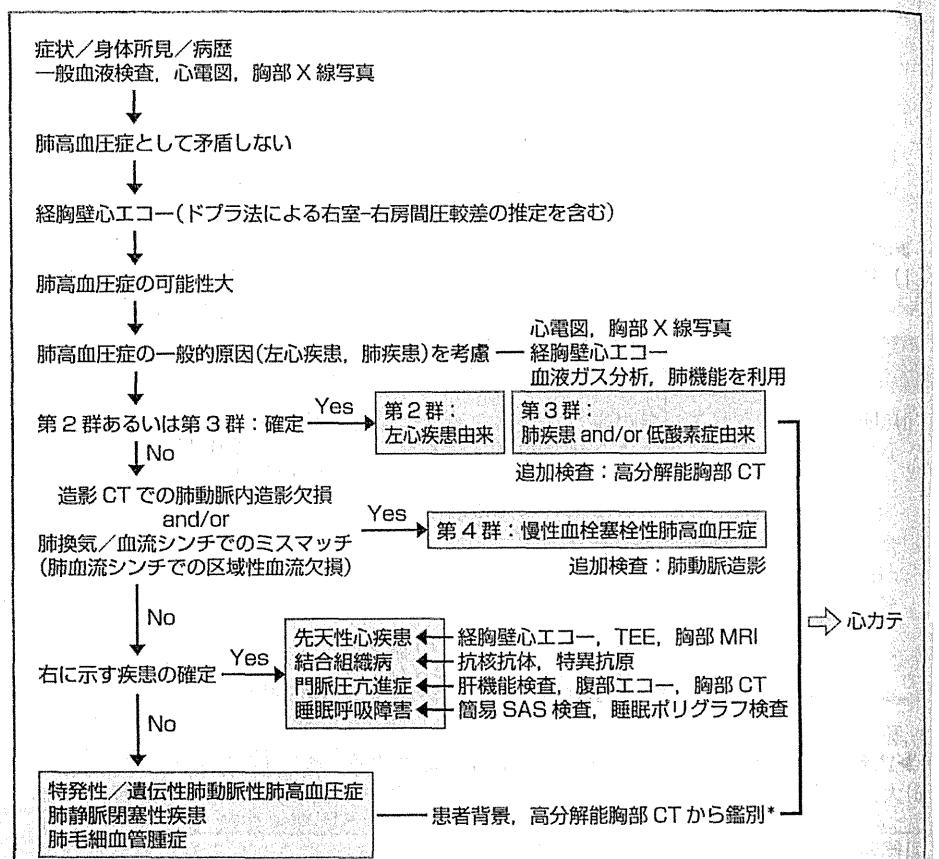
肺高血圧症治療ガイドライン 2012 年改訂版(2012)

東京大学大学院医学系研究科循環器内科学助教　波多野　将

アルゴリズム

①肺高血圧症(PH)　診断アルゴリズム

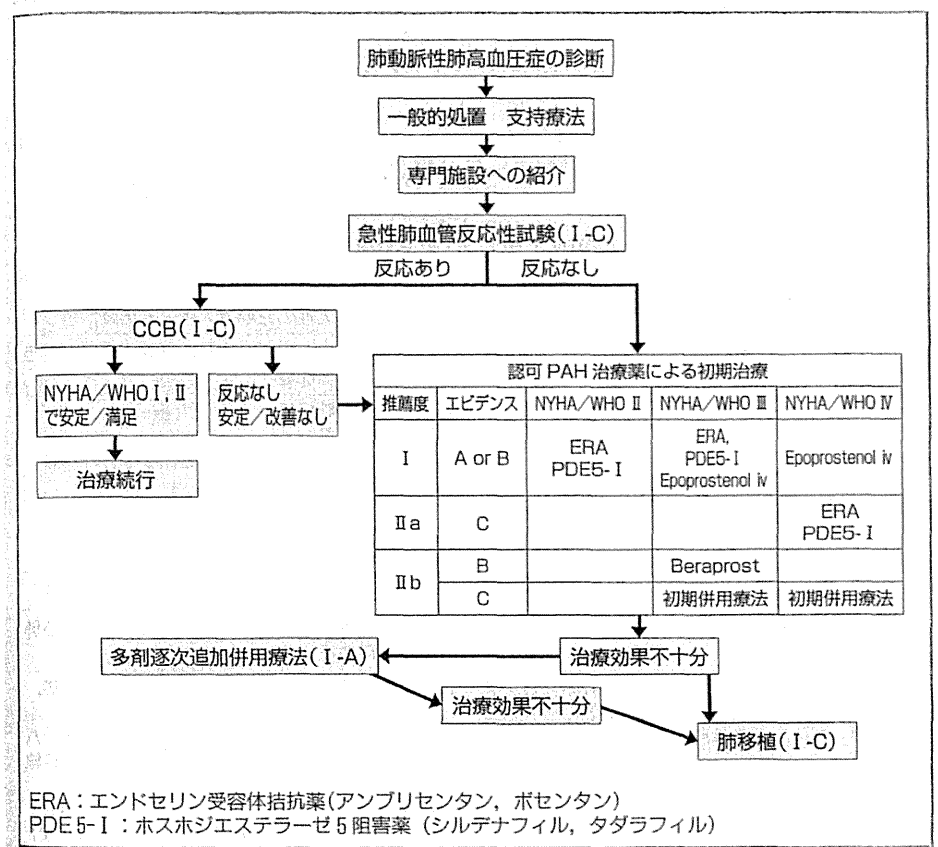
- まず，労作時呼吸困難，息切れ，易疲労感などの症状から PH を疑うことから始まる。
- 心電図，胸部 X 線写真，血液検査(BNP もしくは NT-proBNP)がスクリーニングとして有用であるが，軽症例では異常を示さないこともあるので，疑いのある症例においては必ず心エコーを行う。



(循環器病の診断と治療に関するガイドライン．肺高血圧症治療ガイドライン(2012 年改訂版)．http://www.j-circ.or.jp/guideline/pdf/JCS2012_nakanishi_h.pdf(2014 年 2 月閲覧)より許諾を得て転載)

②肺動脈性肺高血圧症(PAH)　治療アルゴリズム

- 特発性／遺伝性肺動脈性肺高血圧症の患者では一酸化窒素吸入やエポプロステノール静注などを用いて急性肺血管反応試験を行う。10%程度の症例で陽性となり(＝心拍出量の低下なく平均肺動脈圧が 10 mmHg 以上低下し，40 mmHg 未満となる)，このような症例では Ca 拮抗薬による治療を考慮する。急性肺血管反応試験は必ず肺高血圧治療に精通した専門施設で行う。
- 急性肺血管反応試験陰性の場合，WHO 機能分類Ⅱないし Ⅲ度の症例ではエンドセリン受容体拮抗薬(ERA)もしくはホスホジエステラーゼ阻害薬(PDE 5-I)内服により治療を開始する。単剤で治療効果不十分の場合には引き続き多剤併用療法を行う。
- 経口プロスタサイクリン(PGI_2)製剤(ベラプロスト)はエビデンスの面で劣るためガイドライン上の推奨度は低いが，わが国では ERA および PDE 5-I とほぼ同等に使用されている。
- WHO 機能分類Ⅲないし Ⅳ度の重症例においては，初期からの併用療法ないしエポプロステノール持続静注療法を行う。エポプロステノールの導入は肺高血圧治療に精通した専門施設で行うのが望ましい。



ERA：エンドセリン受容体拮抗薬(アンブリセンタン，ボセンタン)
PDE 5-Ⅰ：ホスホジエステラーゼ 5 阻害薬(シルデナフィル，タダラフィル)

(循環器病の診断と治療に関するガイドライン．肺高血圧症治療ガイドライン(2012 年改訂版)．http://www.j-circ.or.jp/guideline/pdf/JCS2012_nakanishi_h.pdf(2014 年 2 月閲覧)より許諾を得て転載)

総説

定義

❶安静時の平均肺動脈圧が25 mmHg以上となる疾患の総称。

❷さらに，2013年2月末にニースで開かれた第5回世界肺高血圧症シンポジウムにより，PHは表1の通り5つのグループに分類される。

❸第1群のPAHは肺動脈楔入圧(PCWP)が15 mmHg以下のものをいい，PCWPが15 mmHgを超えるものは第2群の左心性心疾患に伴うPHに分類される。

診断

❶前述の診断アルゴリズムに従い臨床分類を行う。

❷スクリーニングは心エコーなどを用いて行うが，確定診断のためには必ず右心カテーテル検査を行う。

❸PHのハイリスク患者(特に膠原病の患者)においては，症状がなくてもスクリーニング検査を定期的に行う。

❹膠原病の患者などでは複数の原因が合併していることもあるので，検査は極力網羅的に行う。

表1　再改訂版肺高血圧症臨床分類(ニース分類2013)

第1群．肺動脈性肺高血圧症(PAH)	第2群．左心性心疾患に伴う肺高血圧症
1)特発性肺動脈性肺高血圧症(idiopathic PAH：IPAH)	1)左室収縮不全 2)左室拡張不全 3)弁膜疾患 4)先天性／後天性の左心流入路／流出路閉塞
2)遺伝性肺動脈性肺高血圧症(heritable PAH：HPAH) 1．BMPR2 2．ALK1，endoglin，SMAD9，CAV1 3．不明	第3群．肺疾患および／または低酸素血症に伴う肺高血圧症
3)薬物・毒物誘発性肺動脈性肺高血圧症	1)慢性閉塞性肺疾患 2)間質性肺疾患 3)拘束性と閉塞性の混合障害を伴う他の肺疾患 4)睡眠呼吸障害 5)肺胞低換気障害 6)高所における慢性暴露 7)発育障害
4)各種疾患に伴う肺動脈性肺高血圧症(associated PAH：APAH) 1．結合組織病 2．エイズウイルス感染症 3．門脈肺高血圧 4．先天性短絡性疾患 5．住血吸虫症	第4群．慢性血栓塞栓性肺高血圧症(CTEPH)
	第5群．詳細不明な多因子のメカニズムに伴う肺高血圧症
第1'群．肺静脈閉塞性疾患(PVOD)および／または肺毛細血管腫症(PCH) 第1"群．新生児遷延性肺高血圧症(PPHN)	1)血液疾患(慢性溶血性貧血，骨髄増殖性疾患，脾摘出) 2)全身性疾患(サルコイドーシス，肺ランゲルハンス細胞組織球症，リンパ脈管筋腫症，神経線維腫症，血管炎) 3)代謝性疾患(糖原病，ゴーシェ病，甲状腺疾患) 4)その他(腫瘍塞栓，線維性縦隔炎，慢性腎不全)区域性肺高血圧

(第5回肺高血圧症ワールド・シンポジウム，2013)

治療方針

❶PAHにおいてはその重症度や予後を規定する因子として表2のようなものが挙げられている。これらの因子が予後良好のカテゴリーに入ること(たとえばWHO機能分類ならばⅠないしⅡ度)を治療目標にする。

❷膠原病性PAHにおいては，膠原病の疾患活動性がある場合やPHが進行性の場合などにはステロイドや免疫抑制剤による治療を考慮する。

❸ERA，PDE 5-I，PGI_2の保険適用はすべてPAHに限られている。第2群～第5群のPHに対するこれらの薬剤の安易な使用は避けるべきである。

❹第2群，第3群のPHにおいては基礎疾患に対する治療を十分に行う(肺疾患に対する在宅酸素療法など)。

❺慢性血栓塞栓性肺高血圧症(CTEPH)では，十分な抗凝固療法および酸素療法とともに，血栓が肺動脈の中枢側に存在する場合には肺動脈血栓内膜摘除術(PEA)を考慮する。末梢型CTEPHの場合には肺動脈バルーン拡張術(BPA)を考慮する。BPAは必ず手技に精通した専門施設で行う(図1)。

❻アドバンスド　現在CTEPHに保険適用のある肺血管拡張薬は存在しないが，可溶性グアニル酸シクラーゼ刺激薬であるRiociguatの有用性が近年報告され，2013年現在わが国でもCTEPHに対して承認申請中である。

表2　PAHの重症度／予後評価

予後良好	予後決定因子	予後不良
無	右心不全の既往	有
遅	症状の進行度	速
無	失神	有
Ⅰ，Ⅱ	WHO-機能分類	Ⅲ，Ⅳ
500 m以上	6 MWT	300 m以下
15 mL/min/Kg以上	CPX (最大酸素摂取量)	12 mL/min/Kg以下
正常，ほぼ正常	BNP	非常に高値，上昇傾向
心嚢液(−)， TAPSE>2.0 cm	心エコー所見	心嚢液(+)， TAPSE<1.5 cm
RA圧<8 mmHg CI>2.5 L/min/m^2	肺血行動態	RA圧≧8 mmHg CI<2.0 L/min/m^2

CPX：心肺運動負荷試験

(McLaughlin VV, et al：Circulation 114：1417-1431, 2006より一部改変)

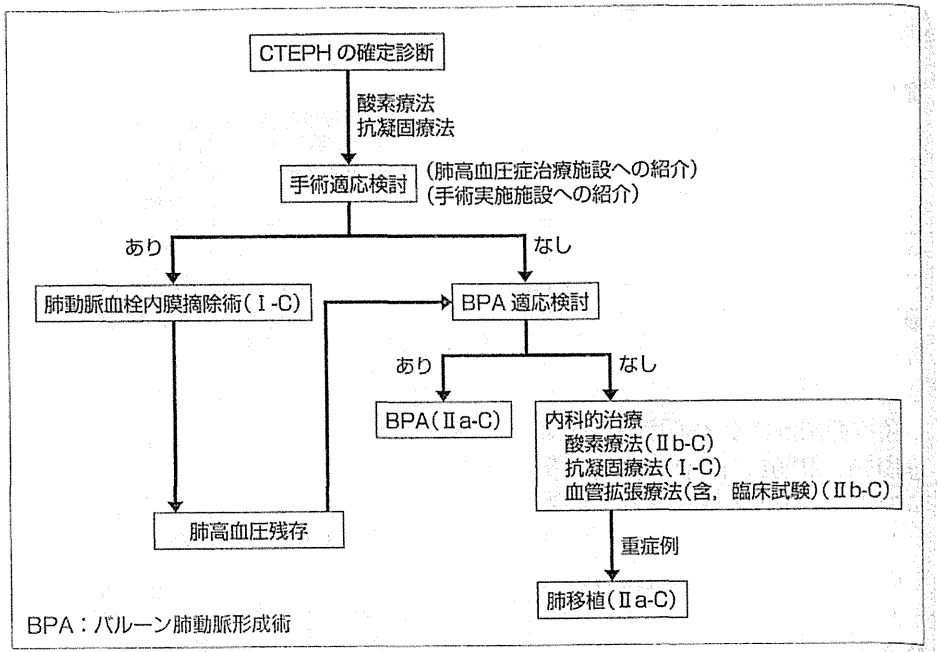


図1　慢性血栓塞栓性肺高血圧症(CTEPH)の治療手順

(循環器病の診断と治療に関するガイドライン．肺高血圧症治療ガイドライン(2012 年改訂版)．http://www.j-circ.or.jp/guideline/pdf/JCS2012_nakanishi_h.pdf(2014 年 2 月閲覧)より許諾を得て転載)

最近の話題

①2013 年 2 月末にフランスのニースで第 5 回世界肺高血圧症シンポジウムが開催された。この中で疾患分類の若干の改訂が行われたが，日本循環器学会では世界に先駆けてガイドラインに反映させている(表 1)。これまでのいわゆるダナポイント分類との主な変更点としては，遺伝性 PAH にみられる遺伝子異常に SMAD 9 および CAV 1 が加わったこと，新生児遷延性肺高血圧症が第 1 群から第 1'' 群に移動したこと，慢性溶血性貧血が第 1 群から第 5 群に移動したことなどが挙げられる。

②近年，慢性骨髄性白血病治療薬であるイマチニブの PAH に対する有効性が報告され，国際共同治験(IMPRESS study)が行われた。最近この結果が報告され，一次エンドポイントである 6 分間歩行距離の変化について，実薬群ではプラセボ群に比して有意な延長を認めた。しかし，イマチニブは臨床的悪化までの時間を延長させることができず，また重大な有害事象の発生率がイマチニブ群で高く，特にワルファリンとイマチニブを併用している患者において 8 人に硬膜下血腫が発生したことが問題となった。このため，イマチニブはわが国をはじめ各国で PAH に対する適応拡大の承認申請が行われたものの，いずれも承認には至らなかった。

POINT ガイドライン活用のポイント

- PH の原因となる疾患にはさまざまなものがあるが，「肺高血圧症治療ガイドライン(2012 年改訂版)」ではそのほぼすべてを網羅しているので，診断においても治療においても大いに参考にするべきである。
- 一方で，第 2 群の左心疾患に伴う PH や第 3 群の肺疾患および／または低酸素血症に伴う PH については，原疾患に対する治療が特に重要である。これについては各原疾患についての専門書を参考にされたい。
- CTEPH に対する BPA については，近年わが国からその有効性を示した複数の論文が発表されている。ニースのシンポジウムでも話題となったが，いまだエビデンスが不足しているとのことで世界的には広く認められるには至っていない。わが国では現在ワーキンググループを組織してガイドライン作成準備中である。

専門医へのコンサルト

以下の場合には専門医への紹介が望ましい。

①急性肺血管反応試験を行う場合。
②エポプロステノールを導入する場合。
③CTEPH に対して PEA もしくは BPA を検討する場合。
④肺(もしくは心肺同時)移植を考慮する場合。
⑤挙児希望のある PH 患者。

具体的処方

病型分類	処方例	ポイント
【治療方針】急性肺血管反応試験陽性の場合には Ca 拮抗薬の有効例があるので投与を考慮する。陰性の場合には，WHO 機能分類Ⅱないし Ⅲ 度の症例では ERA，PDE 5-I もしくは経口 PGI_2 製剤(ベラプロスト)内服により治療を開始する。単剤で治療効果不十分の場合には引き続き多剤併用療法を行う。WHO 機能分類Ⅲないし Ⅳ 度の重症例においては，初期からの併用療法ないしエポプロステノール持続静注療法を行う。WHO 機能分類 Ⅰ 度の症例に対して肺血管拡張薬を使用するべきかどうかについては，いまだに結論は出ていない。		
▶急性肺血管反応陽性例	①ヘルベッサーR 【適応外処方】 100～200 mg×1～2 回/日 ②アダラート CR 【適応外処方】 20～80 mg×1～2 回/日	①②忍容性のある限り高用量で使用するのがよいとされる。ただし，PAH に対しては保険適用外。

病型分類	処方例	ポイント
▶急性肺血管反応陰性例，WHO機能分類Ⅱ～Ⅲ度	①ドルナー またはプロサイリン 20～60 μg×3～4回/日 ②ケアロードLA またはベラサスLA 60～180 μg×2回/日 ③レバチオ 20 mg×3回/日 ④アドシルカ 20～40 mg×1回/日 ⑤トラクリア 62.5～125 mg×2回/日 ⑥ヴォリブリス 5～10 mg×1回/日	①②経口PGI_2製剤。②は①の徐放製剤。 ③④PDE 5-I。 ⑤⑥ERA。*トラクリア*では約1割の症例で肝機能障害が出現するので，125 mg/日から開始し，肝機能障害が出ない場合には4週後以降に250 mg/日に増量する。一方，*ヴォリブリス*では浮腫の発現頻度が高いとされる。
▶急性肺血管反応陰性例，WHO機能分類Ⅲ～Ⅳ度	急性肺血管反応陰性例の処方例①～⑥のうち，必要に応じて作用機序の異なる薬剤を2つ以上組み合わせて用いる。もしくは ①フローラン またはエポプロステノール 0.5～1 ng/kg/分から開始，バイタルサインなどをみながら適宜増量	①静注PGI_2製剤。必ず単独ルートで投与する。*フローラン*は熱に不安定なため，常温では8時間以内に投与を終了する。在宅で投与する場合にはアイスパックで冷却しながら投与する。*エポプロステノール「ACT」*は室温(1～30°C)ならば24時間以内の投与が可能。

7. 腫瘍塞栓性肺動脈微小血管症による肺高血圧症

東京大学大学院医学系研究科循環器内科学　波多野　将

key words　pulmonary tumor thrombotic microangiopathy (PTTM), platelet-derived growth factor (PDGF), ground-glass opacity, D-dimer, imatinib

動　向

腫瘍塞栓性肺動脈微小血管症(pulmonary tumor thrombotic microangiopathy: PTTM) は急速に進行する右心不全，呼吸不全により，通常症状出現から2，3カ月以内に死の転機を辿る予後不良の疾患である．かつては生前診断すら困難であったが，疾患の認知度が高まるにつれ，生前診断が可能となる症例の報告も散見されるようになってきており，原疾患に対して化学療法を行うことなどにより1年以上の生存を得られる場合もある．さらに最近ではPDGFなどの増殖因子が本疾患の病態形成に関与していることが明らかになり，PDGF阻害薬などの分子標的薬の効果にも期待がもたれている．

A. PTTMの病態生理と疫学

PTTMは悪性腫瘍患者において肺の亜区域枝よりも末梢の細動脈，細小動脈への腫瘍塞栓に引き続き，内膜の線維，細胞性（fibrocellular）肥厚により特徴づけられる病態である[1]．腫瘍表面で凝固系が著明に活性化されフィブリン血栓を形成し，さらに小肺動脈から細動脈にかけて広範に線維細胞性の内膜増殖がみられるのが従来の顕微鏡的腫瘍塞栓症例と大きく異なる特徴であるとされる．結果として腫瘍細胞は完成した病変の中にごく一部存在するに過ぎない．このように特異な組織所見を呈する原因の詳細は明らかではないが，腫瘍細胞の直接作用ではなく間接的な内膜増殖刺激によるものとされている．肺細動脈に微小塞栓を形成した腫瘍細胞にはvascular endothelial growth factor (VEGF)，platelet-derived growth factor (PDGF)，tissue factor，placental growth factor，osteopontinといった種々の増殖因子などが発現しており（図1），これらが凝固を亢進させると同時に内皮障害を引き起こし，この障害された内皮がさらに様々な成長因子を産生し，内膜でのmyofibroblast増殖を誘導すると考えられている[2-4]．PTTMは原発巣が粘膜内にとどまるような早期癌においても発症しうると言われており，実際発症1カ月前に行った上部消化管内視鏡によっても発見することができなかった早期胃癌によるPTTMのために入院3日後に死亡した症例も報告されている[5]．病変が粘膜内にとどまるような早期癌においては，リンパ節転移の頻度は3%程度とされているが，印環細胞癌のような低分化癌においてはより早期に転移を来し，PTTMを発症させる可能性がある．

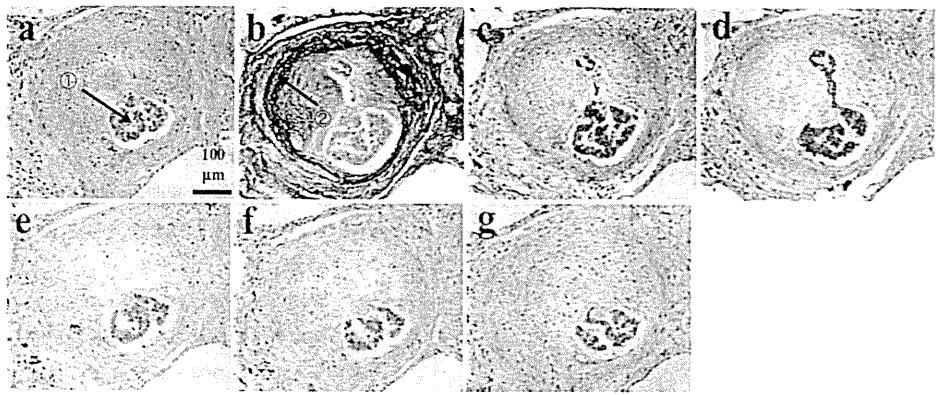


図1　PTTM患者の病理組織像（Uruga H, et al. Intern Med. 2013; 52: 1317-23)[3]
a. HE染色にて肺動脈に腫瘍塞栓を認める（矢印①）
b. EVG染色にて内膜の線維細胞性肥厚を認める（矢印②）
腫瘍細胞の各種免疫染色にてvasucular endothelial growth factor(c), tissue factor(d), placental growth factor(e), platelet-derived growth factor(f), osteopontin(g)が陽性となる．

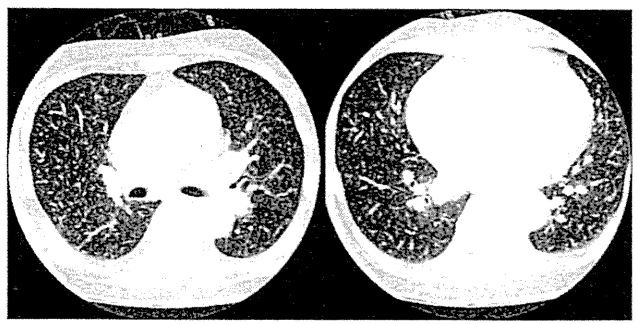


図2　PTTM患者の胸部CT画像（肺野条件）
すりガラス陰影(ground-glass opacity)および下肺野優位の粒状陰影を認める．

Urugaらによれば，PTTMは全悪性腫瘍剖検例の1.4%（30/2215）にみられ，そのほとんどが腺癌である[3]．原発巣としては胃癌（55～60%）（とくに印環細胞癌に多い），次いで肺癌（6～17%）が多く，乳癌，食道癌，肝細胞癌，膵臓癌，子宮体癌なども報告されている[3,6]．

進展経路に関しては一定の見解は得られていないが，鈴木らは，①大静脈系へ腫瘍が直接浸潤し右心系から肺動脈に至るケース，②腫瘍が所属リンパ管を通じ，胸管→上大静脈→右心系→肺動脈（PA）に至るケースの二通りの可能性を述べている[7]．

B. PTTMの症状と診断

PTTMの症状としては進行性の咳嗽と呼吸困難

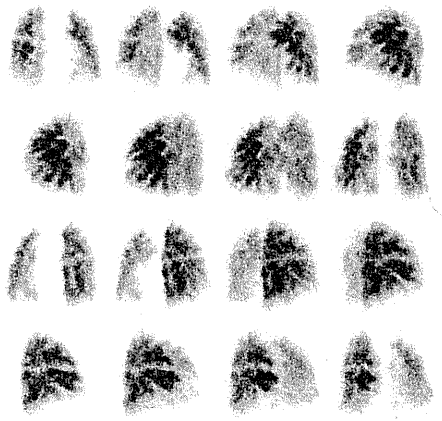


図3　PTTM患者の肺血流シンチグラフィ
多発性，対称性，末梢性の血流欠損像を認める．

が特徴的であり，血痰を認めることもある．血液検査所見ではFDPやDダイマーの上昇を認めることが多く，約半数の症例ではDICを合併する．胸部造影CTでは腫瘍塞栓とは異なり葉・区域などの中枢肺動脈に血栓，塞栓は見られず，肺実質領域での明らかな腫瘤形成は原則認めない．その他の胸部CT所見としては，すりガラス陰影(ground-glass opacity)，下肺野優位の粒状陰影，tree-in-bud様の分岐状陰影などを認める（図2）．肺血流シンチグラフィでは肺血栓塞栓症と比してより多発性，対称性，末梢性の欠損像を示すことがあり（図3），診断の手がかりとなることがあるが，その感度は不明である．また，肺血流シンチグラフィを施行することでさらに塞栓が進行し，症状が増悪する可能性も示唆されているため検査の施行には慎重を要する[8]．

生前の確定診断は困難であることが多く，ほとんどが剖検により診断される．生前の確定診断の方法としてはCTガイド下肺生検，経気管支肺生検（TBLB），開胸肺生検などの報告があり[9,10]，近年ではスワンガンツカテーテルでの吸引細胞診での診断の報告がなされるようになってきた[11]．しかし，PTTMにおいて肺血管内に存在する腫瘍細胞はまばらであり，von Herbayらも肺生検で腫瘍細胞が認められない場合にもPTTMを考慮してもよいとしている[1]．また，SGカテーテルで血液採取をする場合，肺動脈内に悪性細胞があることを証明するために肺動脈を楔入して採取することが重要である．

Patrignaniらは，PTTMに認められる以上のような症状および検査所見から，生前診断を可能とするために図4のような診断アルゴリズムを提唱している[6]．実際にはその極めて高いリスクからTBLBや開胸肺生検などが行われるケースは少ないが，診断が得られれば下記のごとく予後を改善できる可能性のある治療も少しずつ出てきているため，今後は生前診断を得るための診断法の進歩が求められる．

C. PTTMの治療

治療に関しては，化学療法を試みるのがオーソドックスな方法と考えられ，それにより腫瘍細胞量が減少し，内膜増殖刺激も低下することが期待され，実際，自覚症状の改善や延命に有効であった症例もある[9]．しかしながら生前診断が困難である上に，PTTMで呼吸困難が出現してからの生存期間は4～12週[12]，ないしほとんどの患者は呼吸困難の出現から1週間以内に死亡する[9]ともいわれるように極めて予後不良であり，確定診断がついてからではまず治療は間に合わない．一方で，病態生理の項でも述べたとおり，PTTMの病態形成にはVEGFやPDGFといった増殖因子が関与しているものと考えられており，これらの受容体を阻害する分子標的薬が有効である可能性がある．実際，高度の肺高血圧症によりPCPSを要した症例にPDGF阻害薬であるimatinib 100mg/dayを投与したところ，劇的な肺高血圧症の改善

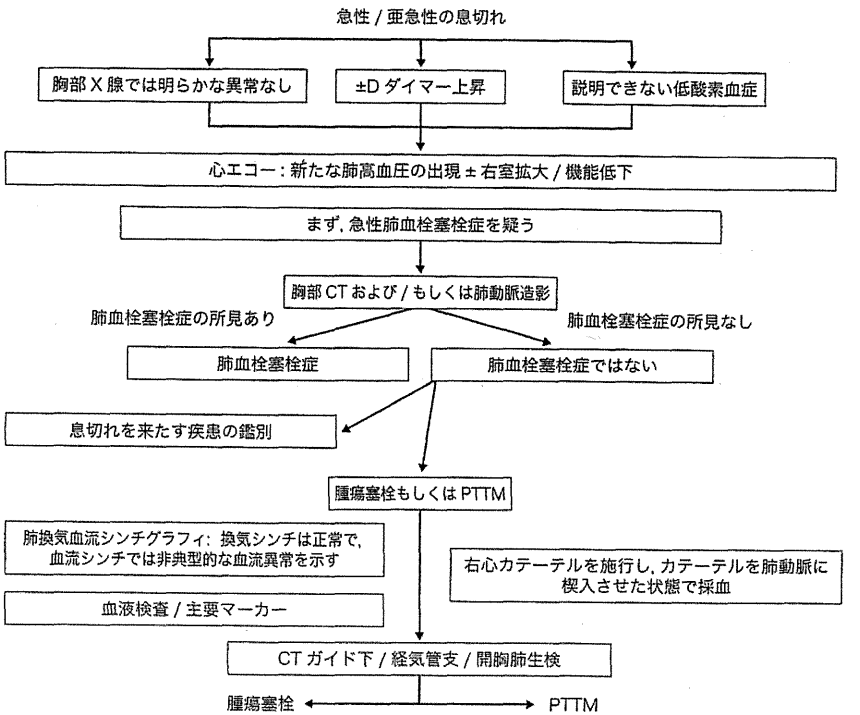


図4　PTTM患者の生前診断アルゴリズム
(Patrignani A, et al. J Cardiovasc Med (Hagerstown). 2013 Feb 22. [Epub ahead of print])[6]

を得てPCPSから離脱可能となり，後日胃低分化腺癌によるPTTMと診断されたとの報告もある[13]．自験例においても，急速に進行する咳嗽と呼吸困難を主訴に入院となった64歳女性に対してPTTMを疑い上部消化管内視鏡を施行したところ，印環細胞癌を認め臨床的にPTTMを疑いimatinib 200mg/dayの投与を行ったところ，短期間のうちに肺高血圧症及び低酸素血症の著明な改善を得，その後1年間生存することができた症例を経験している（図5）[14]．本症例においては肺高血圧の改善を得た後に開胸肺生検を行い病理学的にもPTTMの確定診断を得たが，この際のPDGF-Bによる免疫染色でも陽性であり（図6），臨床的にimatinibが著効したことと併せ，この症例におけるPTTMの発症にPDGFが関与していたことが示唆される．この症例は最終的に胃全摘術及びTS-1によるadjuvant chemotherapyを行い，平均肺動脈圧は13mmHgと正常化し，酸素飽和度も室内気で99.7％と低酸素血症も著明な改善を得た（図7）．一方，PTTMにおける腫瘍細胞においてはPDGFよりもVEGFの発現率の方が高いとの報告もあり[3]，未だ報告はないもののVEGF阻害薬なども有効である可能性がある．また，肺腺癌によるPTTMに対してepider-

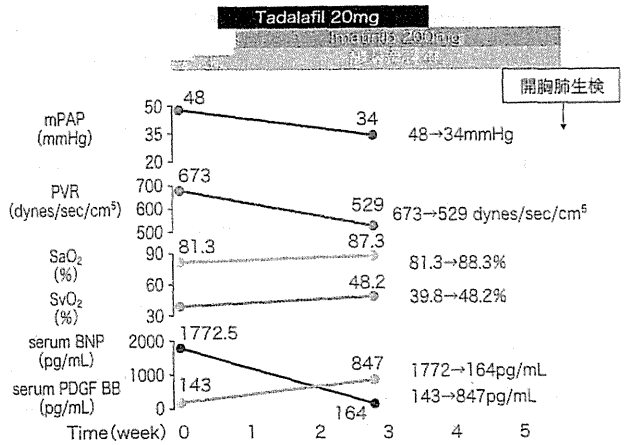


図5　imatinib投与が有効であった胃印環細胞癌によるPTTM患者の経過①

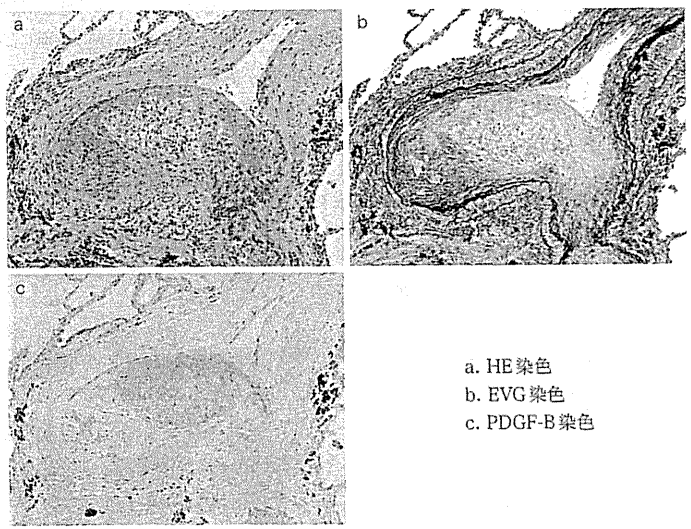


図6　胃印環細胞癌によるPTTMの患者の開胸肺生検組織像

mal growth factor receptor（EGFR）-チロシンキナーゼ阻害薬であるgefitinibによって肺高血圧が改善したとの報告もある[15]．gefitinibはEGFR遺伝子に異常がある場合の奏効率は81%と報告されており[16]，この症例でもEGFR遺伝子にexon19欠損を認めたことから抗腫瘍効果により肺高血圧が改善したものと考えられるが，最近の研究では動物モデルの肺高血圧に対してgefitinibが部分的に治療効果を認めたとの報告もあり[17]，抗腫瘍効果以外にも肺高血圧を改善する作用がある可能性も示唆される．

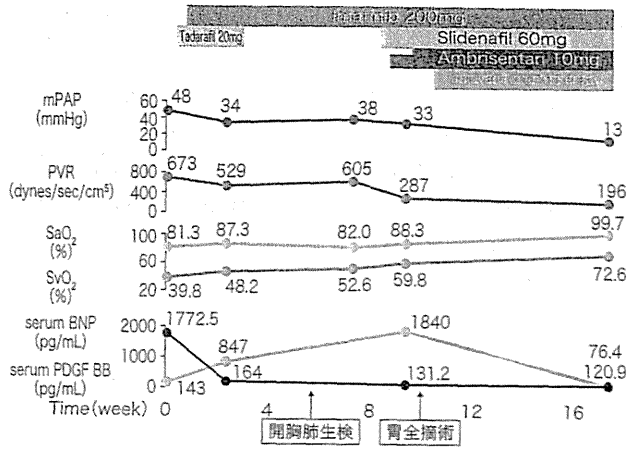


図7　imatinib投与が有効であった胃印環細胞癌によるPTTM患者の経過②

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膠原病，内分泌疾患に伴う心疾患

cardiovascular disorder in collagen or endocrine diseases

波多野　将　東京大学医学部附属病院循環器内科

病態と診断

Ⓐ 病態

膠原病，内分泌疾患のなかには「特定心筋症」の病態を呈するものが存在する．特定心筋症とは原因または全身疾患との関連が明らかな心筋疾患の総称で，1995年に設定されたWHO/ISFC分類の「特定心筋疾患」に相当する（表）．以下，心疾患を合併する膠原病，内分泌疾患のうち，代表的なものについて述べる．

1. 全身性エリテマトーデス，関節リウマチ　しばしば心外膜炎，心嚢液貯留を認める．心筋炎を呈することもあり，頻脈・不整脈の原因となる．5%程度に肺高血圧を合併するが，こちらについては「右心不全・肺性心」の項（⇨383頁）を参照のこと．

2. 強皮症　ほとんどの症例でびまん性の心筋線維化を認める．進行すると収縮不全を呈することもあるが，収縮能が正常な症例であっても，多くの場合拡張障害を認める．また，10%程度に肺高血圧症を合併する．

3. 糖尿病　糖尿病は動脈硬化の重要な危険因子であり，高率に冠動脈疾患を合併するが，冠動脈に有意狭窄を認めないにもかかわらず収縮能低下を認めることがある．これは糖尿病性心筋症とよばれ，心筋微小血管障害，心筋代謝異常などが原因とされる．また，収縮障害に先行して拡張障害が先行するのが特徴である．

4. 甲状腺機能亢進症・低下症　甲状腺機能亢進症では頻脈や心房細動，さらには高拍出性の心不全を認める．甲状腺機能低下症では心筋の浮腫状肥厚や左室拡大，心嚢液貯留などを認める．

5. 褐色細胞腫，先端巨大症　高血圧や心肥大・拡大を認め，進行すると心不全を呈する．

Ⓑ 診断

心エコーがスクリーニングに有効であるが，強皮症や糖尿病のように拡張障害が先行することも少なくないので，収縮能のみならず拡張能も評価することが重要である．心臓MRIは心筋の線維化の評価などに有用である．心筋障害マーカーのBNP，NT-proBNP，心筋トロポニンTなども診断および重症度評価に有用である．

治療方針

Ⓐ 心筋症に対する治療

本疾患に対する特異的な治療法はなく，原疾患の治療に並行して心不全や不整脈の一般的な治療を行う．

処方例　心不全が認められた場合，長期予後を改善するために下記1)-3)のいずれか，または1)と2)，1)と3)を併用する．

1) アーチスト錠（2.5 mg）　0.5-4錠　分1-2　朝

2) レニベース錠（2.5 mg）　1-2錠　分1　朝

3) ブロプレス錠（4 mg）　1-2錠　分1　朝

忍容性があれば，必要に応じてアーチストは20 mgまで，レニベースは20 mgまで，ブロプレスは12 mgまで増量可能（心不全に対する保険適用は8 mgまで）．必要に応じて4）を加える．

4) アルダクトンA錠（25 mg）　1-2錠　分1　朝

表　膠原病および内分泌疾患に伴う特定心筋症

膠原病に伴う心筋症
全身性エリテマトーデス，結節性動脈周囲炎，関節リウマチ，皮膚筋炎，強皮症
内分泌疾患に伴う心筋症
甲状腺機能亢進症，甲状腺機能低下症，副腎機能不全，褐色細胞腫，先端巨大症，糖尿病

（1995年WHO/ISFC合同委員会定義より）

Ⓑ 膠原病に伴う心膜炎の治療

心膜炎に対しては一般に非ステロイド系消炎鎮痛薬（NSAIDs）もしくはステロイドを用いる．コントロール不良例に対しては免疫抑制療法や心膜腔へのステロイド注入を行う．重症例では，外科的に心膜開窓術が必要になることもある．専門医と連携のうえ，基礎疾患の活動性などを十分に考慮したうえで治療方針を決定することが重要である．

処方例　関節リウマチによる心膜炎の場合，1)2)を併用する．

1) ロキソニン錠（60 mg）　3錠　分3　空腹時は避ける　昼

2) サイトテック錠（200 μg）　3-4錠　分3-4　食後・就寝前

上記無効例や全身性エリテマトーデスをはじめとするその他の膠原病の場合には，ステロイドを用いる．

3) プレドニン錠（5 mg）　6-12錠　分3

Ⓒ 甲状腺機能亢進症に伴う不整脈の治療

抗甲状腺薬の効果が現れるまでの間，レートコントロールを中心とした治療を行う．甲状腺機能が正常化しても心房細動が持続する場合には，電気的もしくは薬理学的除細動を考慮する．血栓症のリスクが高い症例に対しては抗凝固療法も併用する．

処方例　下記のいずれかを用いる．

1) インデラル錠（10 mg）　3-6錠　分3　朝

2) メインテート錠（2.5 mg）　1-2錠　分1　朝

血栓症予防には3）を用いる．PT-INR 2.0程度を目標に用量を調節する．

3) ワーファリン錠（1 mg）　3-5錠　分1　朝

患者説明のポイント

- β受容体遮断薬やステロイドを使用する場合には，自己中断をしないように注意する．
- ワーファリンを使用する場合には食事指導も行う．

看護・介護のポイント

- 心不全を認める患者には，薬物療法とともに水分・塩分制限を含めた食事・生活指導が重要である．体重・血圧測定や浮腫の観察などを指示し，体重増加や浮腫の出現を認めた場合には早めに専門医を受診するよう指導する．

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Scientific Research

Clinical Evaluation of Moisturizers with Physiological Analysis of Stratum Corneum TARC and TSLP

Satoshi Fukushima[1*], Eishin Morita[2], Miki Tanioka[3], Yoshiki Miyachi[3], Yumi Murakami[4], Hiroshi Matsunaka[4], Hironobu Ihn[1]

[1]Department of Dermatology and Plastic Surgery, Faculty of Life Science, Kumamoto University, Kumamoto, Japan; [2]Shimane University Faculty of Medicine, Shimane, Japan; [3]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan; [4]TOKIWA Pharmaceutical Co., Ltd., Tokyo, Japan.
Email: *satoshi.fukushima.tb@gmail.com

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ABSTRACT

To verify the usefulness of moisturizers, a multi-center study was conducted on patients with atopic dermatitis who visited 3 university hospitals in Japan between November 2009 and March 2012. Thirty-seven patients with dry skin and stable symptoms who were receiving topical and oral treatments were given moisturizers for 8 weeks. The moisturizers contained components such as glycerin and seawater minerals in 3 forms: lotion, emulsion, and cream. The moisturizers were chosen by physicians based on the degree of dryness of the patients' skin. In addition to observing the skin condition of the entire body, high-frequency conductance as a parameter of skin surface hydration and transepidermal water loss (TEWL) in the buccal region and the medial side of the forearm were measured, and those of the back were used for comparison. Furthermore, stratum corneum levels of thymic stromal lymphopoietin (TSLP) and thymus and activation-regulated chemokine (TARC), both of which were objective parameters for atopic dermatitis skin lesion severity, were analyzed using the tape stripping method. At the beginning of the study, TSLP showed a correlation with skin symptoms (dryness, itching) and high-frequency conductance, whereas TARC showed a correlation with skin symptoms (erythema, dryness, itching) and TEWL. In addition, a correlation was noted among TSLP, TARC, and itching. At the end of the study, erythema, dryness, itching, TEWL, TSLP, and TARC were significantly reduced, whereas high-frequency conductance was significantly increased. The moisturizers clearly improved the dry skin symptoms of these patients with atopic dermatitis and improved the physiology of their sensitive and damaged skin. These findings also support the involvement of cytokines/chemokines in the pathogenesis of atopic dermatitis lesions.

KEYWORDS

TSLP; TARC; Atopic Dermatitis; Moisturizer; Skin Physiology; Dry Skin

1. Introduction

In addition to its allergic aspect, atopic dermatitis involves physiological aspects of the skin, such as barrier function failure and abnormalities of the epithelium, particularly the stratum corneum [1,2]. Lipid reduction between corneocytes, such as ceramide in the stratum corneum [3]; itching related with invasion of the epidermal nerve fibers [4] and increased levels of serum TARC as indicators reflecting disease condition are well known in atopic dermatitis [5,6]. Furthermore, filaggrin gene variation has been reported in the onset of atopic dermatitis [7,8]. It is also suggested that skin care products such as moisturizers, are useful for repairing the skin barrier function as symptomatic treatment for the symptoms of atopic dermatitis, particularly dryness [9,10].

In the actual treatment of atopic dermatitis in dermatology, steroids and immunosuppressive drugs are used to treat inflammation from the allergy aspect. Skin phy-

*Corresponding author.

siological abnormality due to skin barrier failure is treated with moisturizers such as Vaseline, which is used externally to prevent dryness and exacerbation of inflammation. In addition, possible prevention of the onset of atopic dermatitis by the application of moisturizers from childhood has been reported in recent years, suggesting the importance of moisturizer use [11,12]. It is also suggested that skin barrier repair using moisturizing agents is useful for preventing transdermal sensitization if the onset of atopic dermatitis is correlated with barrier function failure and its related epicutaneous sensitization.

To verify the usefulness of moisturizers in sensitive, damaged skin from the aspect of physiological function, we evaluated the external use of moisturizers in patients with atopic dermatitis and dry skin. To evaluate skin physiology, we analyzed changes in the levels of thymic stromal lymphopoietin (TSLP) and thymus and activation-regulated chemokine (TARC) in the stratum corneum [13-16], which induce allergy symptoms, promote the production of various cytokines, and are involved in the Th2 shift in addition to the generally used evaluations of high-frequency conductance as a parameter of skin surface hydration and transepidermal water loss (TEWL).

There were correlations between itching stratum corneum TSLP (scTSLP) with skin symptoms (dryness, itching) and high-frequency conductance. In addition, stratum corneum TSLP (scTARC) showed a correlation with skin symptoms (erythema, dryness, itching) and TEWL as well as with scTSLP and scTARC. In addition, improvement of the skin symptoms was related with moisturizer use. We successfully verified a significant reduction in TEWL, TSLP, and TARC; significant improvement of high-frequency conductance; and the usefulness of moisturizers from the physiological aspect.

2. Methods

2.1. Subjects

The subjects included 37 patients aged >20 years with atopic dermatitis, dry skin, and stabile symptoms following external and oral treatment who visited 3 university hospitals in Japan between November 2009 and March 2012. There were no serious underlying diseases. The physician in charge determined the appropriateness of the present test. Before the study was initiated, the patients were provided a thorough explanation of the study content and objectives. The subjects participated in the study of their own free will. There were no specific criteria regarding age or sex, but the subjects were only included after we had obtained written consent from them or their guardians (in case of a minor).

2.2. Study Period and Institution

Each subject was studied for 8 consecutive months; the study extended from November 2009 to March 2012. The institutions involved were the dermatology departments of Kumamoto University Hospital, Kyoto University Hospital, and Shimane University Hospital. The study was conducted after approval was obtained from the ethics review board of each institution.

2.3. Study Samples

The study samples included a lotion, emulsion, and cream marketed by TOKIWA Pharmaceutical Co., Ltd (Osaka, Japan) as treatment to improve the dry skin condition in atopic dermatitis. Three moisturizers were used for the study, all of which included Oligomarine®. Oligomarine® consists of concentrated seawater and includes high concentrations of trace elements. The major ions of Oligomarine® include Mg^{2+}, K^{+}, Zn^{2+}, Se^{4+}, and Na^{+}. The main moisturizing ingredients of the preparations used in this study are indicated below.

Lotion: 1, 3-butylene glycol, glycerin, hyaluronic acid.

Emulsion: glycerin, dipropylene glycol, betaine, squalane, behenyl alcohol, pentaerythrityl tetraethylhexanoate, petrolatum.

Cream: glycerin, 1, 3-butylene glycol, mineral oil, microcrystalline wax, behenyl alcohol, phytosteryl macadamiate, dipentaerythrityl tetrahydroxystearate/tetraisostearate, stearic acid, palmitic acid. These samples belong to the cosmetics category (quasi-drug) under the Japanese Pharmaceutical Affairs Law.

2.4. Usage

Skincare products and makeup such as cleanser and foundation used prior to the study were continued during the study. However, products with the same objective as the moisturizers were replaced with the study samples. The standard application was as follows: 2 - 3 mL/cm^2 lotion and 1 - 2 mg/cm^2 emulsion or cream. The doctor in attendance decided whether the degree of dryness of the face and limbs would respond well to the lotion, emulsion, or cream. The study samples were applied twice a day: once in the morning and once in the evening (after bathing); application was adjusted according to the dry skin condition and lifestyle. One type of formulation was applied to the regions, but if the degree of dryness differed between the left and right side, we used different moisturizing agents for the two sides. The back, to which the study samples were not applied, was used for comparison.

Treatments for previously existing underlying diseases and complications were continued during the study period. In principle, the type, method, and dosage of the treatment drugs (oral and external use) were not modified during the study period; however, they were switched if the physician in charge decided that they would affect the study. Accordingly, those patients were excluded from

the study.

2.5. Observation and Evaluation Methods

The physician in charge filled in a case card with each patient's information, (to avoid the possibility of connection) including identification number, age, sex, complications, and medication combination during the study period (drug, method, and dosage), with the identity of the patient concealed. The whole-body disease severity of atopic dermatitis was evaluated according to 4 stages (very mild, mild, moderate, and severe). In addition, the following items were measured and evaluated at the beginning and end of the study. Measuring points included cheek, medial side of the forearm, and back (the unapplied control). Additionally, if different formulations were used for the left and right sides, the observations were tabulated as different regions.

2.5.1. Skin Findings

The degree of the skin condition (erythema, dryness, and itching) of the buccal region and the medial side of the forearm, to which the study samples were applied, was scored according to 5 stages (none, 0; very mild, 1; mild, 2; moderate, 3; severe, 4).

2.5.2. Evaluation of Skin Physiology

After washing with soap, the measurement site was exposed to constant air conditioning (room temperature, 21°C ± 2°C; room humidity, 50% ± 3%) and was evaluated after 10 min.

1) High-Frequency Conductance

High-frequency conductance, which is a parameter for the hydration state of the skin surface, was evaluated 5 times using a 3.5-MHz high-frequency conductance measurement device (SKICON-200EX®; IBS Ltd., Hamamatsu, Japan). After exclusion of the highest and lowest values, the mean of the remaining 3 values was used as the measurement value of the high-frequency conductance.

2) TEWL

TEWL was evaluated twice using a Tewameter® TM 210 unit (Courage + Khazaka electronic GmbH, Cologne, Germany), and the obtained mean was used as the measurement value.

2.5.3. Stratum Corneum TSLP and TARC Level (scTSLP and scTARC)

Immunohistochemical staining was performed using anti-TSLP antibody (rabbit anti-human TSLP polyclonal antibody [ab47943; Abcam, Cambridge, England]) and anti-TARC antibody (mouse anti-human CCL17/TARC monoclonal antibody [MAB364; R & D Systems, Minneapolis, MN, USA]). After staining, fluorescence images were captured using a fluorescence microscope (BZ-8100, Keyence, Osaka, Japan), saved in Adobe® Photoshop® CS5, and the mean value of 5 visual fields of cell area luminescence was calculated as the TSLP and TARC values.

2.5.4. Safety

Details of adverse events (details of symptoms, degree, presence or absence of cessation, measures, and outcomes) were recorded on the case card. An event was considered a side effect if a causative correlation with the present study samples was found.

2.6. Statistical Analysis

Correlations among the evaluation values at the beginning of the study were analyzed using Spearman's rank correlation, whereas the changes in values between the beginning and end of the study were analyzed using a paired *t*-test or Wilcoxon's signed rank test.

3. Results

3.1. Subject and Case Characteristics

The mean age of the subjects was 27.7 ± 10.3 years. Whole-body disease severity was characterized as follows: very mild, 11 cases; mild, 15 cases; and moderate, 11 cases; there were no severe cases (Table 1). Complications included hay fever, asthma, allergic rhinitis, and allergy-related conjunctivitis. There were no changes to the treatment drugs (type, method, or dosage) for any

Table 1. **Characterization of subjects.**

		Atopic dermatitis (AD)	
		Male	Female
Age	0 - 9	0	2
	10 - 19	0	0
	20 - 29	13	10
	30 - 39	5	3
	40 - 49	0	3
	50 - 59	0	1
	60 - 00	0	0
	Total n	18	19
	Mean ± SD	26.9 ± 6.3	28.5 ± 13.2
	Total n	37	
	Mean ± SD	27.7 ± 10.3	
AD Severity	Very mild	5	6
	Mild	4	11
	Moderate	9	2
	Severe	0	0

cases during the study period.

3.2. Skin Findings

The scores of the skin conditions (erythema, dryness, and itching) in the buccal region and medial part of the forearm at the beginning and end of the study are listed in Table 2. At the end of the study, a significant reduction in erythema, dryness, and itching in the buccal region; dryness and itching in the medial part of the forearm; and dryness in the back were noted.

3.3. Skin Physiology

The high-frequency conductance and TEWL values of the buccal region, medial side of the forearm, and back at the beginning and end of the study are listed in Table 3. The significant increase in high-frequency conductance and a significant reduction in TEWL in the buccal region and medial part of the forearm were noted. The high-frequency conductance increased markedly even in the untreated back area.

3.4. scTSLP and TARC

TSLP and TARC values of the buccal region, medial side of the forearm, and the back, at the beginning and end of the study are shown in Table 3. At the end of the study, there was a significant decrease in the scTSLP and scTARC levels. Stained images of the scTSLP and scTARC are shown in Figure 1.

3.5. Safety

None of the patients dropped out due to worsening skin condition or their own personal taste. All 37 patients successfully completed the 8-week study. All the study products were considered to be "without side effects."

3.6. Correlation Analysis of Measurement Values

At the beginning of the study, scTSLP showed a correlation with skin symptoms (dryness, itching) and high-frequency conductance. Additionally, scTARC was correlated with skin symptoms (erythema, dryness, itching) and TEWL as well as scTSLP and scTARC (Table 4).

4. Discussion

The studied skin condition was soothed with continuous treatment. We believe that the 8-week moisturizer application improved the skin conditions of the patients with atopic dermatitis and dry skin. The skin physiological tests generally used for studying the high-frequency conductance and TEWL were evaluated and exhibited improvement. In addition, to analyze the improvement of the skin condition from the physiological aspect and cellular level in detail, we evaluated TSLP and TARC in the stratum corneum.

TSLP is produced by keratinocytes during inflammation and promotes an inflammatory response related with the Th2 cytokine. This study's findings demonstrated a correlation with stratum corneum moisture levels and the improvement of dry skin after moisturizer use. TARC, a chemokine that exhibits chemotaxis properties with white blood cells, is produced in epidermal keratinocytes of lesion areas in atopic dermatitis and is involved in the local migration of lymphocytes (Th2 cells expressing CCR4), inducing IgE production, eosinophil infiltration, and activation related with the Th2-dominant immune response, and is known to express various allergic symptoms. In addition, because TSLP stimulates monocytes and produces T cell-suppressing chemokines such as TARC, a detailed evaluation of skin with atopic dermatitis can be achieved by analyzing local TSLP and TARC changes.

Table 2. **Skin findings.**

		Erythema score			Dryness score			Itching score		
		n	Mean	S.E.	n	Mean	S.E.	n	Mean	S.E.
Cheek	Before	38	0.92	0.18	38	1.53	0.19	36	1.33	0.20
	After	38	0.53	0.15	38	0.63	0.16	36	0.58	0.20
	p		<0.01	**		<0.01	**		<0.01	**
Forearm	Before	29	1.00	0.19	29	1.83	0.25	28	1.68	0.24
	After	29	0.59	0.19	29	0.72	0.21	28	0.64	0.24
	p		0.118	N.S.		<0.01	**		<0.01	**
Back (Control)	Before	17	0.412	0.173	17	1.294	0.306	17	0.76	0.26
	After	17	0.235	0.136	17	0.824	0.231	17	0.53	0.26
	p		0.083	N.S.		0.038	*		0.206	N.S.

Wilcoxon's signed-rank test, $^{**}p < 0.01$, $^{*}p < 0.05$.

Table 3. **Evaluation of skin physiology.**

		n	Before		After		*p*	
			Mean	S.E.	Mean	S.E.		
Conductance (μS)	Cheek	30	95.8	18.2	169.3	20.5	0.002	**
	Forearm	30	49.7	8.5	90.1	11.9	0.002	**
	Back (Control)	17	66.3	19.5	65.4	14.9	0.950	N.S.
TEWL (g/m²·h)	Cheek	30	19.3	2.3	14.2	1.6	0.029	*
	Forearm	30	19.3	2.9	12.8	1.8	0.050	*
	Back (Control)	17	20.3	3.3	16.2	2.8	0.199	N.S.
scTSLP level	Cheek	39	78.9	12.8	68.4	11.7	0.187	N.S.
	Forearm	30	77.9	10.7	57.8	5.7	0.031	*
	Back (Control)	14	26.0	3.3	21.3	2.6	0.122	N.S.
scTARC level	Cheek	39	59.5	7.7	46.8	4.5	0.086	N.S.
	Forearm	30	9.5	1.2	7.8	1.1	0.017	*
	Back (Control)	14	19.1	3.7	14.1	2.1	0.087	N.S.

Paired *t*-test, $^{**}p < 0.01$, $^{*}p < 0.05$.

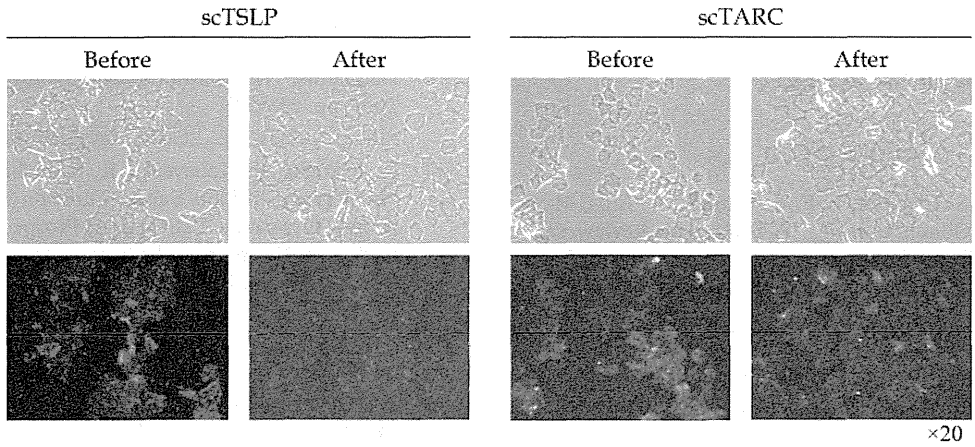

Figure 1. **Immunohistochemical staining of scTSLP and scTARC.**

Table 4. **Correlation analysis of measurement values.**

		scTSLP level	Conductance (μS)	TEWL (g/m²·h)	Erythema score	Dryness score	Itching score
scTSLP level	r	25	−0.416	0.294	0.398	0.728	0.698
	p	-	0.043 *	0.163 N.S.	0.060 N.S.	<0.01 **	<0.01 **
scTARC level	r	0.632	−0.203	0.547	0.635	0.595	0.656
	P	<0.01 **	0.342 N.S.	<0.01 **	<0.01 **	<0.01 **	<0.01 **

Spearman's rank correlation, $^{**}p < 0.01$, $^{*}p < 0.05$.

At the beginning of the study, scTSLP showed a correlation with skin symptoms (dryness, itching) and high-frequency conductance. In addition, scTARC showed a correlation with skin symptoms (erythema, dryness, itching) and TEWL as well with scTSLP and scTARC. This means that skin physiology and functional findings reflect the degree of skin symptoms and changes in these measurements. Following moisturizer application, reductions were seen in the skin condition score (erythema, dryness, itching), TEWL, scTSLP, and scTARC, whereas

improved high-frequency conductance was noted. This finding suggests improvement of dry skin symptoms (stratum corneum moisture level was increased), and because decreased stimulation of epidermal keratinocytes was noted (TSLP was reduced), TARC production was controlled and the skin's inflammatory reaction was suppressed. The results also indicated improvement of the skin barrier (reduced TEWL). In the back, although no significant change with a skin physiology functional parameter was found, improvement of the shape of the dryness is accepted. The improvement of constitutional symptoms was probably caused by reduced cytokine levels. Since the subjects in the present study had skin conditions such as dry skin and inflammation prior to the moisturizer application, it is unknown whether the stratum corneum moisture level, TEWL, TSLP, or TARC primarily improved the skin symptoms. However, there was at least a close correlation between them. Thus, the improvement of dry skin conditions using moisturizers that enhance skin barrier function can be explained from the aspect of skin physiology.

Conflict of Interest

The cost and materials required were provided by TOKIWA Pharmaceutical Co., Ltd.

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Abbreviations

TEWL: Transepidermal water loss;
TSLP: Thymic stromal lymphopoietin;
TARC: Thymus and activation-regulated chemokine;
scTSLP: Stratum corneum thymic stromal lymphopoietin;
scTARC: Stratum corneum thymus and activation-regulated chemokine.

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ORIGINAL ARTICLE

Phase II study of i.v. interferon-gamma in Japanese patients with mycosis fungoides

Makoto SUGAYA,[1] Yoshiki TOKURA,[2] Toshihisa HAMADA,[3] Ryoji TSUBOI,[4] Yoichi MOROI,[5] Takeshi NAKAHARA,[5] Masahiro AMANO,[6] Syuichi ISHIDA,[7] Daisuke WATANABE,[8] Mamori TANI,[9] Hironobu IHN,[10] Jun AOI,[10] Keiji IWATSUKI[3]

[1]Department of Dermatology, Faculty of Medicine, University of Tokyo, Tokyo, [2]Department of Dermatology, Hamamatsu University School of Medicine, Shizuoka, [3]Departments of Dermatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, [4]Department of Dermatology, Tokyo Medical University, Tokyo, [5]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, [6]Department of Dermatology, Faculty of Medicine, University of Miyazaki, Miyazaki, [7]Department of Dermatology, Yokohama City University School of Medicine, Kanagawa, [8]Department of Dermatology, Aichi Medical University, Nagoya, [9]Department of Dermatology, Osaka University Graduate School of Medicine, Osaka, and [10]Department of Dermatology and Plastic Surgery, Kumamoto University, Kumamoto, Japan

ABSTRACT

A multisite, open-label, non-randomized, single-arm phase II study was conducted to evaluate the efficacy and safety profiles of interferon-γ in Japanese patients diagnosed with stage IA–IIIA mycosis fungoides (MF). Interferon-γ was administrated i.v. to 15 patients at a dose of 2 million Japan reference units once daily over 5 days a week for the first 4 weeks, followed by subsequent intermittent injection. The primary efficacy end-point was the overall skin response during the study as assessed according to the evaluation criteria for chemotherapeutics for malignant skin carcinomas. Of the 15 patients, 11 (73.3%) achieved the objective response. Of the other four patients, three remained on treatment during study with stable disease and one showed disease progression. The median duration of stable disease was not reached but was 170 days or more (range, 29 to ≥253 days). As assessed according to the modified severity weighted assessment tool, nine patients (60.0%) achieved the objective response. The most common drug-related adverse event (AE) was influenza-like illness occurring in all patients enrolled, which did not lead to discontinuation of the study. Two serious AE were reported in two patients: aggravation of MF and aggravation of cataract, neither of which was considered directly related to the study drug. The patient with aggravation of MF died 50 days after the initiation of the study treatment. Another patient was withdrawn from the study due to drug-related cough, which disappeared after discontinuation of the drug. Overall, interferon-γ was effective and well-tolerated in Japanese patients with MF.

Key words: clinical trial, cutaneous T-cell lymphoma, interferon-gamma, i.v. drip, mycosis fungoides.

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a representative disease of cutaneous lymphomas and the most common variants of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS). MF accounts for approximately half of CTCL patients.[1] The staging and classification criteria for MF and SS are based on disease manifestations in skin, lymph nodes, visceral involvement and blood.[2] According to the Japanese Skin Cancer Society, approximately 150–200 patients are newly diagnosed with MF/SS annually, over 90% of whom are diagnosed with stage IA–III in Japan.[3] Patients with stage IA, an early-stage MF, have a median survival of 20 years or more and the majority of deaths for these patients are not caused by MF.[4] In contrast, disease progression of MF results in a poor prognosis and over 50% of patients with stage III–IV die of MF, with a median survival of less than 5 years.[4–6] Therefore, it is important to prevent or slow disease progression in the treatment of MF/SS.

Guidelines for the management of cutaneous lymphomas (2011) recommend preferred treatment options depending on the stage of disease.[7] Recombinant human interferon (IFN)-γ (currently marketed by Shionogi, Osaka, Japan under the trade name Imunomax-γ), a pluripotent cytokine, is recommended as second-line therapy for patients with stage IA–IIA MF/SS and as first-line therapy in combination with topical therapies for

Correspondence: Makoto Sugaya, M.D., Department of Dermatology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: sugayam-der@h.u-tokyo.ac.jp
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stage IIB–IIIB patients. MF/SS are regarded as T-helper (Th)2 cell diseases, with eosinophilia and high levels of immunoglobulin E and CC chemokine ligand (CCL)17, CCL11 and CCL26 often detected in patients in advanced stages.[8–10] Early data have also suggested that tumor cells of SS have Th2-like properties with increased interleukin (IL)-4 and IL-5.[11,12] Not only does IFN-γ induce antitumor immune response by stimulating $CD8^+$ T cells and natural killer cells, but also it attenuates a Th2-dominant environment that is favorable for tumor cells. However, IFN-γ has not been available for treatment of MF/SS in Japan since April 2010, and hence patients may not have the opportunity to receive sufficient treatment in line with the guidelines. Because Imunomax-γ has the same sequence of amino acids as Biogamma, a previously marketed IFN-γ product for treatment against MF that has been taken off the market, it is expected to be similarly effective for MF. Imunomax-γ is currently approved to treat patients with kidney cancer and those with chronic granulomatous disease for reducing the frequency and severity of serious infections. Imunomax-γ, however, is not approved for treatment of MF/SS.

The aim of this study was to evaluate the efficacy and safety profiles of IFN-γ when administrated i.v. to Japanese patients with MF/SS at a dose of 2 million Japan reference units (JRU) once daily over 5 days a week for the first 4 weeks, followed by subsequent intermittent injection.

METHODS

This was a multisite, open-label, non-randomized, single-arm phase II study, evaluating the efficacy and safety profiles of IFN-γ in Japanese patients diagnosed with MF/SS. The study protocol was reviewed and approved by the institutional review boards of all 10 participating medical sites and the study was carried out in accordance with Good Clinical Practice and the ethical principles that are outlined in the Declaration of Helsinki. All patients provided written informed consent before enrollment. The study was registered at JapicCTI-121825.

The study was conducted between May 2012 and March 2013. The patients, if they so desired, could continue receiving treatment with IFN-γ in an ongoing extension study (JapicCTI-132076) until the marketing approval of IFN-γ for MF/SS.

Patient eligibility

All patients were diagnosed with MF/SS based on the type and extent of skin lesions, and histopathological and hematological analyses. Prior treatments for MF/SS were limited as follows: treatment naive; no treatment for at least 4 weeks prior to enrollment; or stable or failed response to topical corticosteroids, topical vitamin D3 and its derivatives, or ultraviolet (UV) light therapy at the time of enrollment compared with response levels observed 4 weeks or more before enrollment. Other inclusion criteria were as follows: the stage of $T_{1-4}N_{0-2}M_0B_{0-2}$; evaluable skin symptoms according to the evaluation criteria for chemotherapeutics for malignant skin carcinomas; aged 20 years or older; life expectancy of longer than 12 weeks; Eastern Cooperative Oncology Group Performance Status of 0–2; and preserved hematological, hepatic and renal function. The exclusion criteria were as follows: active multiple cancers; visceral invasion assessed by body imaging within 4 weeks prior to enrollment; receiving IFN-γ within 1 year prior to enrollment; pregnant or lactating; fever 38.0°C or higher; infections requiring hospitalization; HIV infection; active hepatitis B or C virus infection; New York Heart Association class III or IV heart failure; or uncontrolled hypertension or diabetes.

The following medications or therapies were prohibited throughout the study: biological agents including IFN and vaccines, etretinate, anticancer agents, immunosuppressants, corticosteroids except for topical application, retinoid psoralen plus UV-A therapy, radiotherapy, extracorporeal photochemotherapy, immunotherapy, thermotherapy or surgical resection. The following medications or therapies were allowed if the patients were on stable treatment regimens throughout the study: topical corticosteroids, topical vitamin D_3 and its derivatives, broadband UV-B therapy, narrowband UV-B therapy, psoralen plus UV-A therapy, UV-A1 therapy and 308-nm excimer light therapy.

Study design and treatment plan

The target diseases of the study were MF and SS. The duration of administration was at least 12 weeks. IFN-γ was dissolved in 200–500 mL of phosphate-buffered saline or 5% glucose for i.v. drip infusion. The dose was 2 million JRU once daily (5 days/week) for 4 weeks, followed by twice weekly dosing for the subsequent 8 weeks. Dose increase up to 4 million JRU once daily was allowed at the discretion of the investigator. Dose reduction or treatment interruption also was allowed to manage AE. The patients were allowed to continue receiving IFN-γ once weekly after completion of the 12-week treatment until the last patient had completed the scheduled 12-week treatment. The dose of IFN-γ was determined based on that of the previously marketed IFN-γ product, Biogamma.

Efficacy assessments

The efficacy end-points were the response of skin lesions as assessed every 4 weeks with the evaluation criteria for chemotherapeutics for malignant skin carcinomas and the modified severity weighted assessment tool (mSWAT).[13,14] Though the mSWAT score has been widely used for evaluation, the efficacy of IFN-γ was primarily assessed with the evaluation criteria for chemotherapeutics for malignant skin carcinomas, which was used in the clinical trials of previously marketed IFN-γ products, Biogamma and Ogamma.[15,16] The evaluation criteria for skin response to chemotherapeutics for malignant skin carcinomas consist of measurements of clinical response of measurable and non-measurable lesions. The clinical response of the measurable lesions was determined based on the percentage change in 1-, 2- and/or 3-way measurements of up to a maximum of five lesions and on whether or not the disease remained stable for at least 4 weeks. The clinical response of the non-measurable lesions was determined based on the assessment of patches and plaques and on whether or not the disease remained stable for at least 4 weeks. The overall skin

response was the best response of measurable and non-measurable lesions recorded during the study, and the response was rated as follows: complete response (CR), all lesions were rated as CR; partial response (PR), all lesions were rated as PR, or the total number of responses rated as CR or PR was greater than or equal to the number rated as SD; stable disease (SD), all lesions were rated as SD, or the number of responses rated as SD was greater than the total number rated as CR or PR; or progressive disease (PD), defined as the presence of any skin lesion rated as PD. The mSWAT score was calculated as previously reported.[13,14] In brief, the investigator measured the percentage of the body surface area (BSA) involving each type of lesion in 12 regions of the body with the patient's palm and fingers accounting for approximately 1% of the BSA. The sum of each lesion was multiplied by a weighting factor of 1 for patches, 2 for plaques and 4 for tumors, and the subtotals of each lesion type were summed to obtain the mSWAT score. CR required 100% clearing of the skin disease, and PR required a 50% or greater reduction in the mSWAT score compared with the baseline. SD was defined as a less than 50% reduction to a less than 25% increase in the mSWAT score compared with the baseline. PD was defined as a 25% or greater increase over the baseline in the mSWAT score. These ratings required confirmation by repeated assessment after 4 weeks or more. The investigator also assessed lymph nodes and viscera with computed tomography imaging or magnetic resonance imaging, along with the response in blood as secondary end-points.

Statistical analyses

The primary analysis population was the full analysis set (FAS). FAS included patients who received at least one study treatment and had at least one set of post-dose efficacy data of skin lesions as assessed according to the evaluation criteria for chemotherapeutics for malignant skin carcinomas. The primary end-point was the objective response rate that was defined as the percentage of patients with CR or PR. The 95% confidence interval (CI) of the objective response rate was calculated by the Clopper–Pearson method.

Time to response was defined as the time between the date treatment was initiated and the date that the criteria were first met for PR or CR. Response duration was defined as the time between the date that the criteria were first met for PR or CR and the date from which the PR criteria were first lost. Duration of SD was defined as the time between the date treatment was initiated and the date criteria were first met for PD. For the patient who had no progression of disease, the duration of SD was defined as the time between the date treatment was initiated and the last date of observation. The median duration of SD was estimated by the Kaplan–Meier method.

Safety assessments

The safety assessments included physical examinations, laboratory tests, vital signs and 12-lead electrocardiogram (ECG). The grade of severity (CTCAE v4.0-JCOG) and relationship to IFN-γ were determined for each AE.

RESULTS

Patient characteristics

Fifteen Japanese patients were enrolled. The baseline patient characteristics are summarized in Table 1. All patients were diagnosed with stage IA–IIIA MF and no SS patient was enrolled. The median age was 61 years (range, 21–81). Eight patients were male and seven were female. The median duration of treatment in the study was 163 days (range, 22–248).

Efficacy

All 15 patients enrolled were included in the FAS. The summary of clinical efficacy by patient is shown in Table 2.

On the basis of the evaluation criteria for chemotherapeutics for malignant skin carcinomas, 11 patients (73.3%; 95% CI, 44.9–92.2%) achieved an objective response; all of whom experienced PR. Of the other four patients, three experienced SD and one experienced PD. The objective response rate was 100% (1/1 patient) for the patients with IA, 85.7% (6/7) for IB, 100% (2/2) for IIA, 25.0% (1/4) for IIB and 100% (1/1) for IIIA. The objective response was achieved regardless of concurrent treatment for MF. The objective response rate for the patients with stage IIB MF, who had at least one tumorous lesion, was relatively low. The tumor volume reduction rates in the four patients with stage IIB ranged from −36.6% (patient 15) to 96.5% (patient 7) in the study. One patient with stage IIIA (patient 2) also had tumorous lesions, which disappeared after treatment with IFN-γ. Four patients received an increased dose of IFN-γ of 4 million JRU once daily. Of them, three patients (patient 3, 6 and 8) did not experience PD during the study. The remaining one patient (patient 11) showed aggravation of the plaques, though the tumors responded to the treatment and the patches remained stable. Representa-

Table 1. Baseline patient characteristics (n = 15)

Characteristics	No. of patients
Age (years)	
Median (range)	61.0 (21–81)
Sex, *n* (%)	
Male	8 (53.3)
Female	7 (46.7)
ECOG Performance Status, *n* (%)	
0	14 (93.3)
1	1 (6.7)
Stage†, *n* (%)	
IA	1 (6.7)
IB	7 (46.7)
IIA	2 (13.3)
IIB	4 (26.7)
IIIA	1 (6.7)
Treatment duration (days)	
Median (range)	163.0 (22–248)
Treatment exposure (million JRU)	
Median (range)	86.0 (32–165)

†Based on the general rules for clinical and pathological studies on malignant neoplasms of the skin (second edition). ECOG, Eastern Cooperative Oncology Group; JRU, Japan reference units.

Table 2. Summary of clinical efficacy

Patient no.	Sex/age (years)	Disease stage	Concurrent treatment for MF		Best overall skin response†	Best overall response (mSWAT)	Treatment duration (days)	Time to response (days)†	Response duration (days)†	Duration of stable disease (days)†
			Drug	Therapy						
1	Female 80	IB	Topical corticosteroids	NB-UVB	PR	SD	≥138	26	57	≥138
2	Male 55	IIIA	Topical corticosteroids	NB-UVB	PR	SD	≥87	26	≥64	≥89
3	Male 65	IA	Topical corticosteroids	NB-UVB, VTRAC	PR	PR	193	32	78	200‡
4	Female 30	IB	Topical corticosteroids	None	PR	PR	≥163	30	50	≥170
5	Female 40	IIB	Topical corticosteroids	PUVA	SD	PR	≥246	ND	ND	≥253
6	Female 63	IB	Topical corticosteroids	NB-UVB	PR	PR	≥239	29	113	≥243
7	Male 55	IIB	None	None	PR	SD	39	29	24§	52§
8	Male 67	IB	Topical corticosteroids	NB-UVB	PR	PR	≥248	29	87	≥248
9	Male 48	IB	Topical corticosteroids	None	PR	PR	≥228	29	88	≥228
10	Female 21	IIA	Topical corticosteroids	NB-UVB	PR	PR	≥127	29	≥99	≥127
11	Female 81	IIB	None	VTRAC	SD	SD	82	ND	ND	85¶
12	Male 65	IB	Topical corticosteroids	NB-UVB	SD	SD	≥166	ND	ND	≥173
13	Male 62	IIA	Topical corticosteroids	None	PR	PR	≥100	26	≥75	≥100
14	Female 61	IB	None	NB-UVB	PR	PR	≥229	26	≥204	≥229
15	Male 58	IIB	None	None	PD	PD	22	ND	ND	29¶

†Assessed according to the evaluation criteria for chemotherapeutics for malignant skin carcinomas. ‡Assessment was terminated because the patient was withdrawn from the study at his request.[13] §Assessment was terminated because the patient was withdrawn from the study due to an adverse event. ¶Assessment was terminated because the patient was withdrawn from the study due to an aggravation of MF. MF, mycosis fungoides; mSWAT, modified severity weighted assessment tool; NB-UVB, narrowband ultraviolet B; ND, not determined; PR, partial response; PD, progressive disease; PUVA, psoralen plus ultraviolet A therapy; SD, stable disease; VTRAC, 308-nm excimer light.

tive photographs of skin lesions are shown in Figure 1 (patient 11) and Figure 2 (patient 13). Although patient 11 experienced SD, she demonstrated a marked improvement of tumors on the right forearm and palpebral part after 8 weeks of treatment (Fig. 1). Patient 13, who achieved PR, demonstrated improvement of patches after 8-week administration (Fig. 2).

The median time to response for the 11 patients, who achieved the objective response after 4 weeks of treatment given 5 days a week, was 29 days (range, 26–32). The Kaplan–Meier estimate for the duration of SD is shown for all 15 patients in Figure 3. Thirteen patients did not experience PD during the study, and hence the median duration of SD was not reached but was 170 days or more (range, 29 to ≥253).

As assessed according to the mSWAT, nine patients (60.0%; 95% CI, 32.3–83.7%) achieved the objective response (all experienced PR), five experienced SD and one experienced PD. Out of 11 patients rated as PR in the evaluation criteria for chemotherapeutics for malignant skin carcinomas, three were of the grade SD as assessed according to the mSWAT. On the other hand, one patient rated as SD in the former scoring system was evaluated as PR in the latter system. Overall responses assessed by both scoring systems significantly correlated with each other ($P = 0.0461$, using Spearman's rank correlation coefficient).

Safety and tolerability

A total of 47 drug-related AE were reported in 15 patients. The most common drug-related AE was influenza-like illness occurring in all patients enrolled. Grade 3 drug-related AE occurred in five patients (33.3%) and grade 4 in one (6.7%). The drug-related AE occurring in two or more patients are shown in Table 3. One patient (patient 7) was withdrawn from the study due to drug-related grade 1 cough. The symptom disappeared after discontinuation of the drug, which suggested that it was not due to interstitial pneumonia.