のがあり，有効性は明らかではない．
・NMDA受容体拮抗薬：ケタミン（ケタラール®）には，がんによる神経障害性疼痛について有効とするある程度の根拠がある．
・コルチコステロイド：脊髄圧迫症候群など神経への圧迫や炎症による痛みの場合に有効であることが経験的に示唆されている．

● **神経ブロック**
・副作用のために薬物療法が十分に行えない場合や，薬物を増量しても十分に効果がない場合には，神経ブロックの適応について専門家に相談する．

消化管閉塞による嘔気・嘔吐

1 癌患者にみられる嘔気・嘔吐

● 終末期癌患者の約5割に嘔気・嘔吐がみられる．

● 嘔気・嘔吐は様々な病態でみられるが，ここでは消化器癌患者で多くみられる消化管閉塞について記述する(表4)[4]．

表4　嘔気・嘔吐の原因

環境に関連した原因	臭い，多すぎる食物，不十分な口腔ケア
病状に関連した原因	便秘，消化管疾患（胃潰瘍，胃腸炎），腎不全
癌に特異的な原因	消化管閉塞，頭蓋内腫瘍，高カルシウム血症
治療に関連した原因	化学療法，腹部への放射線治療，薬剤（オピオイド，NSAIDs，ステロイド）
その他の原因	感染症，不安，前庭器官の炎症，片頭痛

（文献4）より一部改変）

2 治療に際しての留意事項

● 一般治療で回復可能な要因を除外する．高カルシウム血症，脳転移，感染症，便秘，胃潰瘍など．

● 消化管閉塞による嘔気・嘔吐の場合，閉塞部位が上部消化管か下部消化管かで治療のストラテジーが異なることに注意する．

3 消化管閉塞による嘔気・嘔吐の治療（図9）

● **上部消化管閉塞の場合**
・一般的には薬物療法単独による制御は困難と考えられている．
・完全閉塞の場合はNGチューブの用い方を工夫する．
　① 症状がある時に間欠的に使用
　② 夜間のみ定期留置
　③ 就眠前にチューブを入れて吸引してから抜く，など
・過量の輸液が消化管分泌を亢進して症状緩和を困難にするとの見解が一般的である．上部消化管閉塞では，輸液量は維持量＋嘔吐量を目安に投与する．
・ドレナージされても持続する嘔気には薬物療法が有効な場合がある．
・口腔内が汚染していると，不快感→飲む→吐く，の悪循環になるため口腔ケアが重要である．

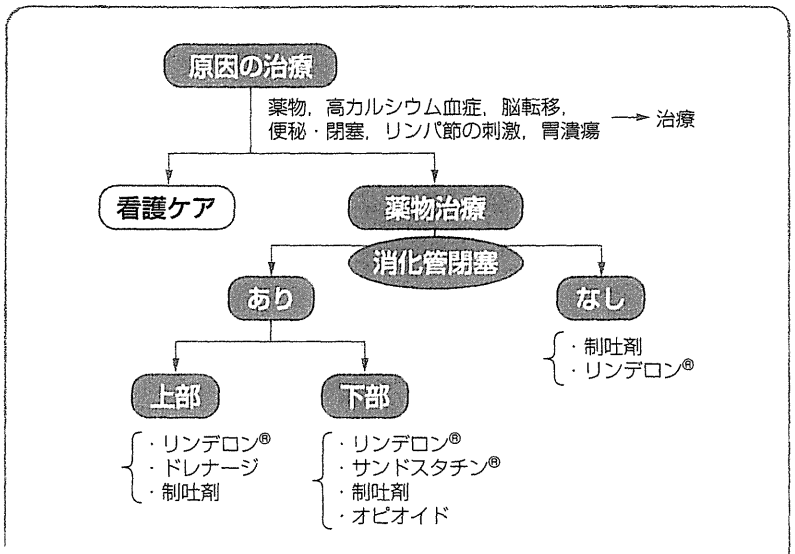

図9　嘔気・嘔吐の緩和治療

● 下部消化管閉塞の場合

・一般的に，経口摂取が一定量に制限できれば，絶飲食にせずに薬物療法単独で症状緩和が得られると考えられている．
・ステロイド＋分泌抑制薬（酢酸オクトレオチド）＋中枢性制吐剤＋患者の希望に合わせた経口摂取＋やや絞り気味の輸液＋オピオイドが一般的である．
・腹部膨満，疼痛には「持続する疼痛」に準じてオピオイドを使用する．腸蠕動を低下させたくない場合はフェンタニルが，腸蠕動を低下させることで鎮痛を図りたい場合にはモルヒネが推奨される．
・NGチューブ，輸液，口腔ケアについては上部消化管閉塞の場合と同様．

4 使用される薬剤

● ステロイド

・消化管閉塞全体として，「使用しないよりは使用する方がおそらく良い」再開通率がある．
・全身状態が許容できれば，ステロイドを投与し，効果があれば効果の維持できる最少量まで減量，または一旦中止して症状が悪化すれば再開する．効果がなければ中止する．
・1ヵ月以上の投与になる場合には，消化性潰瘍，耐糖能異常，満月様顔貌，精神症状，易感染性などのステロイドの副作用を生じるリスクが上がるため，利益が不利益を上回ると判断した場合に使用する．

● 消化管分泌抑制薬

・消化管閉塞全体を対象としたRCTでは，オクトレオチド酢酸塩（サンドスタチン®）がブチルスコポラミン臭化塩（ブスコパン®）より有意に優れた効果が認められている．
・上部消化管閉塞では有効な症例報告がある程度で，一般的には効果は10～20%以下である．
・下部消化管閉塞では，小腸の拡張が著明になる前から投与を開始する方が有効である．

● 制吐剤（表5）[4]

・完全閉塞の場合，メトクロプラミド（プリンペラン®）は症状を悪化させ，腸管内圧の上

表5　制吐剤の種類

抗精神病薬	ハロペリドール，プロクロルペラジン，クロルプロマジン
抗ヒスタミン薬	ヒドロキシジン，ジフェンヒドラミン，マレイン酸クロルフェニラミン
消化管蠕動亢進薬	メトクロプラミド，ドンペリドン
5-HT$_3$受容体拮抗薬	グラニセトロン，オンダンセトロン

（文献3）より一部改変）

昇による穿孔の危険があるため望ましくない．
・完全閉塞でないと考えられる場合，メトクロプラミドの持続点滴を蠕動が亢進しない程度で使用する．
・中枢性制吐剤を眠気の生じない範囲内で使用するとよい場合がある．例えばクロルフェニラミンマレイン酸塩（クロールトリメトン®），プロクロルペラジン（ノバミン®），ハロペリドール（セレネース®）など．
・いずれも投与開始後，症状緩和効果と眠気とのバランスを患者個々に判断して投与量を調節する．

癌性腹水による腹部膨満

1 癌患者における腹水

● 腹水のある患者の約10%の原因が癌である．

● 腹水は少量であれば無症状であるが，大量になると腹部膨満，腹痛，嘔気・嘔吐，下肢の浮腫，呼吸困難等の症状がみられる．

2 治療に際しての留意事項

● 腹水性状によって治療方法が異なることに注意する．

● 肝不全，転移性肝腫瘍による漏出性腹水は保存的治療が有効な場合があるが，一般的に癌性腹水は保存的治療に抵抗性である．

3 癌性腹水による腹部膨満に対する治療

● 腹腔穿刺・腹腔静脈シャント術
・腹腔穿刺によるドレナージはタンパク喪失のリスクをともなうが，確実な症状緩和手段である．在宅でも行うことが可能である．
・全身状態が良い患者では腹腔静脈シャント術の適応となる場合がある．

● 輸液
・観察的研究で，輸液量はやや脱水に置く方が腹水の貯留を有意に抑制できることが確かめられている．
・終末期で経口補給できない患者では，1日の水分負荷を経口量と合わせて1L以下を目安とし，浮腫や胸水など全身の溢水状態が増悪する前に対処する[6]．

● **化学療法**

・腹腔内化学療法，全身化学療法が一部の患者で有効と考えられている．

4 使用される薬剤

● **利尿剤**

・癌性腹水の場合，利尿剤は腹腔穿刺よりも腎不全，電解質異常の合併率が高いので強くは推奨されない．

・ただし有効な場合があるので，肝転移による腹水に準じて利尿剤を投与して反応をみるのは初期治療として試す価値がある．

・肝転移による漏出性腹水の場合，スピノロラクトン（アルダクトン®）±フロセミド（ラシックス®）の使用が勧められる．効果は3～7日後に出るため，特に投与初期は週1～2回は電解質と腎機能をチェックし，腎機能の悪化がみられたら利尿剤の適応は乏しい．

● **アルブミン製剤**

・肝転移による漏出性腹水や感染症など一時的な低アルブミン血症の場合，アルブミン製剤＋利尿剤は経験的によく用いられてきた方法である．癌性腹水では推奨されない．

● **オピオイド・抗不整脈薬**

・腹水量に働きかけずに腹満感を減らす方法として，少量のオピオイドが経験的に用いられている．

・国内ではリドカイン，ケタミン塩酸塩が勧められることもあるが，国際的には標準的ではない．

倦怠感・食思不振

1 癌患者にみられる倦怠感・食思不振

● 全身倦怠感と食思不振は終末期癌患者によくみられる症状である．

● 食思不振の原因には可逆性のものもあるが，死に向かう過程において食思不振の出現は自然であることを認識しておく．

2 治療に際しての留意事項

● 倦怠感・食思不振の原因となっている病態を除外する．貧血，感染症，高カルシウム血症，

side MEMO **腎不全患者へのオピオイド投与**

腎不全下ではモルヒネは有害な代謝産物が蓄積するので，せん妄やミオクローヌスなどを起こしやすくなる．

・モルヒネの少量投与であれば，症状に注意しながら継続投与

・内服可能なら，オキシコドン経口薬に変更

・内服不可能なら，フェンタニル（貼付薬，注射薬）またはオキシコドン注射薬（パビナール®）に変更

低ナトリウム血症，肝障害，口内炎，脳転移などが見逃されやすいが治療しうる病態である．

● 味覚障害があれば，ビタミンB群，亜鉛の補給を検討する．

3 倦怠感，食思不振に対する治療

● 消化管蠕動亢進薬

・ドンペリドン（ナウゼリン®）やメトクロプラミドは必ず毎食直前か24時間持続投与とする．食思不振に慢性嘔気をともなう時，肝腫大にともなう胃の拡張不全症候群がある時に60%で有効である．

● ステロイド

・60%以上の患者で有意な食欲増進作用があるが，効果は短期間（2～6週間）しか持続しない．
・1ヵ月以上になるとステロイドによる一般的な副作用のリスクが高くなるので，利益が不利益を上回ると判断される場合に選択できる方法である．

呼吸困難

1 癌患者にみられる呼吸困難

● 呼吸困難は終末期癌患者の約5割にみられる．

● 呼吸困難は疼痛と同じく主観的なものであり，理学所見や検査所見とは必ずしも相関しない．

● 呼吸困難は不安や死の恐怖につながりやすく，迅速かつ適切な説明と治療が必要である．

2 治療に際しての留意事項

● 一般治療で回復可能な要因を除外する．肺炎，心不全，不整脈，貧血，胸水，喘息など（表6）．

● 死亡直前に酸素飽和度はよいが頻呼吸で呼吸困難を訴える場合，代謝性アシドーシスによる死亡が迫っている可能性がある．

● 死亡直前期では気道分泌，浮腫，呼吸困難が増悪すれば輸液の減量（500mL以下）が推奨される[5]．特にルート確保のためだけの持続点滴はせん妄の原因にもなるため必須でなけ

表6　呼吸困難の原因

状況に関連した原因	急性不安
病状に関連した原因	疼痛，貧血，全身衰弱，肺塞栓，胸腔内感染，腹部膨満
癌に関連した原因	気管支の閉塞，癌の浸潤，癌性リンパ管症，上大静脈閉塞，胸水貯留
治療に関連した原因	気胸，肺切除，化学療法後の線維化，放射線治療後の線維化
その他の原因	喘息，肺気腫，心不全，心筋梗塞，不整脈，代謝性アシドーシス，異物誤飲

（文献3）より一部改変）

れば日中のみの間欠投与にする.

3 呼吸困難に対する治療（図10）

● ステロイド

・ステロイド投与はエビデンスのレベルは低いがよく行われる方法である．効果があれば有効量まで減量することが勧められる.
・ステロイドによる一般的な副作用に加えて，終末期では精神症状（せん妄）を惹起することがある．生じた場合にはステロイドを中止するか，継続するのであれば抗精神病薬を併用する.
・気道狭窄，上大静脈症候群，多発肺転移では比較的効果がある場合がある．他の病態における作用機序は不明である.

● 抗不安薬

・呼吸困難全体を対象とした抗不安薬の投与はRCTで有用性が不利益を上回らないのでルーチンでの使用は勧められない.「不安・焦燥状態を示す患者」でのみ併用が推奨される.
・定型的にはアルプラゾラム（ソラナックス®）を頓用で使用してみて，よければ定期使用とする.
・内服ができない時は，ジアゼパム（セルシン®）舌下投与，アタラックス®P皮下注または静注，セニラン®坐薬，ダイアップ®坐薬などが経験的に使用されている.
・全身状態が良い患者では，SSRI（選択的セロトニン再取り込み阻害薬）を併用する.

● 吸入療法

・フロセミド（ラシックス®）の吸入は，現在RCTが行われているが否定的であり，「有意としても効果の幅は小さい治療」である.
・モルヒネなどの薬剤の吸入と生理食塩水の吸入では効果に差がみられていないため，生理食塩水の吸入でも良い.「何か方法がある」ということが患者の自己コントロール感につながり有用な場合が多い.

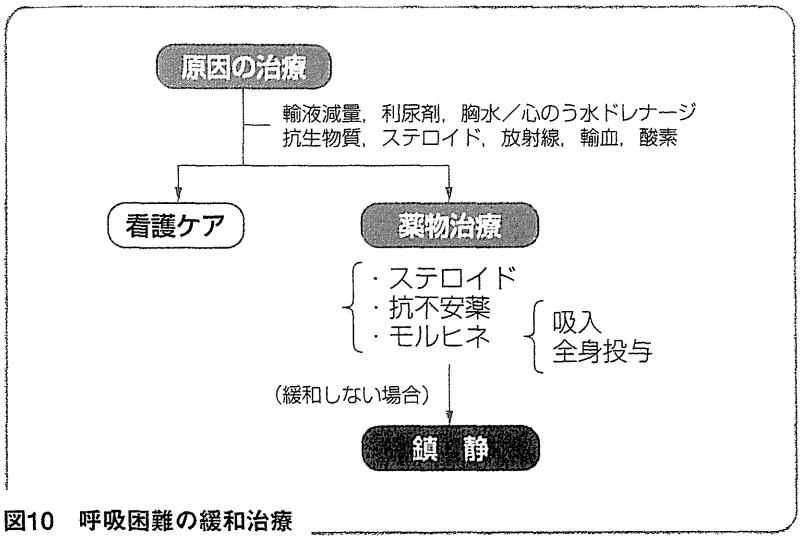

図10　呼吸困難の緩和治療

● **モルヒネの全身投与**

・呼吸困難に有効であることが確かめられているオピオイドはモルヒネだけである.
・呼吸困難にモルヒネを投与すると，効果の幅は少ないが有意な呼吸困難改善効果があることが確かめられている.
・全身状態がよい場合には必ずしも意識やバイタルサインの低下を引き起こさないが，全身状態が不良な場合は「傾眠状態で苦痛がない」を目的とせざるを得ない場合も多くある.
・経験的に，喀痰喀出困難のない多呼吸をともなう呼吸困難で最も有効である.
・喀痰喀出困難による呼吸困難は喀痰管理ができないと薬物治療は困難．看取りの時期では臭化水素酸スコポラミン（ハイスコ®）で分泌抑制ができるが，鎮静され会話は困難になることが多い.
・全身状態が不良の場合には，何を目的とするかで対処が異なるので，患者，家族と「意識を保って頑張る」のか，「眠気が出てもとにかく楽に」を目指すのかをよく相談する.

● **鎮静**

・様々な治療を行っても緩和できない苦痛症状に対しては，鎮静（セデーション）を考慮する．その適応についてはガイドライン[7]に則り，多職種による検討を重ねて慎重に判断する.

せん妄

1 癌患者とせん妄

● 終末期患者に起こる認知障害には，せん妄と認知症という2つの病態があり，その鑑別が重要である.

● せん妄は癌患者の60～90%にみられる頻度の高い病態である.

● 患者のみならず家族にとっても苦痛が強いが治療可能であるため，せん妄の診断，治療は重要である.

2 治療に際しての留意事項

● 全身状態のスクリーニングを行い，感染症，脱水，電解質異常，肝不全，腎不全，低酸素血症，脳転移などを除外する（表7）[4].

● 投与薬剤（オピオイド，ベンゾジアゼピン系薬剤，抗うつ薬，H_2受容体拮抗薬など）をチェックする．それまで継続投与され副作用がなかったオピオイドがせん妄の原因になることは

表7　せん妄の原因

病状に関連した原因	疼痛，脱水，高カルシウム血症，低ナトリウム血症，腎不全，肝不全
癌に関連した原因	頭蓋内腫瘍，腫瘍随伴症候群
治療に関連した原因	オピオイド，向精神薬，抗うつ薬，H_2受容体拮抗薬，ステロイド，抗癌剤の中止（ニコチン，向精神薬など）
その他の原因	感染症，尿閉，低酸素血症，ビタミン欠乏症，頭部外傷

（文献4）より一部改変）

稀である.

● 原因治療が可能か不可能かによって，患者と家族の価値観を聞きながら，個別に目標を立てる.

3 せん妄に対する治療（図11）

● オピオイドローテーション

・腎不全をともなう患者にモルヒネが投与されている場合，オキシコドンかフェンタニルへ変更する.

・終末期の臓器不全によるせん妄はオピオイドローテーションだけでは改善は期待できないため，鎮痛を優先してモルヒネを継続してもよいことがある.

● 看護ケア

・コミュニケーションへの支援，環境整備，家族ケアなどが薬物以上に重要である.

● 薬物治療

・基本的には抗精神病薬［ハロペリドール（セレネース®），リスペリドン（リスパダール®），フマル酸クエチアピン（セロクエル®）］の単独投与であるが，回復困難な終末期では睡眠を重視してベンゾジアゼピン系薬剤を併用する方がよい場合がある.

● 鎮静

・様々な治療を行っても緩和できない苦痛症状に対しては，鎮静（セデーション）を考慮する.その適応についてはガイドライン[6]に則り，多職種による検討を重ねて慎重に判断する.

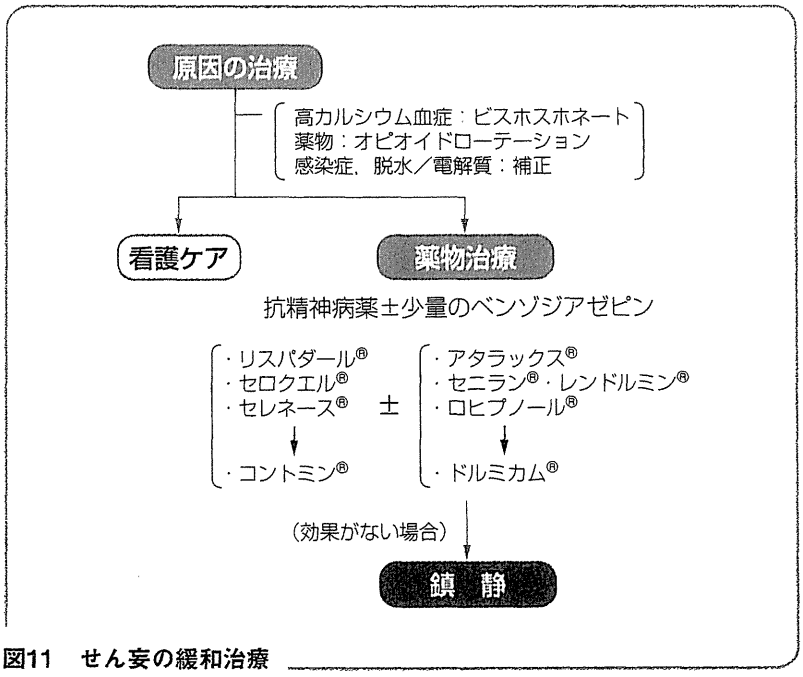

図11　せん妄の緩和治療

side MEMO　見落とされがちな副作用：錐体外路症状

副作用対策として用いられる薬剤（メトクロプラミド，ハロペリドール，プロクロルペラジンなど）が原因となって錐体外路症状を引き起こすことがしばしばあるので注意が必要である．症状として，不眠，焦燥感やイライラ感，手の震えなどがみられる．

結　語

- 癌患者によく見られる症状（痛み，嘔気・嘔吐，腹部膨満，倦怠感・食思不振，呼吸困難，せん妄）とその治療について概説した．
- すべての癌患者が適切な緩和医療を受けられるために，癌治療に関わる医療者は基本的な緩和医療の知識を身につけておくべきである．
- 癌患者の苦痛をやわらげるためには，様々な側面から患者を支援することが重要であり，そのためには多職種からなるチーム医療が不可欠である．

（天野功二／森田達也）

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Original Article

Treatment Response to Psychiatric Intervention and Predictors of Response Among Cancer Patients with Adjustment Disorders

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Abstract

Context. Although adjustment disorders (ADs) are common among patients with cancer and such patients are frequently referred to consultation-liaison psychiatrists, little is known about the clinical courses of these patients.

Objectives. The present study investigated treatment response to psychiatric intervention and predictors of response in a relatively large sampling of cancer patients with ADs.

Methods. We created a database of all referral cases with ADs that included data on the patients' demographic and medical factors and physician-rated Clinical Global Impression (CGI) scale to assess treatment response and clinical course. A CGI-Improvement scale score of better than "much improved" was regarded as indicating a response to treatment; the number of patients who responded to treatment during a four-week follow-up period was assessed. Also, predictors of treatment response were explored by examining demographic and medical factors using a multivariate analysis.

Results. Among the 238 eligible patients, 136 (57.1%) responded to psychiatric treatment; most of these responders improved to a subthreshold level of illness. On the other hand, 56 patients (23.5%) did not respond to psychiatric treatment, seven patients (2.9%) developed major depressive disorders, and 39 patients (16.4%) discontinued treatment before achieving a response. Among the predictive factors that were explored, suffering from pain significantly predicted a good treatment response, whereas a worse performance status predicted a poor treatment response.

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Conclusion. Cancer patients with ADs can respond to psychiatric treatment, but a few cases develop major depressive disorders. Several predictors of treatment response were identified. J Pain Symptom Manage 2011;41:684–691.

Key Words
Adjustment disorders, prognosis, cancer, psychiatry, therapeutics, oncology

Introduction

Adjustment disorder (AD) is the most common psychiatric issue in patients with cancer, with a reported prevalence of 4%–35%.[1–7] AD is a diagnosis that bridges normality and pathology, has an indefinite symptomatology in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR),[8] and has an essential place in psychiatric taxonomy.[9] Many patients assigned the diagnosis of AD have had suicidal ideation or suicidal behavior,[10,11] low quality of life,[12] longer length of hospital stay,[13] and severe caregiver distress.[14] Previous studies have shown that about 10% of the cases referred to consultation-liaison psychiatrists in general hospitals have AD,[15,16] and this percentage may be higher in cancer centers.[17] Indeed, one-third of the referred patients to our department were diagnosed as having AD.

Although AD is such a prevalent, burdensome, and frequently treated disorder, little is known about its treatment response in cancer patients compared with other disorders that are also frequently referred to psychiatrists, such as major depressive disorders or delirium, and psychiatrists must care for these patients with few benchmarks available for reference. Razavi et al.[18,19] conducted two pharmacologic trials, one which showed the superiority of trazodone to clorazepate for patients with AD and another that showed that fluoxetine did not have a significant effect, compared with a placebo, in patients with AD or major depressive disorders. Other similar trials are lacking. Our previous study suggested that a multifaceted psychosocial intervention program can decrease the prevalence of ADs in patients with advanced cancer, with six of eight patients with AD responding to treatment.[11] The relatively small sample sizes and limited number of studies prevent conclusions about the percentage of patients who respond to psychiatric intervention or who worsen and develop major depressive disorders despite intervention. Moreover, predictors of treatment response have not yet been assessed, and the types of patients who tend to respond to treatment also remain unclear.

The primary aim of this study was to investigate the response of cancer patients with AD to psychiatric treatment; the secondary aim was to explore predictors of treatment response. We assessed the percentage of referred cases with AD who responded to commonly used psychiatric interventions in combination with brief supportive psychotherapy and pharmacotherapy.[15] Also, we explored the demographic and medical factors capable of predicting the treatment response to intervention.

Method

Study Sample

The study period was from May 2005 to April 2008. Consecutive patients referred to the Psycho-Oncology Division of the National Cancer Center Hospital East and diagnosed by psychiatrists as having AD based on the DSM-IV criteria were included. Patients who could not be followed up because they were physically too ill, had died, or because of hospital transfer were excluded.

This study was approved by an institutional review board. Because all the data assessed in this study were obtained as part of routine clinical assessments, written consent was not obtained from the patients, in accordance with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

Referral Process and Psychiatric Intervention

Patients who were suspected of having any psychiatric problem were referred to the Psycho-Oncology Division by oncologists. At this time point, the patients had not completed

any self-reported distress scale, and oncologists usually do not speculate as to the specific psychiatric diagnosis as they are not qualified to do so. If patients accepted the consultation, each referred patient was assigned to one of the five trained psychiatrists of the Psycho-Oncology Division, and a clinical diagnostic interview based on the DSM-IV criteria was conducted. The diagnosis of AD in medically ill patients is confounded by the symptoms of the medical illness itself, and this is an ongoing problem that the DSM must address. In cases where the symptoms were not definitively caused by a medical illness or for psychiatric disorders with vegetative signs, the accuracy of the psychiatric diagnoses of the patients was discussed at a weekly meeting of the psychiatry department.

Although no consensus guidelines exist for the treatment of AD in medically ill patients, our psychiatric intervention for AD involves a combination of psychotherapy and pharmacotherapy, both complying with our original treatment manuals, which were developed based on the evidence of previous studies and have been described in detail elsewhere.[20] Regarding psychotherapy, group therapy was not provided, and most of the patients received brief individual supportive counseling sessions; additional techniques, such as relaxation, also were used depending on each patient's situation and preference. Ambulatory patients were usually seen every one to two weeks, when they visited their oncologists; inpatients were usually seen once or twice a week.

For patients who did not respond to psychotherapy alone, pharmacotherapy was considered, with anxiolytics used as the drugs of first choice.[21] For patients with a limited life expectancy and without liver dysfunction, we often chose a short-acting drug, such as alprazolam, because the risk of addiction is not a notable problem for these patients. But for long-term survivors or patients with liver dysfunction, we often use a benzodiazepine, such as lorazepam, on a short-term basis, considering the hepatic metabolism. For patients who did not respond to anxiolytics and who manifested considerable depressive symptoms, the use of an antidepressant was considered. These intervention principles are in agreement with those of teaching hospitals in the United States, Canada, and Australia.[15]

Demographic and Clinical Variables

During the study period, we constructed a database of patients with AD to clarify their response to treatment and clinical course. This database was designed so that all the items assessed during routine clinical practices could be extracted from the patients' medical charts, including patient age, sex, cancer site, disease stage, marital status, employment status, and performance status as defined by the Eastern Cooperative Oncology Group (ECOG) criteria (ranging from 0 [no symptoms] to 4 [bedridden]). To assess pain, the psychiatrists directly asked the patients about their pain at the time of the first interview; each patient's pain was rated from 0 (not at all) to 3 (intolerable pain).

Assessment of Severity and Response to Treatment

The psychiatrist in charge assessed the severity of AD and determined whether any improvement had occurred at every clinical examination. To assess the severity of AD, the physician-rated Clinical Global Impression-Significant (CGI-S) scale was used. This scale ranges from 1 to 7 and is rated using the following benchmarks: 1 = normal, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = among the most extremely ill. To assess improvement, the physician-rated Clinical Global Impression-Improvement (CGI-I) scale was scored during follow-up assessments. This scale ranges from 1 to 7 and is scored using the following benchmarks: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.[22] A treatment "response" was regarded as a CGI-I rating of 1 or 2. A correlation between the CGI and generally used rating scales, such as the Hamilton Depression Rating Scale, the Montgomery Åsberg Depression Rating Scale, and the Beck Depression Inventory, has been previously reported.[23]

Analysis

The patients' demographic and medical characteristics were obtained from the database and were described separately for the eligible and excluded group. Intergroup comparisons were made using a univariate analysis with the *t*-test, Mann-Whitney *U*-test, and Chi-squared test

used for parametric variables, nonparametric variables, and categorical variables, respectively.

All the eligible cases were classified into the following four categories, and the proportion of cases in each category was determined: 1) "responded case:" a response was observed at a four-week follow-up assessment or treatment was terminated before four weeks after a treatment response had been achieved; 2) "nonresponded case:" no response was observed at a four-week follow-up assessment; 3) "case developed major depressive disorder:" the depressive symptoms worsened, and the patient developed major depressive disorder; and 4) "case dropped out from treatment:" treatment was terminated before four weeks without achieving a treatment response.

We used a multivariate logistic regression analysis to examine predictors of treatment response. For this purpose, the patients were dichotomized into "responded case" and "others," which included the other three categories described above. Age, sex, tumor stage, pain, performance status, marital status, and employment status, which have been suggested to be associated with the development of AD in previous observational studies,[3,5–7,24] were entered as independent variables. All the reported *P*-values are two-tailed. All the data analyses were conducted using SPSS 14.0 J for Windows statistical software (SPSS Japan Institute, Tokyo, Japan).

Results

Clinical Demographics

During the study period, 259 patients were referred to the Psycho-Oncology Division for the treatment of ADs. Among these 259 patients, 238 (91.9%) were eligible for this study and 21 (8.1%) who could not be followed up because they were physically too ill, had died, or because of hospital transfer were excluded from the study sample. The clinical characteristics of both the eligible and excluded group, including the subtype of AD, age, sex, tumor sites, tumor stage, pain intensity, ECOG performance status, marital status, and employment status, are listed in Table 1 and compared between the two groups. The excluded group had a worse performance status and tended to have greater pain than the eligible group.

Treatment Response and Course of Severity

Among the 238 eligible patients, a "response" was achieved in 95 (39.9%) patients at a four-week follow-up examination, and 41 (17.2%) patients terminated treatment before four weeks after a "response" had been achieved. Overall, 136 of the 238 patients (57.1%) were classified as "responded case," 56 (23.5%) patients were classified as "nonresponded case," seven (2.9%) were classified as "case developed major depressive disorder," and 39 (16.4%) were classified as "case dropped out from treatment."

The mean CGI-S score of all the eligible patients was 3.45 ± 0.78 at baseline and 2.25 ± 0.94 at a four-week follow-up examination or at the termination of treatment, representing a significant decrease ($P < 0.001$). Among the 136 patients who responded to treatment, 111 (81.7%) decreased to a subthreshold illness level (CGI-S score of 1 or 2).

Predictors of Treatment Response

The results of a multivariate analysis investigating predictors of response to treatment are shown in Table 2. Among the factors, suffering from pain predicted a good response to treatment, whereas a performance status worse than 2 predicted a poor response, compared with a performance status of 0.

Discussion

The results of this study demonstrated that more than half (57.1%) of the cancer patients with AD responded to the psychiatric intervention within four weeks and that the degree of AD severity decreased to normal or a borderline illness level in most of the patients who responded. On the other hand, a comparatively small proportion of patients (2.9%) developed major depressive disorders. Among the factors that were explored, suffering from pain predicted a good response to treatment, whereas a worse performance status predicted a poor response.

Snyder et al.[25] assessed the course of referred patients who were diagnosed as having AD with a depressed mood in an acute care inpatient hospital setting, and 76.4% of these patients were judged to have exhibited improvements after psychiatric intervention.

Table 1
Characteristics of Patients

Clinical Characteristics	Followed Patients (%)	Not Followed Patients (%)	*P*-value
Total patients	238 (100)	21 (100)	—
Age (mean ± SD), years	59.1 ± 11.6	57.1 ± 14.0	0.14
Sex	—	—	0.36
Male	107 (45.0)	12 (57.1)	—
Female	131 (55.0)	9 (42.9)	—
Subtype of adjustment disorders	—	—	0.62
Mixed anxiety and depressed mood	97 (40.8)	8 (38.1)	—
With anxiety	76 (31.9)	5 (23.8)	—
With depressed mood	60 (25.2)	7 (33.3)	—
Mixed disturbance of emotions and conduct	2 (0.8)	0 (0)	—
Unspecified	3 (1.3)	1 (4.8)	—
Primary cancer site	—	—	0.55
Lung	49 (20.6)	5 (23.8)	—
Head and neck	38 (16.0)	4 (19.0)	—
Breast	35 (14.7)	2 (9.5)	—
Colon	24 (10.1)	5 (23.8)	—
Esophageal	21 (8.8)	1 (4.8)	—
Stomach	17 (7.1)	1 (4.8)	—
Others	54 (22.7)	3 (14.3)	—
Clinical tumor stage	—	—	0.10
Stage I–III	89 (37.4)	4 (19.0)	—
Stage IV or recurrent	149 (62.6)	17 (81.0)	—
Performance status (ECOG)[a]	—	—	0.01
0	81 (34.0)	1 (4.8)	—
1	79 (33.2)	8 (38.1)	—
2–4	78 (32.8)	12 (57.1)	—
Pain	—	—	0.03
Absent or little (0–1)	153 (64.3)	8 (38.1)	—
Tolerable or intolerable (2–3)	85 (35.7)	13 (61.9)	—
Married	—	—	0.49
Yes	189 (79.4)	18 (85.7)	—
No	49 (20.6)	3 (14.3)	—
Employment	—	—	0.30
Employed	86 (36.1)	10 (47.6)	—
Not employed	152 (63.9)	11 (52.4)	—

SD = standard deviation.
[a]Performance status as defined by the Eastern Cooperative Oncology Group.

Together with our results, these findings suggest that medically ill patients with AD tend to recover after psychiatric intervention.

Several studies have assessed the clinical course of AD. Andreasen et al.[26] indicated that 75.3% of adult patients tend to recover from AD within six months but that 43% of adolescent patients with AD developed a major psychiatric disorder, such as schizophrenia, major depression, substance abuse, or a personality disorder. In a follow-up study of cancer patients with AD treated in a palliative care setting for two months, 41.7% of the patients recovered from their mental illnesses, but the remaining patients continued to exhibit symptoms of AD.[7] For advanced lung cancer patients with AD, 53.8% of the patients had recovered at a six-month follow-up, but the other patients continued to exhibit the symptoms of AD.[5] As these findings suggest, some patients with AD are curable without intervention, and a certain percentage of our subjects may have recovered spontaneously.

On the other hand, 2.9% of the patients developed major depressive disorders. A previous study showed that 21% of adults with AD had developed a major depressive disorder or alcoholism at the time of a five-year follow-up examination,[26] and 41.7% of cancer patients in a palliative care setting had developed a major depressive disorder at a two-month follow-up.[7] These results cannot be compared with the present results, as the follow-up periods of the two studies were different. It is

Table 2
Predictive Factors for Treatment Response of ADs—Logistic Regression Analysis

Predictive Factors	Responded Case (%)	Others (%)	OR (95%CI)	*P*-value
Total patients	136 (100)	102 (100)	—	—
Age (mean ± SD), years	60.0 ± 12.0	58.0 ± 11.1	0.99 (0.96–1.01)	0.25
Sex				
Male	60 (44.1)	47 (46.1)	—	—
Female	76 (55.9)	55 (53.9)	0.91 (0.50–1.63)	0.74
Clinical tumor stage				
Stage I–III	48 (35.3)	41 (40.2)	—	—
Stage IV or recurrent	88 (64.7)	61 (59.8)	0.82 (0.46–1.47)	0.51
Performance status (ECOG)[a]				
0	50 (36.7)	31 (30.4)	—	—
1	45 (33.1)	34 (33.3)	1.41 (0.72–2.76)	0.31
2–4	41 (30.1)	37 (36.3)	2.27 (1.09–4.74)	0.03
Pain				
Absent or little (0–1)	82 (60.3)	71 (69.6)	—	—
Tolerable or intolerable (2–3)	54 (39.7)	31 (30.4)	0.52 (0.28–0.99)	0.05
Married				
Yes	110 (80.9)	79 (77.5)	—	—
No	26 (19.1)	23 (22.5)	1.36 (0.70–2.65)	0.36
Employment				
Employed	46 (33.8)	40 (39.2)	—	—
Not employed	90 (66.2)	62 (60.8)	0.91 (0.49–1.71)	0.78

SD = standard deviation; OR = odds ratio; CI = confidence interval.
[a]Performance status as defined by the Eastern Cooperative Oncology Group.

not clear whether our comparably low rate of major depression was because of the effectiveness of treatment or if more patients might have developed major depression after a longer observation period. Further studies of AD in cancer patients treated with psychiatric intervention with longer follow-up periods are needed to clarify this point.

We explored the demographic and physical factors that predicted a response to treatment. Suffering from pain predicted a favorable treatment response, and a performance status worse than 2 predicted a poor treatment response, compared with a performance status of 0. No other studies have shed light on predictors of treatment response, and these results provide valuable information for physicians. Pain is a strong stressor and has been associated with AD or major depressive disorders in previous studies;[5,27,28] consequently, this result seems paradoxical because patients who were suffering from pain at baseline responded to treatment more often than patients who were not suffering from pain, with an odds ratio of 0.52 (95% confidence interval, 0.28–0.99). Although the mechanism responsible for this result is unclear, we speculate that this pain might have been alleviated during the follow-up period, contributing to the better outcome. As we lack follow-up data on pain to test this speculation, further study examining the clinical courses of both pain and ADs is needed.

A poor performance status also has been shown to be strongly associated with AD,[7,29] and our results showed that a poor performance status predicted a poor treatment response. A poor performance status can elicit persistent psychological distress and may hinder remission from AD because the performance status of cancer patients usually deteriorates continuously and rarely improves,[30,31] unlike the pain experienced by cancer patients.

The present study had several limitations. First, this study was based on a consultation case basis, and the actual incidence of AD might have been much greater if every patient in the ward had been screened. Furthermore, a patient selection bias may exist because the subjects of this study comprised preselected patients who may have had more obvious conditions or may have been more willing to see a psychiatrist. Second, this study was held in a single cancer center, and we should consider institutional bias because of physician influence and other factors. Third, there is

a possibility of assessment bias. Although we made the clinical diagnoses according to DSM-IV criteria and the psychiatric diagnoses were confirmed at a weekly meeting of the psychiatry department, it is a less robust method than a structured diagnostic interview. Also, the CGI is a subjective scale and does not have a specific anchor point. Fourth, the predictors of treatment response that were explored in this study were limited to those that could be extracted from the patients' medical charts, and some important factors, such as educational status,[3] were not included. Fifth, no information was presented with respect to two medical issues: the time since diagnosis and how many patients were receiving medical treatment. Both of these factors may have affected distress levels and the speed of spontaneous recovery.

Although our study has several limitations, some highly suggestive results emerged as helpful information for clinical practice and for suggesting future studies. To elucidate the entire picture of treatment response for AD in cancer patients, further research addressing the present study's limitations is needed.

Disclosures and Acknowledgments

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Case Report

Coexistence of TDP-43 and tau pathology in neurodegeneration with brain iron accumulation type 1 (NBIA-1, formerly Hallervorden-Spatz syndrome)

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We report here an autopsy case of sporadic adult-onset Hallervorden-Spatz syndrome, also known as neurodegeneration with brain iron accumulation type 1 (NBIA1), without hereditary burden. A 49-year-old woman died after a 27-year disease course. At the age of 22, she suffered from akinesia, resting tremor, and rigidity. At the age of 28, she was admitted to our hospital because of worsening parkinsonism and dementia. Within several years, she developed akinetic mutism. At the age of 49, she died of bleeding from a tracheostomy. Autopsy revealed a severely atrophic brain weighing 460 g. Histologically, there were iron deposits in the globus pallidus and substantia nigra pars reticulata, and numerous axonal spheroids in the subthalamic nuclei. Neurofibrillary tangles were abundant in the hippocampus, cerebral neocortex, basal ganglia, and brain stem. Neuritic plaques and amyloid deposits were absent. Lewy bodies and Lewy neurites, which are immunolabeled by anti-α-synuclein, were absent. We also observed the presence of TDP-43-positive neuronal perinuclear cytoplasmic inclusions, with variable frequency in the dentate gyrus granular cells, frontal and temporal cortices, and basal ganglia. TDP-43-positive glial cytoplasmic inclusions were also found with variable frequency in the frontal and temporal lobes and basal ganglia. The present case was diagnosed with adult-onset NBIA-1 with typical histological findings in the basal ganglia and brainstem. However, in this case, tau and TDP-43 pathology was exceedingly more abundant than α-synuclein pathology. This case contributes to the increasing evidence for the heterogeneity of NBIA-1.

Key words: Hallervorden-Spatz syndrome, neurodegeneration with brain iron accumulation type 1, neurofibrillary change, tauopathy, TDP-43 proteinopathy.

INTRODUCTION

Hallervorden-Spatz syndrome (HSS) is an autosomal recessive[1] or sporadically occurring neurodegenerative disorder characterized clinically by rigidity and/or spasticity in the limbs, extrapyramidal movement disorders, and mental deterioration.[2] Due to historical discussions, the syndrome was renamed "neurodegeneration with brain iron accumulation type 1" (NBIA-1),[3] and due to recent molecular genetic findings, it has been classed as a pantothenase kinase-associated neurodegeneration (PKAN).[4,5] The known mutations are detected in around 25% of NBIA-1 patients. Neuropathological changes are characterized by iron accumulation, variable neuronal loss and gliosis, and axonal spheroids, mainly affecting the globus pallidus and substantia nigra.[6] Besides the axonal spheroids and iron accumulation, other neuropathological lesions have been

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reported in NBIA-1. Lewy bodies were first observed with routine staining[6–9] and later confirmed with modern immunohistochemical methods.[3,10–15] These observations led to the suggestion that NBIA-1 should be included among the α-synucleinopathies with Parkinson's disease, multiple-system atrophy, and Lewy body dementia.[16] Similarly, neurofibrillary tangles (NFTs) in NBIA-1 brains were first visualized using the classic argentic methods[9,17–23] and more recently confirmed with immunohistochemistry for hyperphosphorylated tau protein.[11,13–15,24,25] In several cases, both α-synuclein and tau pathology coexisted.[9,11–15,19,24,25] Thus, it has been debated whether this disease should be classified as an α-synucleinopathy.

TAR-DNA-binding protein 43 (TDP-43) has recently been identified as a major disease protein in the ubiquitinated inclusions in frontotemporal lobar degeneration (FTLD) with ubiquitin-positive and tau-negative inclusions (FTLD-U) and amyotrophic lateral sclerosis (ALS).[26] However, subsequent studies have detected TDP-43-positive inclusions in other neurodegenerative disorders, including Parkinson's disease and dementia with Lewy bodies (DLB),[27] parkinsonism–dementia complex (PDC) and ALS in Guam,[28,29] corticobasal degeneration (CBD),[30] and Alzheimer's disease (AD).[30,31]

Here we report the clinical, pathological, and genetic findings of a patient with NBIA-1 whose postmortem examination revealed neuroaxonal dystrophy with widespread NFTs and TDP-43-positive inclusions. We also review the previously reported cases of NBIA-1 accompanied by tau and/or α-synuclein pathology.

CASE REPORT

Clinical course

The patient was a Japanese woman who was 49 years old at the time of death. She had neither a family history of neurological disease nor dementing disorder anamnesis. The patient was normal at birth and attended school until the age of 15; her school performance was unsatisfactory. She developed akinesia, resting tremor, and rigidospastic gait at the age of 22. Over the next 6 years, her gait disturbance and limb rigidity progressed very slowly. Neurological examination at age 22 showed an akinetic gait, rigidity and hyper-reflexia of the upper and lower extremities, pathological reflexes, slow eye movement, childish speech, and mental deterioration. There were no sensory abnormalities or cerebellar signs. The patient became unable to walk at the age of 24. Dopaminergic treatment was ineffective. Thereafter, dementia, dysphasia, spastic tetraparesis, and gaze limitation progressed rapidly. She developed myoclonic jerks of her upper extremities at age 32. The myoclonus increased in frequency and spread to involve the lower extremities. A generalized convulsion occurred at the age of 33. Anti-convulsive treatment was initiated and was effective. She progressed to a rigid vegetative state with incontinence at age 33, and by age 35, she was mute and immobile. Numerous investigations were done including examinations of the eye, bone marrow, serum corticosteroids, α- and β-glucosidase, α- and β-galactosidase, α-mannosidase, α-fucosidase, β-glucuronidase, N-acetyl β-glucosaminidase, hexosaminidase A, arylsulfatase A, copper and iron, ceruloplasmin, amino acids, anti-mitochondrial antibody, and vitamin B_{12} levels, all of which were within normal limits. Cerebrospinal fluid revealed normal protein, IgG, glucose, and cell count. Electroencephalograms showed irregular 8- to 9-Hz α-waves mixed with 5- to 7-Hz θ-waves. At age 34, head MRI showed a slight decrease in signal intensity in the globus pallidus and substantia nigra, and severe atrophy of the frontal, temporal lobes, cerebellum, and brainstem (Fig. 1). Although the patient presented with progressive parkinsonism and dementia, we could not establish a definite clinical diagnosis because no biochemical and radiological findings confirmed one. At the age of 49, she

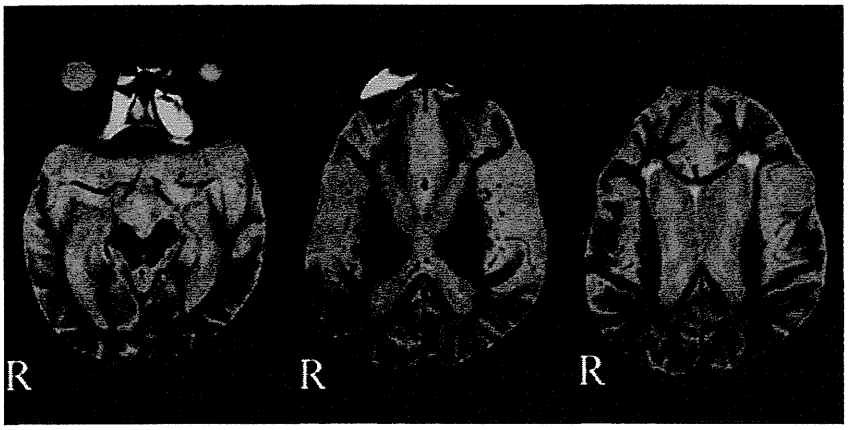

Fig. 1 Cranial MRI (axial, T2-weighted image), showing a slight decrease in signal intensity in the globus pallidus and substantia nigra and severe atrophy of the frontal, temporal lobes, and brainstem. (R, right side).