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Feasibility and usefulness of the 'Distress Screening Program in Ambulatory Care' in clinical oncology practice†

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Abstract

***Objective*: Although the implementation of routine screening for distress is desirable, doing so is difficult in today's busy clinical oncology practice. We developed the 'Distress Screening Program in Ambulatory Care' (DISPAC program) as a practical means of screening for and facilitating the treatment of major depression and adjustment disorders in cancer patients. This study assessed the feasibility and usefulness of the DISPAC program in actual clinical situations.**

***Methods*: As part of the DISPAC program, nurses administered a psychological screening measure, the Distress and Impact Thermometer (DIT), to consecutive cancer patients visiting an outpatient clinic in the waiting room. The attending physician then recommended psycho-oncology service referral to all positively screened patients. We compared the proportion of patients referred to a psycho-oncology service during the DISPAC period with the usual care period.**

***Results*: Of the targeted 491 patients treated during the DISPAC period, 91.9% (451/491) completed the DIT; the results were positive in 37.0% (167/451), recommendations for referrals were given to 93.4% (156/167), and 25.0% (39/156) accepted the referral. Ultimately 5.3% (26/491) of the targeted patients were treated by psycho-oncology service as having major depression or adjustment disorders, a significantly higher proportion than during the usual care period (0.3%; $p < 0.001$). The nurses required 132 ± 58 s per person to administer the DIT.**

***Conclusions*: The DISPAC program is useful for facilitating the care of cancer patients with psychological distress. Nevertheless, the acceptance of referrals by patients and the reduction of the burden placed on nurses are areas requiring improvement.**

Keywords: screening; cancer; oncology; distress; depression

Introduction

As cancer is a life-threatening illness, patients may experience strong psychological distress and frequently develop psychiatric disorders such as major depression or adjustment disorders [1]. The prevalence of major depression has been reported to be 3–26%, and the prevalence of adjustment disorders in patients with cancer has been reported to be 4–35% [1–8]. Major depression and adjustment disorders have a negative impact on quality of life [9], patient decision-making regarding cancer treatment [10], the length of the hospital stay [11], patient suicide [12], and caregiver distress [13]. Since evidence suggests that psychotherapy [14] and pharmacotherapy [15] are effective means of treating these disorders, these treatments should be provided when necessary. Psychological distress, however, is often under-recognized by medical staff members, including oncologists and oncology nurses, in clinical oncology settings [16–18].

Screening is the optimal strategy for detecting diseases (such as major depression and adjustment disorders) that are prevalent, not evident, and treatable and that benefit from early treatment [19]. For physically healthy patients with major

depression, programs that combine psychological screening and adequate collaboration with mental health specialists have been shown to improve psychological symptoms and general functioning [20]. In oncology settings, although less empirical evidence is available than for physically healthy patients, a high risk of depressive disorders has been reported [6], and psychological screening has been shown to be capable of detecting depressive disorders in cancer patients [21,22]; furthermore, psychological interventions have been shown to alleviate depressive disorders detected by psychological screening [23,24]. This evidence supports the efficacy of psychological screening for cancer patients, and guidelines such as the National Comprehensive Cancer Network and the National Institute for Clinical Excellence have recommended routine screening for depressive disorders in clinical practice. However, a limited number of institutions have introduced such programs because of insufficient resources [25], and a practical program that can be implemented in busy clinical settings with limited resources is needed.

Our group has spent several years developing a practical psychological screening program for cancer patients. First, we developed and validated some distress-screening tools [26–28]. Among them, the Distress and Impact Thermometer (DIT), which was developed by modifying the Distress Thermometer [21,27], has shown a high performance and is brief enough to use in busy clinical settings [28]. We next developed and introduced a distress screening and psychiatric referral program as part of a clinical screening protocol targeting hospitalized patients. The feasibility and usefulness of this program has been reported elsewhere [29,30].

Recently, oncology treatment has undergone major changes, and many patients now receive treatment as outpatients [31]. As an inevitable consequence of this transition from inpatient to outpatient care, interactions between patients and the medical staff have decreased, and there is a concern that patient distress is being increasingly under-recognized. In response to this transition in care, we have designed a new program, the 'Distress Screening Program in Ambulatory Care' (DISPAC) program, which can be implemented within the tight schedules of outpatient clinics.

The primary aim of this study was to assess the usefulness of the DISPAC program in real clinical oncology settings. We hypothesized that the use of the DISPAC program would result in the referral of more cancer patients with major depression or adjustment disorders to psycho-oncology services. The secondary aim was to assess the feasibility of the DISPAC program, specifically the implementation of the DIT, the recommendations for referral to psycho-oncology services, and the patients' acceptance of such referrals.

Method

Study sample

Consecutive patients visiting the outpatient clinic of the 'Breast and Medical Oncology Division' of the National Cancer Center Hospital (NCCH), Japan, during the usual care period when DISPAC was not in use and the intervention period when the DISPAC was in use were eligible. The DISPAC period was designated as a 2-week period in June 2008, and the usual care period was designated as the preceding 2-week period. Patients with a non-cancer diagnosis and who were under 18 years of age were excluded from the study.

We estimated that the rate of referral to psycho-oncology services for the treatment of major depression and adjustment disorders was 1% during the usual care period and that a 4% improvement could be obtained during the DISPAC period. At a 5% significance level (two-sided test) and 80% power, a sample size of 285 patients was needed for each period. As the assignment of clinicians to the outpatient clinic changes according to the day of the week, a study period consisting of a multiple of weeks was needed to avoid a physician bias. Since approximately 250 patients visit the outpatient clinic of the 'Breast and Medical Oncology Division' every week, we concluded that a 2-week study period would be adequate for comparing the usual care period and the DISPAC period.

As the implementation of a psychological screening program is a desirable clinical practice recommended by guidelines, the patients in this study were unlikely to be harmed by the study protocol. Since all the data assessed in this study were obtained as part of routine clinical assessments, we did not obtain written consent from the patients, in accordance with the guidelines of the Japanese Ministry of Health, Labor and Welfare. We obtained institutional review board approval for this study in advance.

Distress and Impact Thermometer

The DIT is a two-item self-administered rating scale. We developed the DIT by adding the Impact Thermometer to the Distress Thermometer [21,27,28]. Each 'distress' and 'impact' question consists of an 11-point Likert scale, with possible scores ranging from 0 to 10 and a high score indicating an unfavorable status.

In our previous study [28], the DIT was validated and the optimal cutoff points for detecting major depression and adjustment disorders were determined to be 4 for the 'distress' score and 3 for the 'impact' score. Patients who scored equal or more than both cutoff points were regarded as positive,

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and the sensitivity and specificity of the measure were 0.82 and 0.82, respectively.

DISPAC procedure

The DISPAC program consists of three stages. In the first stage, consecutive outpatients were approached by nurses in the waiting room prior to the physician's assessment. After a brief instruction, they were invited to complete the DIT and submit the completed form to their attending physicians. As the nurses' time resources were limited and a lengthy period of time could not be spent delivering an introduction, a booklet explaining cancer and distress, the types of care delivered by psycho-oncology services, and how to complete the DIT was given to the patient at the same time as the DIT.

In the second stage, the attending physician played a central role. The physician collected the completed DIT results from the patients and evaluated the screening result. If the patient scored equal to or more than the cutoff points, the physician recommended that the patient consult a psycho-oncology service. If the patient accepted the recommendation, the attending physician called the head of the psycho-oncology service and scheduled a consultation. As returning to the hospital on a separate day would create a burden for the patient, every effort was made to schedule the appointment on the same day. Considering the tight outpatient schedule, the timing of the psycho-oncology service consultation was adjusted so that the patient would not be inconvenienced. For example, if a patient had time between an X-ray examination and treatment in the outpatient chemotherapy center, the spare time was used for the consultation.

In the third stage, the patients were seen by either of the two resident psychiatrists, a psychologist, or a nurse specialist, supervised by a staff psychiatrist, and clinical diagnostic interviews based on the DSM-IV criteria were conducted. At the end of the interview, a staff psychiatrist also saw the patients and confirmed the diagnosis and treatment plan. If the patients were diagnosed as having a psychiatric disorder, the patients were provided with psychotherapy, which was mainly supportive-expressive, and/or pharmacotherapy, depending on the medical needs and the patients' wishes.

Psycho-oncology service referral during the usual care period

During the usual care period, the attending physician recommended a referral to the psycho-oncology service if they thought that the patient exhibited manifestations of moderate or severe distress. If the patients accepted the recommendation, they were seen by the psycho-oncology service.

Outcome measures

The usefulness of the DISPAC was evaluated by calculating the proportion of patients referred for major depression and adjustment disorders, which was the proportion of patients newly referred to the psycho-oncology service and treated for a diagnosis of major depression or adjustment disorders amongst all the patients who visited the outpatient clinic. The number of patients referred to the psycho-oncology service during both the usual care period and the DISPAC period were confirmed using the computerized database of the psycho-oncology division [32].

The feasibility of the DISPAC was measured as follows. The implementation of the DIT was evaluated by calculating the proportion of patients that were screened, which was the proportion of patients who completed the DIT amongst all the patients who visited the outpatient clinic. Also, we measured the amount of time required for the nurse to instruct each patient regarding the use of the DIT on 20 random occasions. The feasibility of the physician's recommendations for referral to the psycho-oncology service was evaluated by calculating the proportion of patients who were recommended to accept a referral, which was the proportion of patients for whom a referral to the psycho-oncology service was recommended amongst all the positively screened patients. We also asked all the physicians who participated in this project how much extra consultation time was required to recommend a referral to the psycho-oncology service. The patients' acceptance of the psycho-oncology service referral was evaluated by calculating the proportion that accepted the referral, which was the proportion of patients who accepted the psycho-oncology service referral amongst all the patients who received recommendations.

Analysis

The patient characteristics, including information on age, sex, cancer sites, and physician-rated performance status according to the Eastern Cooperative Oncology Group (during the DISPAC period only) were obtained from the patients' charts and were recorded separately for the usual care period and the DISPAC period. The characteristics of the patients treated during the usual care period and the DISPAC period, including age, sex, and cancer sites, were then compared.

The usefulness of the DISPAC was evaluated by comparing the proportion referred for major depression and adjustment disorders during the usual care period and the DISPAC period.

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The characteristics of the 'positive' patients who refused the psycho-oncology service referral were evaluated by dichotomizing the recommended patients into an acceptance group and a refusal group and comparing their characteristics and DIT scores.

All statistical analyses were bivariate, and inter-group comparisons of parametric variables, non-parametric variables, and categorical variables were performed between groups using the t test, the Mann–Whitney U test, and the chi-squared test, respectively. All the tests were two-tailed. All analyses were performed using SPSS 14.0 J for Windows statistical software (SPSS Japan Institute).

Result

Patient characteristics

Five hundred and seventy-four patients visited the outpatient clinic of the Breast and Oncology Division of NCCH during the usual care period, and 491 patients visited during the DISPAC period. As presented in Table 1, the characteristics of the eligible patients in each period were comparable in terms of age, sex, and curable or incurable stage, but not in terms of cancer sites. Fewer breast cancer patients and more gynecological cancer patients were seen during the usual care period than during the DISPAC period.

Usefulness of the DISPAC

During the usual care period, two patients were referred to the psycho-oncology service. Both these patients were diagnosed as having adjustment disorders and received treatment. The proportion of patients referred for major depression and adjustment disorders during the usual care period was 0.3% (2/574).

During the DISPAC period, 39 patients were referred to the psycho-oncology service as a result of the DISPAC program. Twenty-six patients were diagnosed as having major depression ($n = 5$) or adjustment disorders ($n = 21$) and were treated. Twelve of the other 13 patients did not fulfill the DSM-IV diagnostic criteria for any psychiatric disorders, and the remaining patient was diagnosed as having schizophrenia. The total proportion of patients referred for major depression and adjustment disorders was 5.3% (26/491). The proportion referred for major depression and adjustment disorders during the DISPAC period (5.3%) was significantly higher than that during the usual care period (0.3%; $p < 0.001$).

DISPAC procedure

Figure 1 shows the numbers of patients recorded at each stage of the DISPAC process. Of the 491 subjects, 451 (91.9%) completed the DIT. The amount of time required for the nurse's instructions ranged from 50 to 1200 s, and excluding one patient who required an unusually long time (1200 s), the mean time was 132 ± 58 s. Of the 451 patients who completed the screening, the results for 37.0% (167/451) were positive.

Among the 167 patients with positive screening results, the attending physicians recommended psycho-oncology service consultations for 156 patients (93.4%). Although the reasons why recommendations were not made were not always recorded, in many cases the patients appeared reluctant to discuss psycho-oncology service recommendations. The physicians estimated that the

Table 1. Characteristics of patients before and after the introduction of the Distress Screening Program in Ambulatory Care

	No. of patients (%)		p-Value
	Before introduction of the program	After introduction of the program	
Total patients	574 (100)	491 (100)	
Age (mean ± SD)	58.3 ± 11.3	58.0 ± 11.3	0.621
Female (%)	548 (95.5)	462 (94.1)	0.312
Primary cancer site			0.009
Breast	433 (75.4)	403 (82.1)	
Gynecological	96 (16.7)	43 (8.8)	
Primary unknown	23 (4.0)	22 (4.5)	
Others	22 (3.8)	23 (4.7)	
State			0.519
Stage IV, recurrent or primary unknown	349 (60.8)	289 (58.9)	
Stage I–III	225 (39.2)	202 (41.1)	
Performance status (ECOG)[a]			
0		373 (76.0)	
1		101 (20.6)	
2		11 (2.2)	
3		5 (1.0)	
4		1 (0.2)	

[a]Performance status as defined by eastern cooperating oncology group.

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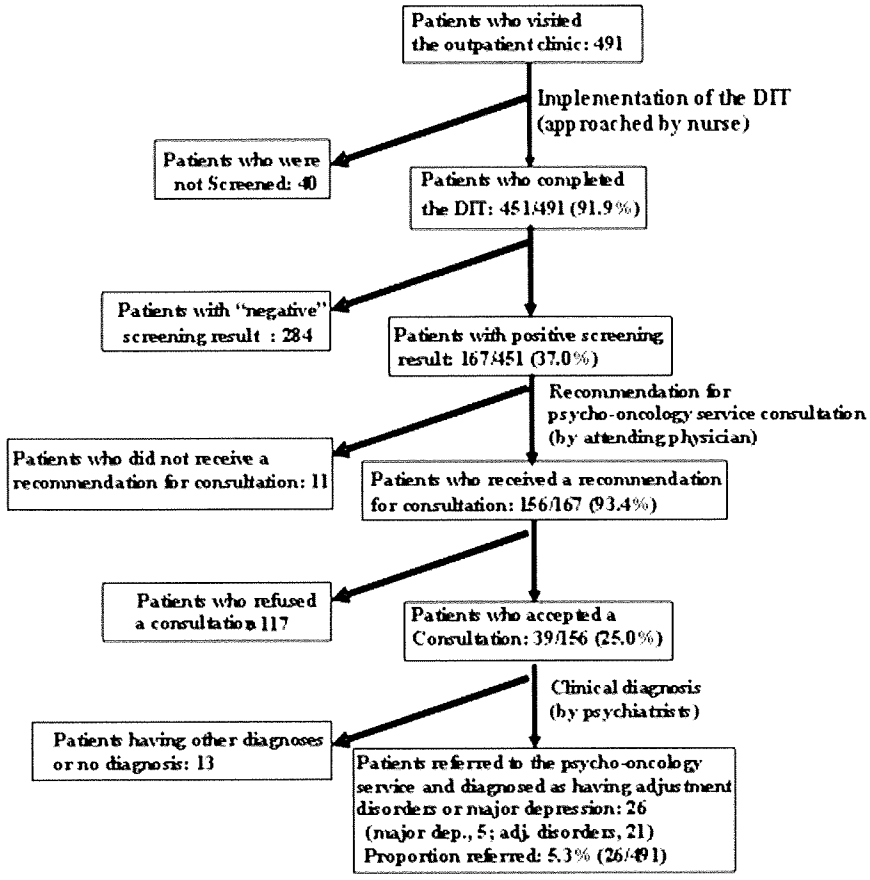

Figure 1. Number of patients recorded at each stage of the screening and referral process

extra consultation time required to recommend patients to the psycho-oncology service was 132 ± 73 s per patient. Among the 156 patients who received recommendations, 39 patients (25.0%) accepted the recommendation. As presented in Table 2, both the distress score ($p = 0.038$) and the impact score ($p = 0.047$) on the DIT were significantly higher in the group that accepted the referral than in the group that refused. No significant differences with regard to age, sex, cancer stage, attending physician, or performance status were observed between the groups.

Discussion

The results of this study demonstrated the usefulness of DISPAC, a clinical psychological screening program for ambulatory cancer patients, as a means of identifying major depression and adjustment disorders in patients with cancer and of initiating appropriate treatment. A large proportion of the patients who visited the outpatient clinic completed the DIT, and most of the patients with positive screening results received recommendations for a referral to the psycho-oncology service from their attending physician. However, a few minutes were required for the nurses and physicians to complete their tasks, and the burden placed on nurses administering the DIT was considerable. Moreover only one-fourth of the 'positive' patients accepted a psycho-oncology service referral. Our findings suggest that screening and psycho-oncology service referral programs like DISPAC was useful in leading a higher proportion of distressed cancer patients toward psycho-oncology service treatment, but that the DISPAC program has room for improvement with regard to patients accepting referrals and the burden placed on nurses implementing the DIT.

Several reports have shown the usefulness of integrated screening programs for cancer patients in randomized controlled trials. Such programs provided psychological intervention delivered by the cancer nurse or social worker under the supervision of a consultant psychiatrist [23,24] to patients who screened positive. We developed an integrated screening program, the DISPAC program, based on these previous studies, and the present study shows that the DISPAC is useful in real clinical oncology settings. Now, we are planning to disseminate this program to nationwide practices and a DISPAC introduction manual is presently being created.

Regarding the implementation of the DIT, a large proportion (91.9%) of the patients who visited the outpatient clinic completed the DIT, illustrating the excellent feasibility of the DIT,

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Table 2. Comparison between patients who accepted and refused psycho-oncology service referral among the patients who screened 'positive'

	No. of patients		p-Value
	Acceptance ($n = 39$)	Refusal ($n = 117$)	
Age (mean ± SD)	52.7 ± 12.6	58.7 ± 13.5	0.651
Sex			0.193
Male	0 (0.0)	7 (6.0)	
Female	39 (100.0)	110 (94.0)	
Attending physician			0.210
a	14 (35.9)	42 (35.9)	
b	0 (0.0)	10 (8.5)	
c	9 (23.1)	13 (11.1)	
d	2 (5.1)	2 (1.7)	
e	6 (15.4)	25 (21.4)	
f	7 (17.9)	20 (17.1)	
g	1 (2.6)	5 (4.3)	
Performance status (ECOG)[a]			0.181
0	24 (61.5)	60 (51.3)	
1	14 (35.9)	46 (39.3)	
2	1 (2.6)	7 (6.0)	
3	0 (0.0)	4 (3.4)	
4	0 (0.0)	0 (0.0)	
Stage			0.569
I–III	13 (33.3)	47 (40.2)	
IV, recurrent, or primary unknown	26 (66.7)	70 (59.8)	
The DIT			
Distress (median)	7	5	0.038
Impact (median)	7	5	0.047

[a]Performance status as defined by eastern cooperative oncology group.

compared with previous reports on other screening measures. A previous study reported that the Hospital Anxiety and Depression Scale (HADS) was administered to 70% of the ambulatory patients [22]; thus, the completion rate in the present study was higher. The HADS consists of 14 items, whereas the DIT contains only two items. The DIT may also be more applicable, since cancer patients often have multiple physical symptoms and asking too many questions can be a burden to them. The most common reason for non-implementation in the present study was a lack of time; in other words, the patients were immediately called by their physicians upon entering the waiting room, before they could be approached by a nurse.

The amount of time required for the nurse to introduce the DIT was a few minutes for every patient. In this study period, one nurse was mainly assigned to working on this program and approached about 50 patients every day; thus, this process may be a burden for institutions with a limited medical staff. This process could be expedited by administering the DIT with an instruction booklet, and without routine instruction from a nurse, but such a strategy may result in a poorer implementation of the screening program.

Regarding the second stage of the program, although most of the patients with positive screening results were recommended to consult the psycho-oncology service, a relatively small proportion (25.0%) chose to accept the physician's referral. This seems to imply that a robust patient-derived barrier existed, which impeded the acceptance of psychiatric referrals by distressed patients. Further improvement in overcoming this barrier is needed, but to do so, the reason underlying the patients' rejection of the psycho-oncology referrals must be determined.

We searched for factors related to the acceptance of psycho-oncology referrals and found that both higher distress and impact scores on the DIT were associated with a greater likelihood of accepting a referral. Three previous studies [29,33,34] and the present study showed a positive association between the distress level and the wish for psychosocial support, although one previous study reported a negative result [35]. Another report has suggested that patients whose screening results are positive but who do not actually require help tend to receive false-positive results upon psychological screening [36]. Mildly distressed patients may prefer and be capable of managing their distress in some other manner and thus may decline referrals to psycho-oncology services. However, we could not assess the prevalence of the targeted patients, and it is conceivable that some patients with these disorders remained undiagnosed and untreated. The DISPAC program is a huge step forward in leading severely distressed patients to psycho-oncology service treatment, but some patients may remain 'undiagnosed and untreated' as a result of patient-derived barriers.

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Previous studies have reported the proportions of distressed patients who accepted consultations with psychiatrists or other mental health providers, with results varying from 12 to 48% [29,33–35,37]. The underlying reason why some patients wish to have psychological support and others do not is unclear. The stigma attached to the words 'psychiatric' and 'psychological' is considered to be a possible cause of the reluctance of patients to consult mental health services. Few objective studies, however, have been conducted on patient-delivered barriers to providing psychological care for distressed patients, and sufficient thought has not been given to this matter.

There are several limitations to our study. First, this study compared the results of the DISPAC program with available data for usual care. The comparison group was not systematically controlled, and the proportion of cancer sites differed between the groups. Second, this study was performed at a single center, and care is needed when generalizing these results to other oncology settings. Third, although the clinical diagnoses were made according to the DSM-IV criteria, this diagnostic approach is not as robust as a structured diagnostic interview. Thus, an assessment bias may exist because the psychiatrists, psychologist, and nurse who diagnosed the referred patients were associated with this study. Fourth, although we explored the factors related to the patients' refusal of psychiatric referral, the factors that were assessed were limited to those that could be obtained by clinical assessment. Some factors, such as education, income, and physical symptoms, were lacking. Fifth, we showed that the DISPAC program resulted in a higher proportion of referrals to the psycho-oncology service. This is surrogate endpoint, and the change in the patients' outcome, e.g. improvement of the patients' QOL or depressive symptoms, is not clear.

In conclusion, a large proportion of the target population was successfully screened using the DIT and received recommendations to consult the psycho-oncology service. More patients were ultimately diagnosed as having major depression or adjustment disorders and treated, and the usefulness of this program was shown. However, further improvement is needed regarding the feasibility of DISPAC in real clinical oncology settings. Additional efforts are required to minimize the burden placed on nurses and to optimize the acceptance of psycho-oncology service consultations.

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Lecture

解　説

化学療法の晩期毒性*

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Key Words : late toxicity, neurotoxicity, cardiotoxicity, gonadal dysfunction, second cancer

はじめに

過去30年で，効果的なスクリーニングと治療によって，血液悪性腫瘍，精巣腫瘍，乳がんなど多くのがん種で，長期生存する集団が増加している．新たにがんと診断された成人患者の60％は，5年以上の生存が期待されている．多剤併用療法や集学的治療が増加しており，化学療法による晩期毒性の対策を必要とする．放射線療法の晩期毒性は治療後6か月以降を指すが，化学療法による晩期毒性の時期を明確に定義するものはない．簡便上，下記に分けて詳細を記す(表1)[1]．

・慢性に発症するもの
　①神経毒性，②心毒性，③肺毒性
・長期生存となるときに問題となるもの
　①性腺機能障害(不妊，骨粗鬆症)，②二次発がん

慢性に発症するもの

1．神経毒性[2]

病因：薬剤の直接作用と，薬物の代謝異常や脳血管障害による間接作用によるものがある．神経細胞を構成する軸索・髄鞘・細胞体などの代謝・維持に必要な産物が不活化されることに起因すると考えられているが，詳細は不明である．中枢，末梢(運動，感覚)，自律神経，聴覚を障害する[3]．

頻度：重篤な末梢神経障害は，単剤で3～7％，多剤併用化学療法で38％[4]．

症状：末梢神経障害・小脳症状・慢性脳炎様症状・聴覚障害(表2)．

原因薬剤：プラチナ系(シスプラチン，オキサリプラチン，カルボプラチン)，非プラチナ系(ビンカアルカロイド，タキサン，メトトレキセート)．

リスク因子：女性，糖尿病などの基礎疾患，パクリタキセルなどの神経毒性を有する薬剤の併用・前治療歴．

治療法：神経症状の改善には投与中止や減量，神経毒性の少ない薬剤への変更が必要となる．予防・治療薬は確立してしない(表3)[5]．

下記，原因薬剤別に記す．

(1)プラチナ系

シスプラチンとオキサリプラチンに多く，カルボプラチンでは少ない．

1)シスプラチン

神経障害は，足・手指から始まり，足，腕に広がり，亜急性のしびれ，麻痺を認め，時に痛みを伴う．蓄積投与量が400mg/m²を超えると神経症状が出現しやすい．深部腱反射が消失するが，温痛覚，筋力は保たれる．Dose-intensityによって重度の増悪はないと考えられている．鑑別診断として，腫瘍随伴症候群がある．治療効果より，毒性が上回る場合は，減量や毒性の少ないカルボプラチンなどの薬剤変更を検討する．シスプラチンを中止後も，30％の患者では，数か月増悪

* Late toxicity of chemotherapy.

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表1　化学療法別の晩期毒性

薬剤	晩期毒性	総投与量(mg/m²)
ドキソルビシン	心毒性	550
シクロフォスファミド	心毒性	＞1,550, 連日 3～4 日間
	肺毒性	6,500, 2～3 日
ミトキサントロン	心毒性	160
マイトマイシン	心毒性	70(単剤)
		30(アンスラサイクリンとの併用)
パクリタキセル	神経毒性	1,000
ブレオマイシン	肺線維症	360ユニット
	色素沈着	270ユニット
メトトレキセート	肺線維症	
	肝線維化	不明
ビンクリスチン	神経毒性	4 か月以内に16mg
エトポシド	骨髄形成	2,000
イフォスファミド	白質脳症	不明
	肺毒性	2～3 日以内に16g/m²
	心毒性	20g/m²
シスプラチン	神経毒性	400～600
	腎毒性	

(文献[1]より引用改変)

表2　代表的な化学療法による末梢神経障害のタイプ

●感覚神経障害	サリドマイド
	プラチナ系
	タキサン系
	ボルテゾミブ
	プロカルバジン
	エトポシド
●感覚運動障害	ビンクリスチン
	シタラビン
●自律神経障害	ドセタキセル
	ビンクリスチン
●脳神経障害	ビンクリスチン

(文献[1]より引用改変)

し続けるが，たいていの患者は，完全ではないものの改善を認める．毒性予防の目的で，amifostine, ACTHアナログorg2766, diethyldithiocarbamate, vitamin E, glutathione, acetyl-L carnitineなどについて，小規模臨床試験での予防効果の傾向が示されているものもあるが，大規模比較試験で有効性は証明されていない．実験レベルでは，神経成長因子，ニューロトロフィン3, 軸索成長因子などが，シスプラチン誘発神経障害を予防または可逆化させるのに有用と考えられ，臨床試験で検討中である．

2)オキサリプラチン

投与を繰り返すことで症状が増悪する蓄積性の神経毒性がある．総投与量が680mg/m²を超えるとグレード2～3の神経障害の出現頻度が有意に増加すると報告されている．しばしば寒冷刺激によって誘発される．また，グレードが上がるほど，回復までに時間を要する傾向にある．予防薬として，glutathione, oxcarbazepine, glutamine, calcium＋magnesiumなどの検討がなされ，calcium＋magnesiumは化学療法の効果を減じることなく，神経障害を軽減する傾向にあるが，現時点では小規模臨床試験での予防効果の傾向が示されているが，大規模比較試験で有効性は証明されていないため予防薬の併用よりも，間歇的投与などの投与法での工夫が行われているのが現状である．

3)カルボプラチン

幹細胞移植での大量投与時に重篤な神経障害が出現することがある．

(2)非プラチナ系

1)ビンカアルカロイド

ビンクリスチンの神経障害は軸索障害が中心であり，感覚神経，運動神経ともに起こる．糖尿病性神経障害の症状と類似しており，四肢末梢の知覚異常から始まる．これらは，しばしば治療後数週間で起こるが，最初の投与で起こる場合もある．また，治療中断後にも症状を認め

たり，改善前に数か月進行したりする場合もある．深部腱反射が低下するが，アキレス腱で頻度が高い．手足両側の下垂など脱力を認めることもある．1回投与量と累積量に依存する．高齢者，パクリタキセルによる治療歴，末梢神経に対する照射歴，照射時のgranulocyte colony-stimulating factor(G-CSF)併用時に，重度の神経障害が起こりやすい．効果的な治療法はなく，症状が増悪した場合は，減量・中止により，数か月で改善する．また，自律神経障害も認め，50%の患者では，腹部疝痛，便秘が起こり，腸閉塞に陥る場合もあり，予防的に緩下剤を投与する．視神経障害，嗄声，顔面神経麻痺，聴覚神経障害などの中枢神経障害をきたすこともある．

2)パクリタキセル

感覚神経障害が中心であり，手足の焼けつくようなしびれと反射低下を認める．また，運動神経障害も認め，近位筋優位に影響を及ぼす．グレード3または4の運動神経障害は，2～10%の患者で認める[6]．治療を完遂した患者の半分は，数か月で症状の改善を認める．転移性乳がんの臨床試験[7]で，毎週80mg/m²または，3週ごと175mg/m²で，グレード3/4の神経毒性は，毎週投与で有意に増加した(19% vs. 12%)．予防薬としてamifostine, gabapentin, vitamin E, glutamine, acetyl-L carnitine, BNP 787などの検討がなされているが，現時点では大規模臨床試験による十分なエビデンスがない．

3)ドセタキセル

感覚・運動神経障害はともに15%以下で，グレード3/4では5%未満である．蓄積投与量に比例し，神経障害が出現するまでの時間は，3週ごと100mg/m²で投与された転移性乳がんの臨床試験において，グレード2以上の神経毒性は，総投与量371mg/m²以上で認める[8]．

4)サリドマイド

治療が長期化すると，75%で末梢神経障害を認める．障害部位が限局的，可逆的である．振戦，めまい，稀ではあるが痙攣など，白質脳症を認めることもある．

5)ボルテゾミブ

末梢神経障害は，有痛性の感覚神経障害が中心で，quality of life(QOL)を低下させるため，投与調整や中止が必要となる場合がある．グレード3/4の神経障害は，再発症例30%，新規症例18%で認める．神経障害の既往，累積投与量が多い人では増悪しやすい．グレード3/4神経毒性が，週1投与 vs. 週2投与で14～18% vs. 2%であった[9]．

6)メトトレキセート

晩期毒性に，白質脳症があり，数か月から数年単位で出現する．過去の放射線治療歴，もしくは放射線同時照射で起こりやすい．軽度の学習障害から重度の痴呆までさまざまである．薬剤の中止で，安定または改善するが，進行し致死的となる場合もある．効果的な治療法はない．

以上のように，化学療法による神経障害はほとんどが用量依存性である．有効な治療薬や予防法が確立していないため，早期の発見に努め，不可逆的な障害を回避するために化学療法の中止を検討する必要が生じる場合もある．将来的には，再現性の高い評価法，神経毒性のメカニズムに焦点をあてた治療薬・予防薬のさらなる検討が望まれる．

2．心毒性

原因：アンスラサイクリンとその関連化合物では，フリーラジカル酸素が産生され，心筋細胞膜の脂質過酸化をひき起こし，空砲形成，心筋が線維組織に置換され，不可逆的な心障害となる．

頻度：アンスラサイクリンによる心筋症(心不全，不整脈，胸痛，心筋梗塞，心筋炎などを含む)の頻度は，総投与量でドキソルビシン450mg/m²，ダウノルビシン900mg/m²，エピルビシン935mg/m²で5%．

症状：疲労感，労作時呼吸困難，起座呼吸，不整脈など．

原因薬剤：広範囲にわたるが，特にアンスラサイクリンとその関連化合物(ドキソルビシン，ダウノルビシン，イダルビシン，エピルビシン，アンスラキノン，ミトキサントロン)での報告が多い．

リスク因子：使用する薬剤の種類，投与量，スケジュール，年齢，併存する心疾患の有無，縦隔への放射線照射の有無，喫煙，糖尿病，高血圧，脂質異常．

表 3 Randomised controlled trials for prevention of CIPN

Agent/Author	Number of patients	Findings	Comments
Vitamin E			
Pace 2003	47	CIPN in 31% patients with vitamin E versus 86% without ($P<0.01$)	Open label ; cisplatin
Argyriou 2005	40	CIPN in 25% patients with vitamin E versus 73.3% without vitamin E ($P=0.019$)	Open label ; cisplatin, paclitaxel, or combination cisplatin/paclitaxel
Argyriou 2006	35	CIPN in 21% of patients with vitamin E group versus 66% without ($P=0.026$)	Open label ; cisplatin
Pace 2007	81	Median CIPN score lower in the vitamin E group ($P<0.05$)	Placebo-controlled ; double-blinded cisplatin ; results based on interim analysis of the first 50 patients, clinical trial ongoing
Calcium/Magnesium			
Nikcevich 2008	104	CIPN occurred in 22% versus 41% by NCI Common Toxicity Criteria ($P=0.04$) and 28% versus 51% by an oxaliplatin specific neuropathy scale ($P=0.02$)	Placebo-controlled ; double-blinded oxaliplatin
Glutamine			
Wang 2007	86	Less grade 1-2 (17% versus 39%) and grade 3-4 CIPN after four cycles (5 % versus 18%) and six cycles (12% versus 32%)	Open-label ; oxaliplatin ; no differences in chemotherapy response
Glutathione			
Cascinu 2002	52	Significantly less peripheral neuropathy any grade cycles 4 and 8 ($P=0.04$), as well as less grade 3-4 neuropathy at cycle 8 ($P=0.01$)	Placebo-controlled ; double-blinded ; oxaliplatin ; no differences in chemotherapy response
Smyth 1997	152	CIPN incidence significantly decreased in treatment arm (31%) versus control (75%) ($P=0.033$)	Placebo-controlled ; double-blinded ; cisplatin
Cassinu 1995	50	After 15 weeks, 4/24 treatment arm versus 16/18 placebo arm experienced neurotoxicity ($P=0.0001$)	Placebo-controlled ; double-blinded ; cisplatin
N-acetylcysteine			
Lin 2006	14	5/7 patients in the control group and 0/7 in the treatment group experienced grade 2-4 neuropathy ($P<0.05$). The incidence of grade 2-4 neuropathy after 12 cycles of chemotherapy was significantly less in the treatment group ($P<0.05$)	Placebo-controlled ; oxaliplatin
Oxcarbazepine			
Argyriou 2006	40	Incidence of peripheral neuropathy was significantly decreased in treatment arm (31%) versus control arm (75%) ($P=0.03$)	Open label ; oxaliplatin
Xaliproden			
Cassidy 2006	649	17% of patients receiving xaliproden versus 11% of patients receiving placebo experienced grade 3 CIPN	Placebo-controlled ; double-blinded oxaliplatin ; no differences in chemotherapy response
Amifostine			
Leong 2003	66	Not effective	Placebo-controlled ; double-blinded ; paclitaxel and carboplatin
Hilpert 2005	72	Not effective	Placebo-controlled ; double-blinded ; paclitaxel and carboplatin
Nimodipine			
Cassidy 1998	51	Not effective	Placebo-controlled ; double-blinded ; neurotoxicity scores were significantly lower in placebo patients ($P=0.002$)

Org 2766			
van der Hoop 1990	55	Vibration perception was maintained on both active arms compared to placebo	Placebo-controlled ; double-blinded cisplatin
Roberts 1997	220	Not effective	Placebo-controlled ; double-blinded ; cisplatin ; may increase the rate and degree of neuropathies ($P>0.05$)
Koeppen 2004	150	Not effective	Placebo-controlled ; vincristine
rhuLIF			
Davis 2005	117	Not effective	Placebo-controlled ; double-blinded ; combination carboplatin/paclitaxel
Nortriptyline			
Hammack 2002	57	No CIPN benefit observed	Placebo-controlled ; double-blinded ; crossover ; cisplatin
Amitriptyline			
Kautio 2008	44	No CIPN benefit observed	Placebo-controlled ; double-blinded
Gabapentin			
Rao 2007	115	No CIPN benefit observed	Placebo-controlled ; double-blinded ; crossover
Lamotrigine			
Rao 2008	131	No CIPN benefit observed	Placebo-controlled ; double-blinded

CIPN：Chemotherapy-induced peripheral neuropathy

（文献[5]より引用改変）

治療法：心筋障害に対する根本治療はなく，対症療法のみ．

(1)アンスラサイクリン

アンスラサイクリン系の抗がん剤は，累積投与量依存性の心筋障害を起こし，重症例は心不全をきたす．成人での初期の報告では，ドキソルビシンの総量として400, 550, 700mg/m²使用し，心毒性はそれぞれ，3, 7, 18%認めた[10]．これに基づき，ドキソルビシンは，総投与量550mg/m²未満で中止することが推奨されてきた．エピルビシンでは，総投与量900mg/m²未満を推奨している[11]．効果を維持しつつ，心毒性のリスクを減じるためのアプローチとして，投与スケジュールの変更やアンスラサイクリン分子の修飾化，dexrazoxane(国内未承認)との併用などがある．Dexrazoxaneは，ethylenediaminetetraacetic acid (EDTA)様のキレートであり，フリーラジカルに対するコーファクターである鉄を結合することによってアンスラサイクリンによる障害を回避すると言われているが，晩期毒性に対する効果は示されていない．晩期の心不全は，非虚血性拡張型心筋症によるものであり，アンスラサイクリン最終投与後10年以上で起こりうる．抗がん剤の注入速度の検討がなされ，ボーラス投与より持続静注で心毒性が軽減したとする報告があるが，十分なエビデンスを得られている手法はない．ドキソルビシンやダウノルビシンのリポソーム結合型では，リポソーム結合のないアンスラサイクリンと同等の効果で，より高い累積投与量を許容し，心不全を軽減したとする報告があるが，さらなる検討を要する．

最大耐容量は薬剤ごとに規定されているものもあるが，個人差があり，心毒性の初期の兆候を早期に発見するため，モニターが重要である．心エコーなどで左室収縮力を評価し，中等度の左室駆出率の減少を認める場合は，核アンギオ検査が役立つ[12][13]．心臓MRI, 脈拍の変化，トロポニンT・I, brain natriuretic peptide(BNP)によるモニターは，まだ日常診療で使用するのに十分なエビデンスはない．アンスラサイクリンの増量の妥当性を検討する場合の心電図モニターは，2003年the American College of Cardiology (ACC), the American Heart Association (AHA),

the American Society of Echocardiography(ASE)で推奨されている．心内膜生検は，アンスラサイクリンによる心毒性の評価において，最も感度や特異度が高いが，生検が侵襲的であり，出血，不整脈，心房穿孔などのリスクがあるため，症例を選択する必要がある．

早期であれば，利尿剤，アンジオテンシン変換酵素(ACE)阻害剤，β遮断薬，強心剤の併用療法で改善を認めることがあるが，心障害は不可逆性であり，米国ではがんの治癒症例に対しては心臓移植が考慮されている．化学療法の心毒性に対するカルベジロールの心保護作用[14][15]，ACE阻害薬の心毒性予防効果に関する報告があるが，今後さらなる大規模試験で確認が必要である．

(2)トラスツズマブ

トラスツズマブ単剤による重篤な心毒性は3～7％に起こる[16]．化学療法との併用では心毒性の頻度は高まり，特にドキソルビシンと併用した場合には27%[17]に発生するため，アンスラサイクリンとの併用は原則として禁忌である．トラスツズマブによる心毒性はアンスラサイクリンによる心筋障害とは異なり可逆性であり，薬を中止すると，心機能は改善するとされるが，晩期毒性に関しての十分な情報は蓄積していない．

以上のように，心障害は不可逆的となることが多く，特異的な治療薬がないため，心毒性のある薬剤を用いる場合には，心電図，心エコーなどによって心機能をモニターし，早期発見，早期治療に努めることが重要である．

3．肺 毒 性[18]

原因：肺細胞または肺胞の血管内皮細胞の直接障害と，それに続くサイトカイン，炎症性細胞の誘導といった，免疫系細胞の賦活化による間接障害の2つの機序が想定されている．

症状：非特異的で，特に慢性期では，乾性咳そう，微熱，労作時呼吸困難，低酸素血症などを認め，肺病変は時に急速に進行し，呼吸不全や急性呼吸促迫症候群に陥ることがある．

原因薬剤：シクロフォスファミド，ブスルファン，ブレオマイシン，ニトロソウレア．

リスク因子：①遺伝子的素因，②年齢，③総投与量，④併用薬，⑤同時または過去の放射線療法，⑥呼吸器基礎疾患，⑦喫煙，⑧酸素吸入，⑨腎障害．

一般に，骨髄・幹細胞移植時以外は，晩期毒性は頻度が少ない．

診断：呼吸不全を示す鑑別疾患を除外し，症状・身体所見，画像(非特異的)，血液検査(末梢血の白血球数・CRP・赤沈・LDH・KL-6・SP-D上昇，時に，アレルギー機序を反映して，末梢血好酸球数や血清IgE抗体の上昇)をもとに診断．時に開胸生検を行う場合もある．

治療法：薬剤性肺障害の治療の基本は，疑わしい薬剤の中止である．重症度を考慮し，ステロイド剤の使用を検討するが，投与法に関して定まった見解はない．慣習的にプレドニゾロン0.5～1.0mg/kg/dayを4週間投与し，漸減することが多いのが現状である．重症例では，メチルプレドニゾロン1g/dayを3日投与(パルス療法)する．非細胞障害性ではステロイド剤が有効なことがあるが，細胞障害性では，治療効果は乏しい．

鑑別疾患：感染症(ウイルス性肺炎，非定形肺炎)，心原性肺水腫，びまん性肺胞出血，がん性リンパ管症，誤嚥・敗血症による急性呼吸促迫症候群など．

注意点：KL-6は過敏性肺炎，放射線性肺炎，ウイルス性肺炎，ニューモシスチス肺炎，一部のレジオネラ肺炎，広範囲の肺結核症，肺胞蛋白症，サルコイドーシス，尿細管性腎炎症候群，肝臓病，悪性疾患(乳がん，肺腺がん)で，SP-Dは喫煙者，細菌性肺炎，ニューモシスチス肺炎，肺胞蛋白症でも上昇することがある．薬剤リンパ球刺激試験は偽陰性率が高く，薬剤濃度の基準がなく，薬剤自体のリンパ球への作用などの問題もあり，結果の解釈は注意を要する．組織採取や気管支肺胞洗浄は，腫瘍の肺への浸潤や感染症を鑑別したり，リンパ球増多などで，ステロイド剤に対する治療効果を予測するには有用なこともある．薬剤ごとの肺障害の出現パターンに留意することが望ましい．

長期生存となるときに問題となるもの[19]

1．性腺機能障害

原因：(男性)化学療法により，細胞分裂の早

表4 Effects of different antitumor agents on sperm production in men

Agents (cumulative dose for effect)	Effect
Radiation (2.5 Gy to testis)	Prolonged azoospermia
Chlorambucil (1.4g/m²)	
Cyclophosphamide (19g/m²)	
Procarbazine (4 g/m²)	
Melphalan (140mg/m²)	
Cisplatin (500mg/m²)	
BCNU (1 g/m²)	Azoospermia in adulthood after treatment before puberty
CCNU (500mg/m²)	
Busulfan (600mg/kg)	Azoospermia likely, but always given with other highly sterilizing agents
Ifosfamide (42g/m²)	
BCNU (300mg/m²)	
Nitrogen mustard	
Actinomycin D	
Carboplatin (2 g/m²)	Prolonged azoospermia not often observed at indicated dose
Doxorubicin (Adriamycin) (770mg/m²)	Can be additive with above agents in causing prolonged azoospermia, but cause only temporary reductions in sperm count when not combined with above agents
Thiotepa (400mg/m²)	
Cytosine arabinoside (1 g/m²)	
Vinblastine (50g/m²)	
Vincristine (8 g/m²)	
Amsacrine, bleomycin, dacarbazine, daunorubicin, epirubicin, etoposide, fludarabine, 5-fluorouracil, 6-mercaptopurine, methotrexate, mitoxantrone, thioguanine	Only temporary reductions in sperm count at doses used in conventional regimens, but additive effects are possible
Prednisone	Unlikely to affect sperm production
Interferon-α	No effects on sperm production

BCNU：carmustine, CCNU：lomustine （文献[1]より引用）

い精巣上皮を直接的に障害する．化学療法開始後，2～3か月で無精子症となるが，幹細胞が障害を受けなければ，造精機能は回復する．

（女性）卵巣組織では，線維化，卵胞の減少・破壊が起こり，無月経が誘発される．無月経に関連する因子として，抗がん剤の種類と総投与量，年齢があげられる．思春期以前よりも思春期以降の方が，化学療法による性腺機能障害を受けやすいとされている．

症状：不妊症，ホットフラッシュや膣乾燥感，気分の変調，抑うつといった更年期症状．骨粗鬆症．

原因薬剤：アルキル化剤，メトトレキサート，フルオロウラシル，タキサン系，ビンブラスチン，ブレオマイシン，エトポシド．

リスク因子：がん種，治療時年齢，性腺機能，抗がん剤の種類，治療プロトコール（表4, 5）．

治療法：性腺機能障害に対する根本治療はなく，妊孕性温存について最も確立した方法は精子や受精卵の凍結保存である．精子数が20×10^6/ml以上で，40%以上の運動を認めることが条件であるが，体外受精や卵細胞質内精子注入法ではもっと少ない数で受胎可能である．卵子の保存やluteinizing hormone-releasing hormone (LHRH) アゴニストによる精巣・卵巣機能の保護は，現時点では研究段階である．薬剤誘発不妊の評価として，男性では，精液の解析（量，濃度，運動能，形態学），ホルモン評価〔follicle-stimulating hormone (FSH)，インヒビンBレベル，luteinizing hormone (LH)，全テストステロン〕，精巣生検を用いて評価する．女性では卵巣予備能を評価する指標は確立していない．

化学療法による骨粗鬆症に関してはビスホスホネート製剤の投与が有用である．ビスホスホネート製剤であるゾレドロン酸は，アロマターゼ阻害剤（AI）治療に伴う骨量減少を抑制するこ

表5　Effects of different cytotoxic agents on ovarian function

Agent	Prepuberty	Age 20 Y	Age 35 Y	Age 45 Y
CUMULATIVE DOSES TO CAUSE PERMANENT OVARIAN FAILURE				
Cyclophosphamide	>48 g	20-50g	6-10g	5 g
Melphalan	—	>240mg/m²	>510mg/m²	340mg/m²
Busulfan	600mg/m²	<600mg/m²	<600mg/m²	—
Chlorambucil	> 3 g	>1.5g	> 1 g	1 g
Mitomycin C	—	—	≧30g	≧30g
Radiation	12 Gy	7 Gy	3 Gy	< 2 Gy
INCIDENCE OF PERMANENT OVARIAN FAILURE				
Cyclophosphamide (7.4g/m²)	0 %	0 %	60%	—
Radiation (pelvic) (4-5 Gy)	<10%	40%	90%	95%
Radiation (total body irradiation) (10Gy)	40%	75%	100%	100%

（文献[1]より引用）

とが知られている．「ZO-FAST」試験[20]では，欧州，アジア太平洋地域，中南米，エジプトの閉経後女性で，AI剤レトロゾールによる術後補助療法を行う1,065人の患者を対象とし，主要エンドポイントは，腰椎（L1～L4）骨塩量の変化，副次エンドポイントは36か月での骨折発生率，病気再発までの期間，全生存，安全性とし，骨量が減少してからゾレドロン酸を投与するよりも，AI治療開始時からの投与が有意に効果的であることを示した．米国でも同様の試験「Z-FAST」が行われている．

抗がん剤治療後も生殖機能を保持したい患者では，効果が同等で性腺毒性が少ない薬剤の選択を常に心がけ，永久的に性腺機能異常をひき起こす薬剤を用いた化学療法は避けるべきである．性腺毒性のある治療を行うすべての男性に，精液バンクのオプションの話をすることが望ましい．女性では，卵子バンクは現時点では実用化されていないため，アルキル化剤をなるべく避けるなど，薬剤の変更や，がん種によっては，治療開始時期を延期する，治療を行わないなどの選択肢も念頭に，治療を選択する．がん腫や病期によって長期生存の可能性は異なるため，がんの予後とともに妊孕性の温存の希望があるかどうか，妊孕性温存の方法について患者とオープンに議論できる環境を用意することが最も重要である．

2．二次発がん

原因：DNA複製が困難となり，発がん物質が生じることによる．

頻度：2003年米国での報告は，全がん種で16%[21]．薬剤別では，シクロフォスファミドで1%，メクロレタミンで4～6%．

原因薬剤：古い世代のアルキル化剤であるメクロレタミン，メルファラン，ニトロソウレア，ブスルファン，クロラムブシル，新世代のシクロフォスファミド，イフォスファミド，プラチナ剤．

治療法：*de novo*発症の白血病に比較し，治療抵抗性で，通常治癒のために同種骨髄移植が必要である．

化学療法後の二次性の原発性悪性疾患は，1970年ごろ，Kyle[22]らが多発性骨髄腫の治療後に発症した急性骨髄性白血病の症例を報告している．化学療法後の固形腫瘍の二次発生に関して，シクロフォスファミドと膀胱がんとの関係は知られているが，そのほかに関しては，十分な検討がなされていない．白血病と骨髄異形成症候群は2つの代表的な発症様式である．一つはアルキル化剤に典型的な，曝露後5～9年ごろみられるもので，骨髄異形成症候群を経て発症し，染色体の5番と7番に異常を伴う．もう一つはアンスラサイクリン系とエトポシドなどのトポイソメラーゼ阻害剤に典型的な，曝露後2～5年ごろにみられるもので，骨髄異形成症候群を経ずに発症し，多くはFrench-American-British (FAB) 分類のM4, M5で*11q23*異常を伴う．いずれも*de novo*発症の白血病に比較し，治療抵抗性で，同種骨髄移植が必要となることが多い．乳がんの補助療法の報告では，二次性白血病と骨髄異形成症候群発症のリスクは，約0.5～1%と考えられている．

おわりに

以上，化学療法による主な晩期毒性を記した．分子標的薬を中心とした新しい治療薬による毒性は臨床データが少ないため，晩期毒性は明らかではない．新規分子標的薬の単剤使用や，殺細胞性抗がん剤との併用療法によって，未知の重篤な晩期毒性を生じる可能性も考えられ，長期成績の報告に留意する必要があるが，過小評価されている可能性もあるので注意を要する．

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治療薬解説

ラパチニブ

坂東裕子*

abstract

HER2過剰発現を有する再発・転移性乳癌治療薬として1998年に米国で，2001年に本邦で抗HER2抗体であるトラスツズマブ（trastuzumab，ハーセプチン®）が承認された．HER2陽性進行再発乳癌の生存期間の延長効果，さらに術後補助療法への適応拡大による再発抑制・生存率の向上が示されており，トラスツズマブの導入は当初の予想を上回る臨床効果と低い毒性から乳癌の治療戦略に大きなインパクトを与えた．そして2009年，新たな抗HER2治療薬としてラパチニブ（lapatinib，タイケルブ®）がカペシタビン（capecitabine，ゼローダ®）との併用において進行再発乳癌の治療に承認された．ラパチニブはHER1およびHER2のチロシンキナーゼ阻害剤である．作用機序はトラスツズマブと異なり，トラスツズマブ不応性のHER2陽性乳癌にも治療効果が期待できる．基礎的背景に基づいた分子標的治療などの新規薬剤と従来の治療法を有効に活用することにより，さらに高い治療効果，低い毒性の治療法が実現されよう．今後新たな治療戦略の構築が望まれる．本稿ではこのたび乳癌に対して適応承認されたラパチニブについて概説する．

Ⅰ HER2

HER2（human epidermal growth factor receptor 2:EGFR2）はヒト上皮増殖因子受容体ファミリーに属する膜貫通型受容体で，ヒト乳癌の15～20%において蛋白の過剰発現や遺伝子増幅が認められる．HER2を過剰発現している乳癌（HER2陽性乳癌）は増殖が速い傾向があり，乳癌の予後不良因子となりえること，また内分泌療法や化学療法の効果予測因子としての意義が報告されている[1), 2)]．2005年以降，St. Gallenコンセンサス会議やNCCNのガイドラインにおいてHER2の過剰発現は乳癌の再発リスク評価の一要因とされている．

Ⅱ トラスツズマブ

トラスツズマブ（trastuzumab，ハーセプチン®）はHER2受容体の細胞外ドメインに対して作成されたマウス由来モノクローナル抗体（4D5）の抗原結合部位をヒト免疫グロブリンの定常部に移植したヒト化抗体であり，テーラーメイド医療のさきがけとして広く用いられてきた．

一般的な免疫グロブリン（IgG）抗体と同様にト

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