Table 4 – Prognostic factor analysis for overall survival using proportional hazards regression model without variable selection.

Factors	Hazard ratio	95%CI	P-value
Performance status			
0	1.00	–	–
1	2.03	1.54–2.67	<0.0001
Neutrophil count			
<4500 mm^{-3}	1.00	–	–
≥4500 mm^{-3}	1.72	1.34–2.19	<0.0001
LDH			
Normal	1.00	–	–
High	1.57	1.20–2.05	0.001
Smoking history			
Non/former smokers	1.00	–	–
Current smokers	1.56	1.18–2.06	0.002
Liver metastases			
No	1.00	–	–
Yes	1.62	1.08–2.43	0.020
Sex			
Male	1.00	–	–
Female	0.74	0.54–1.02	0.064
Weight loss			
<5%	1.00	–	–
≥5%	1.30	0.96–1.76	0.092
Skin metastases			
No	1.00	–	–
Yes	1.78	0.85–3.72	0.124
Bone metastases			
No	1.00	–	–
Yes	1.21	0.90–1.63	0.204
Stage			
IIIB	1.00	–	–
IV	1.24	0.88–1.75	0.222

are the other examples of haematopoietic growth factors that cause neutrophilia by *in vivo* administration.[23,24] A variety of non-haematopoietic malignant tumours including mesothelioma,[25] squamous cell carcinoma of the oropharynx,[26] melanoma,[27] glioblastoma[28] and carcinoma of the lung[29] have been reported to secrete G-CSF or GM-CSF and cause significant leucocytosis. Although there have been several reports of the existence of autocrine growth loops for G-CSF and GM-CSF in non-haematopoietic tumour cells, implying G-CSF- and GM-CSF-producing tumours are more aggressive,[30,31] the relationship between paraneoplastic production of myeloid growth factors and prognosis remains unclear. Furthermore, considering the linear relationship we observed between pretreatment neutrophil count and survival in this study, ectopic production of myeloid growth factors, which often causes marked neutrophilia, does not seem to be the sole reason for the observed association between neutrophil count and prognosis.

Other possible factors that cause neutrophilia are coexistent infection and cancer-related inflammation. In this study, patients with active infection were excluded based on the eligibility criteria of the trial, and there is no clear reason to assume the existence of latent infection as the cause of neutrophilia and poor prognosis.

The association between cancer and inflammation was initially pointed out during the 19th century. However, recent advances in understanding of tumour biology have stimulated renewed interests in searching for links between cancer and inflammation.[3–6] Today, it is widely accepted that chronic inflammation contributes to the initiation and progression of cancer. Furthermore, it is now known that inflammatory processes almost always accompany cancer, and persistence of chronic inflammation-like processes within cancer tissue causes suppression of anti-tumour immunity by several mechanisms, such as activation of type 2 T-helper responses, recruitment of regulatory T cells and activation of the chemokine system, and results in promotion of cancer growth and metastasis. Thus, inflammation may result in the aggressive growth of a tumour. The cytokines interleukin (IL)-6 and tumour necrosis factor-alpha (TNFα), which are implicated in the pathogenesis of cancer-related inflammation as well as of acute inflammatory processes, are also known to induce neutrophilia.[32–34] It is possible that the neutrophil count at diagnosis indicates the severity or nature of inflammation occurring within the tumour, and thus reflects prognosis. In a recent report, a proportion of patients with metastatic cancer were shown to have IL-6-mediated elevation in serum cortisol levels. This may partly explain the neutrophilia of cancer

patients, although its contribution to outcome is not yet known.[35]

We did not measure inflammatory markers such as C-reactive protein or haemogram of total white cell count in this study. However, we are investigating correlations between several cytokines and prognosis in a correlative study of another clinical trial (ClinicalTrials.gov identifier NCT00616031).

Besides inflammation in cancer tissue, host factors may influence the prognosis of cancer patients. It is now known that lifetime exposure to infectious diseases and other sources of inflammation not only is related to the pathogenesis of cancer, but also plays an important role in ageing and influences longevity.[36,37] Ageing is a complex process, and numerous genes are known to have associations with longevity.[38] Polymorphisms of the genes that encode proteins involved in inflammatory processes (e.g. IL-1, IL-6, IL-10 and TNFα) are suspected to affect ageing and longevity. Given the close relationship between cancer and inflammation, it is natural to speculate that genetic polymorphisms in inflammation-related genes may also influence host responses to cancer and prognosis; peripheral neutrophil count may be an indicator of this association.

Another possibility is that neutrophil directly down-regulates host cellular immunity against cancer, thereby affecting the prognosis. *In vitro* studies showed that neutrophils suppress the cytolytic activity of lymphocytes and natural killer cells when co-cultured with neutrophils and lymphocytes from normal healthy donors; the degree of suppression was proportional to the number of neutrophils added.[39–41] The clinical relevance of these effects seen in *in vitro* studies is currently unknown. The biological basis for the multi-factorial and complex association is also unknown, and merits further research.

5. Conclusion

Using the dataset from a randomised controlled trial, we have confirmed that pretreatment peripheral blood neutrophil count is an independent prognostic factor in patients with advanced NSCLC receiving modern chemotherapy. The results need to be investigated for generalisability in other populations. Since neutrophil count is easily measured at low cost, it may be a useful predictor of prognosis in clinical practice. Considering the strength of the association reported here, neutrophil count should be taken into account as a stratification factor in future randomised clinical trials of patients with advanced NSCLC.

Conflict of interest statement

Kaoru Kubota has received honoraria from Eli Lilly, Sanofi-Aventis, and Chugai. All other authors declared no conflicts of interest.

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Postoperative Adjuvant Chemotherapy for Node-Positive Cervical Adenocarcinoma

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Abstract: We examined the effectiveness of postoperative adjuvant chemotherapy for node-positive cervical adenocarcinoma. During the period from 1994 to 2002, 98 consecutive patients with clinical stage I and II cervical adenocarcinoma were treated surgically without having undergone any prior treatment. Surgical procedures included radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Postoperatively, 21 patients were found to have lymph node metastasis, and all were treated with chemotherapy in the absence of radiotherapy. All patients were followed up for at least 5 years. Recurrence developed in 9 of the 21 patients, all 9 died of the disease. Six of the 9 recurrences were extrapelvic lesions. Five-year disease-free survival and overall survival were 57% and 67%, respectively. Recurrence was more common in patients with 6 or more positive nodes than in those with fewer than 3 positive nodes. These data suggest the potential role of postoperative chemotherapy for treatments of cervical adenocarcinoma. However, the effectiveness of chemotherapy alone in node-positive cervical adenocarcinoma was likely not as high as that in squamous cell carcinoma. Despite our use of postoperative chemotherapy in the absence of pelvic radiation, the disease recurred predominantly at distant sites.

Key Words: Cervical cancer, Adenocarcinoma, Chemotherapy

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Although the efficacy of radical hysterectomy and pelvic lymphadenectomy has been shown for early-stage cervical adenocarcinoma,[1] the presence of surgically detected pelvic lymph node metastasis correlates with treatment failure.[2–8] Node-positive patients with cervical adenocarcinoma have traditionally been treated with radiotherapy (RT) alone, but improving the prognosis for such patients has been a major issue in gynecologic oncology. In 2000, Peters et al[9] reported that concurrent chemoradiotherapy (CCRT) was more effective for treatment of high-risk cervical cancer, including cervical adenocarcinoma, than RT alone.

Concurrent chemoradiotherapy is accepted as a standard treatment of high-risk cervical cancer,[10] but alternative treatments have been investigated in an attempt to improve survival or more importantly to reduce treatment-related morbidity. Several studies have suggested the potential role of chemotherapy (CT) alone for treatment of node-positive cervical cancer.[11–14] At our facility, cervical cancer patients with lymph node involvement have been treated with CT alone since 1993. Here, we report the results of treatment of node-positive cervical adenocarcinoma with CT alone and discuss the possible use of this treatment.

PATIENTS AND METHODS

During the period from 1994 to 2002, 98 consecutive patients with clinical stage IB to IIB adenocarcinoma of the uterine cervix were treated surgically at the Cancer Institute Hospital (Tokyo, Japan). Patients with adenosquamous carcinoma and those who had received neoadjuvant CT were excluded from the study. Surgical procedures consisted of radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. The lymphadenectomy procedure included complete bilateral pelvic lymphadenectomy with the aim of removing all of the external iliac, internal iliac, common iliac, obturator, suprainguinal, and presacral lymph nodes. A median of 32 (range, 15–61) lymph nodes was obtained in this series. Of the 98 patients, 21 (21.4%) were found to have lymph node metastasis and formed the study population.

All 21 node-positive patients received CT postoperatively without RT. In 19 (90.5%) of the 21 patients, CDDP(cisplatin)-based CT regimens were administered. A CT regimen consisting of ifosfamide (700 mg/m^2 on days 1–4), epiadriamycin (50 mg/m^2 on day 5), and cisplatin (15 mg/m^2 on days 1–5) was used in 14 patients (67%). In 2 patients, a non–CDDP-based regimen consisting of irinotecan hydrochloride (120 mg/m^2 on days 1 and 15) and mitomycin C (7 mg/m^2 on day 1) was used (Table 1). These regimens were generally scheduled to be repeated every 4 weeks for 5 cycles.

Treatment outcomes, including toxicity of CT, were investigated. All patients were followed up for at least for 5 years. Disease-free survival and overall survival rates were calculated by the Kaplan-Meier method and analyzed by log-rank test. Differences in ratios were analyzed with the Fisher exact test. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (Version 3).

RESULTS

Patients' characteristics are shown in Table 1. Median age was 45 years (range, 31–69 years). Of the 21 node-positive patients, 13 showed 100% stromal invasion, and 8 showed parametrial involvement. The 5-year disease-free survival and overall survival rates in total cases were 57% and 67%, respectively (Fig. 1). Relapse rates by

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TABLE 1. Patients' characteristics (n = 21)

Age, mean (range), y	45 (31–69)
Clinical stage	
IB1	14
IB2	4
IIB	3
Pathologic type	
Endocervical type	
Well differentiated	13
Moderately differentiated	1
Poorly differentiated	5
Serous type	2
Capillary space involvement	
Yes	20
No	1
Depth of stromal invasion	
1–50%	3
51–99%	5
100%	13
Parametrial invasion	
Yes	8
No	13
Tumor size, cm	
<4	15
≥4	6
Chemotherapy regimen	
IEP	14
Other CDDP-based	5
CPT-11/MMC	2

CPT-11 indicates irinotecan hydrochloride; IEP, ifosfamide, epiadriamycin, and cisplatin; MMC, mitomycin C.

the number and sites of metastatic nodes are shown in Table 2. Recurrence was more frequent in patients with more than 6 positive nodes than in those with fewer than 3 positive nodes. Sites of relapse are shown in Table 3. Six of the 9 recurrences were extrapelvic lesions. Disease-free survival in relation to parametrial involvement is shown in Figure 2. Involvement of the parametrium decreased the 5-year disease-free survival rate from 64% to 43%, but this change was not statistical significant ($P = 0.3346$).

Toxicity was generally acceptable, and there was no treatment-related deaths. Grade 3 hematologic toxicity was observed in 47.6% of patients, and grade 4 was observed in 14.3%. Grade 3 gastrointestinal toxicity was observed in 14.3% of patients and sometimes necessitated termination of CT. Grade 2 alopecia was observed in most patients.

DISCUSSION

Although it is controversial whether there is a difference in survival between women with squamous cell carcinoma and those with adenocarcinoma of the cervix,[15,16] it seems that the most significant difference in prognosis between the 2 types of cervical cancer occurs in patients with surgically detected pelvic lymph node metastasis.[5,6] Nakanishi et al[6] analyzed the literature regarding prognosis of patients with cervical cancer treated surgically and concluded that the difference in prognosis between adenocarcinoma

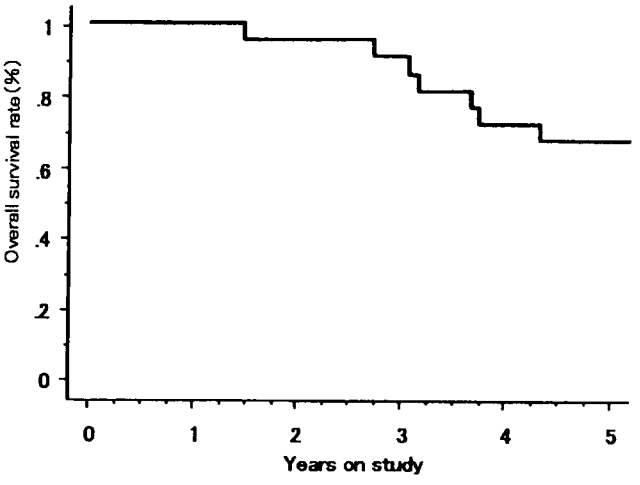

FIGURE 1. Overall survival in node-positive patients with cervical adenocarcinoma treated postoperatively with CT alone. The 5-year overall survival rate was 67% in 21 node-positive patients with cervical adenocarcinoma.

and squamous cell carcinoma depends on the ratio of node-positive cases with adenocarcinoma.

Node-positive cervical adenocarcinoma has been treated postoperatively by RT. The reported 5-year survival rates range from 33.3% to 63.2%, suggesting that node-positive cervical adenocarcinoma shows lower radiosensitivity and poorer prognosis than node-positive squamous cell carcinoma.[2–7] Recently, Chargui et al[8] reported an 8% 5-year survival rate of node-positive patients with cervical adenocarcinoma; however, RT was usually performed before surgery in their series. Yokosuka and Hasumi[4] reported a 40.9% 5-year survival rate in 25 node-positive patients with cervical adenocarcinoma; this is our historic control study in which RT was used postoperatively as adjuvant therapy (Table 4). On the basis of these observations, alternative treatments for node-positive cases have been sought.

The rationale for postoperative use of CT alone for node-positive cervical cancer is as follows. First, distant metastasis is the major problem in the treatment of high-risk cervical cancer, and CT is considered the most powerful means of eradicating subclinical metastases. Second, treatment of local recurrence is considered to be

TABLE 2. Relapse rates by the number and sites of metastatic nodes

	Relapse rate	*P*
No. metastatic nodes		
1–2 (n = 12)	25%	
3–5 (n = 5)	40%	0.012*
≥6 (n = 4)	100%	
Laterality of metastatic nodes		
Ipsilateral involvement (n = 8)	25%	0.367
Bilateral involvement (n = 13)	54%	
Involvement of common iliac nodes		
Yes (n = 7)	71%	0.159
No (n = 14)	29%	

*For 1 to 2 versus 6 or more metastatic nodes.

TABLE 3. Sites of relapse

Intrapelvic	
Pelvic lymph nodes	2
Parametrium	1
Extrapelvic	
Lung	3
Para-aortic lymph node	1
Intra-abdominal	1
Virchow node	1

easier because of the presence of RT reserved for recurrence. Finally, CT alone may yield a better quality of postoperative life by precluding radiation-related morbidities, such as small bowel obstruction and leg lymphedema. The potential role of CT for the treatment of node-positive cervical cancer has been discussed in several reports.[11–14]

The current study is the first reported study of more than 20 node-positive patients with cervical adenocarcinoma treated postoperatively with CT alone. The survival data suggest that the effectiveness of postoperative CT is equal to or better than that of RT in node-positive patients with cervical adenocarcinoma. Recurrence tends to occur more frequently in patients with many (>6) positive nodes. A similar finding was noted in patients treated with RT. Ishikawa et al[17] reported a 5-year survival rate of 61.3% in patients with cervical adenocarcinoma and fewer than 3 positive nodes but only 13.0% in those with 3 or more positive nodes. In the present study, parametrium involvement tends to be associated with poor prognosis; however, this association did not reach statistical significance. Lai et al[12] reported that postoperative CT was effective in patients with lymph node metastasis but free of parametrial extension, whereas postoperative RT was effective in those without lymph node metastasis but at high risk of recurrence.

We previously reported[18] favorable results of postoperative CT as treatment of node-positive squamous cervical cancer, showing a disease-free survival rate of more than 80%. The treatment outcome of node-positive cervical adenocarcinoma in the present series was considerably worse than that of squamous cell carcinoma.

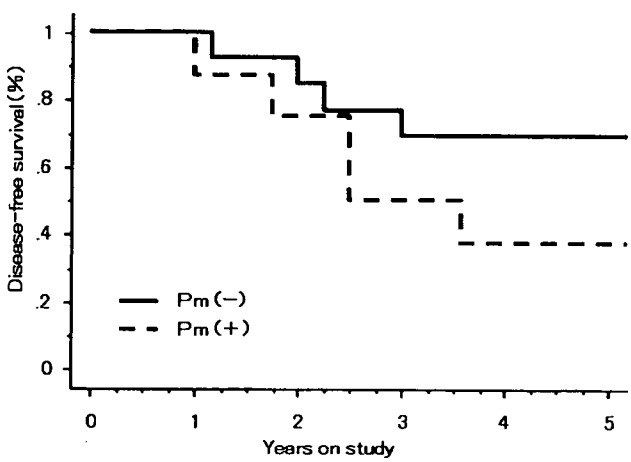

FIGURE 2. Relation between disease-free survival and parametrial involvement. The 5-year disease-free survival rate was 64% in 14 node-positive patients without parametrial involvement (pm −) and 43% in 7 node-positive patients with parametrial involvement (pm +) ($P = 0.3346$).

TABLE 4. Survival in cases of node-positive cervical adenocarcinoma

	Postoperative therapy	Clinical stage	No. cases	5-y survival rate, %
Kilgore et al[2]	RT	IB	13	42.7
Vesterinen et al[3]	RT	IB-IIB	44	40–55.6
Yokosuka and Hasumi[4]	RT	IB-IIB	25	40.9
Shingleton et al[5]	RT	IB-IIA	31	33.3
Nakanishi et al[6]	RT	IB	19	63.2
Irie et al[7]	RT	IB-IIB	18	47.9
Peters et al[9,19]	CCRT	IB-IIA	29*	82.0
Current study	CT	IB-IIB	21	66.7

*Includes 11 cases of adenosquamous carcinoma.

With respect to sites of recurrence, it is surprising that despite the use of postoperative CT in the absence of pelvic RT, recurrences occurred predominantly at distant sites. In 2000, Peters et al[9] examined 2 treatment modalities, RT and CCRT, in 243 patients with high-risk cervical cancer and obtained 4-year disease-free survival rates of 63% and 80%, respectively. Most importantly, they reported no difference in survival rate between squamous cell carcinoma and nonsquamous carcinoma when CCRT was used to treat high-risk cases. An 82.0% 5-year survival rate was reported for 29 patients with adenocarcinoma or adenosquamous carcinoma.[9,19]

Our study is limited by retrospective data collection, a small number of patients, and varying CT regimens. Nevertheless, we believe that the current study provides some information to help in the design of future trials. Prospective studies are necessary to verify the utility of postoperative adjuvant CT for cervical cancer. The Japanese Gynecologic Oncology Group has a plan to perform a phase 2 trial in this aspect. On the basis of the present results, we consider that node-positive patients with adenocarcinoma should be excluded from the study.

In summary, our findings suggest the potential role of postoperative CT for treatment of cervical adenocarcinoma. The effectiveness of CT alone for node-positive patients with cervical adenocarcinoma is equal to or better than that of RT alone. However, a high survival rate for patients with node-positive cervical adenocarcinoma has been reported only for those treated with CCRT. Although CT is probably advantageous over CCRT with respect to treatment-related morbidity,[18] at present, CCRT is considered the best treatment of node-positive cervical adenocarcinoma.

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Current Organ Topics:

Gynecologic Cancer
婦人科がん
婦人科がん治療ガイドライン策定の背景と今後の動向

Ⅰ．子宮頸癌の初回治療

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はじめに

現在，婦人科領域の悪性腫瘍治療ではガイドラインが作成され，標準的治療というものが示されるようになった。子宮頸癌治療においても，臨床実務にガイドラインは幅広く使用されている。しかし，これらのなかでさらに検討されるべき分野も多く，今回はこのような子宮頸癌治療に関する最近の話題を概説したい。

1．縮小手術

本邦では子宮頸部癌治療の基本手術として岡林式広汎性子宮全摘出術が用いられてきたが，近年これを改良し，神経の温存を重視する手術術式が盛んに検討されてきた[1]。しかし，最近の動向として，特にⅠB1期症例のなかでも直径2 cm以下のものはより縮小した手術が可能ではないかと，考えられるようになってきている。当科のⅠB1期症例の検討では，術前のMRIで腫瘍径が2 cm以下の場合（59症例），2 cm以上の場合（66症例）では子宮傍組織浸潤の頻度は0%と9.1%，リンパ節転移の頻度は6.8%と19.7%であった[2]。このように腫瘍径が2 cm以下の場合には，従来の広汎性子宮全摘出術はover treatmentである可能性が考えられる。

当科では腫瘍径が2 cm以下のⅠB1症例に対して，基靭帯処理は行うが，膀胱子宮靭帯後層処理（膀胱膣靭帯切断）を省略する縮小広汎性子宮全摘術を提唱している[3]（図1）。現在この術式による膀胱機能および予後への影響を検討中である。また，腫瘍径が2 cm以下には準広汎性子宮全摘術をという意見もあり，実地適応の可能性があると思われる。基靭帯処理の必要性については微妙な問題であるが，先の当科の検討では腫瘍径が2 cm以下には子宮傍組織浸潤がなかったものの，腫瘍径が2～3 cmの症例において子宮傍組織浸潤例が認められた経緯がある。いずれにしても，これらの領域で今後多くの臨床試験が行われるものと考えられる。

2．術前化学療法

現在ガイドラインでは，術前化学療法（NAC）は臨床試験の下で行われるべき試験的治療と規定されている。子宮頸癌のNACの有用性を考えるのに重要な前向き研究として，日本腫瘍臨床グループ（婦人科腫瘍グループ）（以下JCOG）で行われたJCOG0102[4]と米国Gynecologic Oncology Group（以下GOG）のGOG141[5]の二つの研究がある。前者はⅠB2-ⅡB期を対象とし，後者はⅠB2期のみを対象とした。二つの研究ではNACの使い方が大きく異なり，前者では4コース前後（BOMP療法）と多くのコース数のNACを施行するのが特徴であり，後者は1コース（1週間ごと3回投与）のみの抗がん剤投与（CDDP/VCR療法）である。NACによる病理学因子（例えばリンパ節転移頻度）の改善は前者である程度認められているが，後者ではコース数が少ないためほとんど認められていない。最も重要なことは，どちらの研究でも予後の改善効果は認められていないことである。また，定義が難しいが“手術の容易さ”への影響も両研究とも明確にはされなかった。

当科で施行された，子宮頸癌ⅠB2-ⅡB期80症例（1994～2004年症例）の治療成績を紹介したい。組織型別の検討を行ったが，表1にNACの奏効率を，図2に治療成績を示した。なお，NACとして扁平上皮癌にはBOMP療法，腺癌系にはIEP（IFO/epi-ADM/CDDP）

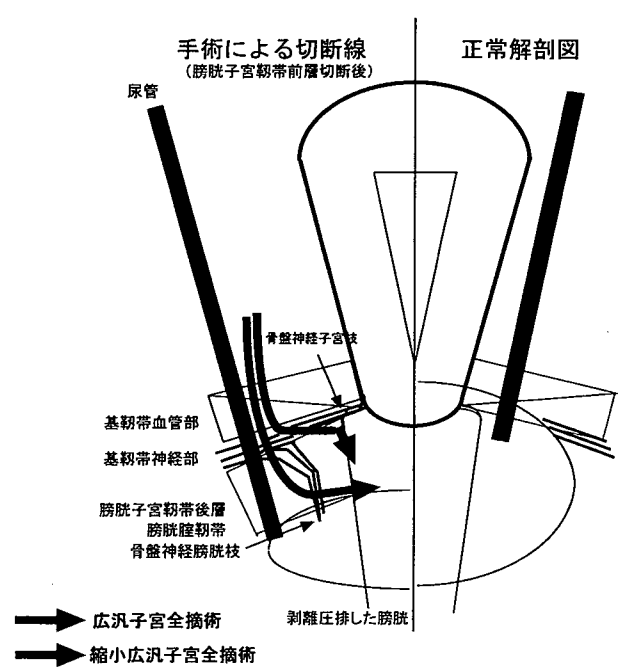


図1 縮小広汎子宮全摘の術式説明

療法を施行した。これらの治療は前向きに行われていたのではなく，日常診療のなかでNAC症例が選ばれており，ⅠB2-ⅡBの進行期の症例のなかでも，より重度のものが選ばれた可能性はあると思われる。しかし，全体としての予後は良好とは言えず，特に腺癌症例で不良であった。また，奏効率が良好であった扁平上皮癌においても治療成績は芳しくなく，このretrospectiveな検討からはNACの有用性は明確でないと思われる。

近年，婦人科悪性腫瘍化学療法研究機構（以下JGOG）で行われたJGOG1065では，CPT/NDPが抗がん剤レジメンとして使用されたが，この研究ではPR inした時点でNACを終了し手術を施行するプロトコールで，結果として多くの症例で1〜2コースのNACとなっている。このように近年のNACはコース数をできるだけ減少させ，予後の温存も視野に入れるが，手術の容易さを追求する傾向にある。われわれは，子宮頸癌のNACを表2のように分類している。かつては多くのコース数を施行し予後の改善が追及されたが，近年のNACは腫瘍が縮小することを目標とし，コース数は少ない。また，これ以外に実践的なNACとして，手術までの期間を調整しながら，腫瘍からの出血量の減少を図り，腫瘍サイズを減少させ手術をやりやすくするという目的の使用が考えられる。当科の検討ではⅠB2-ⅡB期でのNAC症例15例中（CPT/NDP使用），14例においてNACにより腫瘍からの出血は著しい減少を認めている。

3．CCRT

子宮頸癌の放射線治療（RT）はCDDP併用の有用性が示されて以来，RT単独で高い治癒率が予想されるⅠB1期以外は化学放射線療法（CCRT）が施行されている[6]。現在はCDDP 40 mg/m^{2}の週1回投与が本邦で安全に使用可能であるかがJGOGで検討され（JGOG1066），またCDDP単独に代わる別のレジメンの可能性が検討される段階に入っている。米国GOGではパクリタキセル（PTX）/CDDPの第Ⅰ相，第Ⅱ相の試験が行われ，同レジメンの使用の可能性，安全性が示され[7]，当科でもまたPTX/CDDPレジメンが日本人女性でどうなのか，第Ⅰ相試験を行った[8]。その結果，本邦ではPTX 50 mg/m^{2}とCDDP 30 mg/m^{2}の週1回投与が推奨量（RD）で，この投与量の治療で良好な治療成績を得ている。なお，GOGのRDはPTX 40 mg/m^{2}とCDDP 40 mg/m^{2}である。当科での第Ⅰ相でのRD決定の経過を図3および表3に示した。なお，近年はPTX/CBDCAを放射線治療と併用する研究も盛んに行われ，このレジメンも有望視されている[9]。

CCRTに関連する最近の話題として，治療終了後に病変が子宮周辺に残存した場合にこれをどう治療すればよいかという問題がある。図4には当科での放射線治療の後，病変が残存した症例の治療法別の生存率を示した。遠隔転移症例が予後不良であるのは当然であるが，子宮摘出に成功した場合の予後は，その他の治療を受けた場合より有意に良好であった[10]。このその他の治療とは主に化学療法を指している。このように，残存病変を含ん

表1　当科における術前化学療法奏効率

	CR	PR	SD	PD	奏効率(%)
腺癌	1	7	6	2	50
腺扁平上皮癌	0	7	2	2	63.6
扁平上皮癌	8	31	11	3	73.6

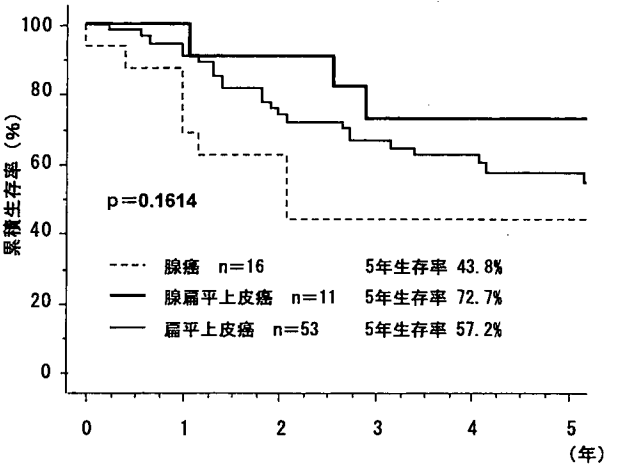
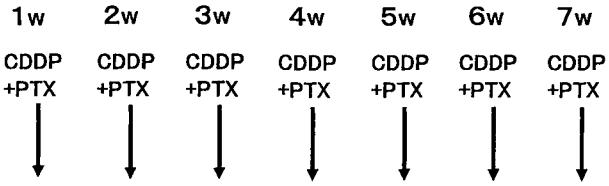


図2　当科におけるⅠB2-ⅡB期子宮頸癌NAC先行80症例の組織型別治療成績

表2　子宮頸癌におけるNACの分類

1．予後追求型NAC：多くのコース数のNACを施行し，純粋に生存期間の延長を目指す
JCOG0102　EORTC55994
2．PR獲得型NAC：PR獲得までNACを施行し予後改善も視野に入れるが，手術のやり易さの追求を第一とする
JGOG1065
3．時間調整型NAC：出血量の減少，腫瘍の縮小を図る事により手術までの期間の有効利用を目的とする
一般臨床



放射線治療
体外照射 ＋ 腟腔内照射

	CDDP(シスプラチン)	PTX(パクリタキセル)
投与レベル -1	30mg/m²	20mg/m²
投与レベル 1	30mg/m²	30mg/m²
投与レベル 2	30mg/m²	40mg/m²
投与レベル 3	30mg/m²	50mg/m²
投与レベル 4	30mg/m²	60mg/m²
投与レベル 5	30mg/m²	70mg/m²

図 3 当科における CCRT の臨床第Ⅰ相試験プロトコール

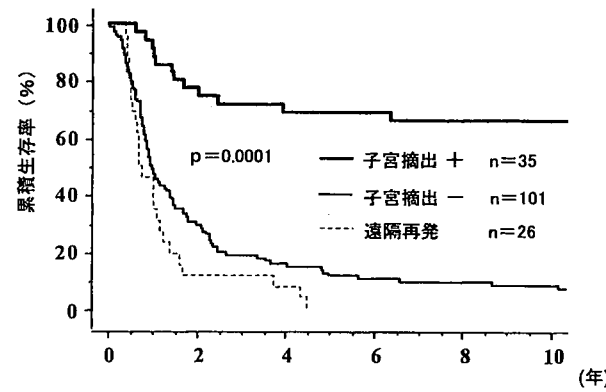


図 4 子宮頸癌不完全放射線治療症例の治療法別治療成績

不完全放射線治療症例 162 例のうち，35 例が子宮摘出を受け，127 例が子宮摘出を施行しなかった（うち 26 例が遠隔転移症例）。積極的に子宮摘出を行うことが予後改善につながることが示唆される。

表 3 第Ⅰ相臨床試験結果

	CDDP（シスプラチン）	PTX（パクリタキセル）	登録症例数	脱落症例数
投与レベル-1	30 mg/m²	20 mg/m²		
投与レベル 1	30 mg/m²	30 mg/m²	5	0
投与レベル 2	30 mg/m²	40 mg/m²	3	0
投与レベル 3	30 mg/m²	50 mg/m²	3+6	1
投与レベル 4	30 mg/m²	60 mg/m²	3	1
投与レベル 5	30 mg/m²	70 mg/m²		

だ子宮は，もし摘出が可能であればこれを手術的に摘出したほうが予後向上に繋がるのではないかと思われる。なお，摘出方法は単純子宮全摘でよく，広汎性子宮全摘術を行った場合は単純子宮全摘より有害事象が多いようである[11]。

またもう一つの話題として，重粒子線治療がある。重粒子線の一つである炭素イオンを使用した治療は放射線医学総合研究所で行われてきた。かつて有害事象が問題とされた時期もあったが，近年は良好な治療成績が得られている。なかでも子宮頸部腺癌ではⅢ-Ⅳ期症例で3年生存率が58%と報告されている[12]。まだ，治療を受けた症例数が少ない状態ではあるが，子宮頸癌，特に腺癌系に有用性が高いのではないかと考えている。

4．術後療法

子宮頸癌の術後のハイリスク症例には米国の前向き研究により，CCRT が推奨されている[13]。本邦での術後治療の実態を示す資料として，2007 年の JGOG 総会でのアンサーパットによる調査を紹介したい（図 5）。これより，本邦では CCRT が広汎性子宮全摘出術後に最も多く用いられ，ハイリスクのみならず中程度リスクにも頻用されていることがわかる。しかし，術後に CCRT を用いる場合は，最初から CCRT を用いてはどうかという問題がある。特に NAC を先行させた場合は術後に補助療法が必要な場合が多く，NAC，手術，術後 CCRT という流れとなり，これでは最初から CCRT を施行する場合に比べ非常に煩雑な治療で，不測の合併症の観点からも不安視される。

CCRT の対極として，期待されるのが術後化学療法であり，retrospective にはある程度の治療成績が示されている[14]。しかし，臨床的エビデンスが十分でなく前向き研究が望まれる。術後化学療法は術後 RT に比べて，リンパ浮腫，排尿障害などの有害事象の面で勝ると思われるが，最初から CCRT を行う場合との治療成績，有害事象の優劣についても今後の検討課題と思われる。

まとめ

今回，子宮頸癌治療で最近話題となっている点に絞って概説した。今後の子宮頸癌治療の流れとして，腫瘍サイズの小さいⅠB1 期の症例においては，引き続き手術療法が推奨されると思われる。実際これらの進行期では組織型にかかわらず，手術療法でほぼ良好な成績が得られている。今後は，腹腔鏡手術やセンチネルリンパ節に関する手技をどう絡めていくかが問題となると思われ

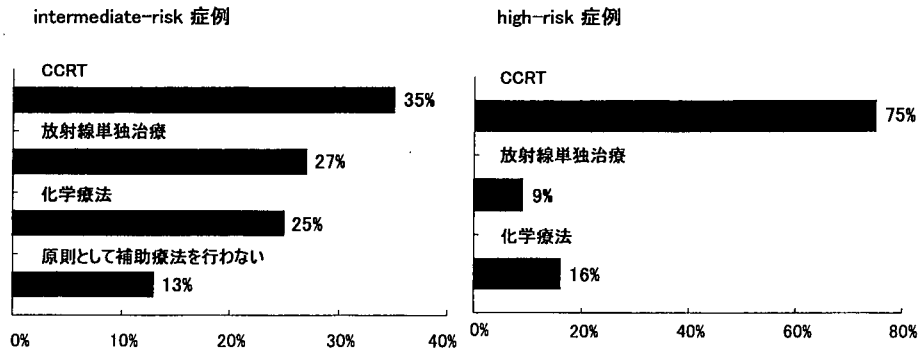


図 5 本邦における子宮頸癌補助療法の動向（平成 19 年 JGOG 総会より）

る。ⅠB2-ⅡB 期の症例においては，大きな治療の流れとして CCRT を使った治療と手術―化学療法の二つの考えがあると思われる。前者では，薬剤および投与法の選択の問題もあるが，CCRT 単独の場合は今後 adjuvant hysterectomy をどう活用していくのかが治療成績改善のポイントではないかと考えている。後者は非放射線治療として期待されるが，一般化には臨床研究によるエビデンスの証明が必要である。Ⅲ期以上の症例ではもちろん CCRT が中心であるが，ここでも adjuvant hysterectomy の価値を検討する必要があり，また新しい治療として重粒子線治療の存在も忘れてはならない。

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Intracranial hemorrhage following allogeneic hematopoietic stem cell transplantation

Yuho Najima,[1] Kazuteru Ohashi,[1]* Maho Miyazawa,[2] Mikako Nakano,[2] Takeshi Kobayashi,[1] Takuya Yamashita,[1] Hideki Akiyama,[1] and Hisashi Sakamaki[1]

Charts and radiographs of 622 allogeneic hematopoietic stem cell transplant (HSCT) recipients, over a 20-year period, were retrospectively reviewed for intracranial hemorrhage (ICH) following transplant. A total of 21 cases of ICH were identified (3.4%) including 15 cases of intraparenchymal hemorrhage (IPH), two cases of subarachnoid hemorrhage (SAH), and four cases of subdural hematoma (SDH). The median time from transplantation to the onset of ICH was 63 days (range, 6–3,488 days). The clinical features of post-transplant ICH patients were similar and included hypertension, diabetes mellitus, chronic graft-versus-host disease (GVHD), systemic infection, and veno occlusive disease (VOD), recently referred to as sinusoidal obstruction syndrome, in addition to severe thrombocytopenia. Mortality rate was especially high (89%) after IPH with a median survival of 2 days (range, 0–148 days). In contrast, all patients with SAH or SDH following HSCT survived. The cause of post-transplant ICH appears to be multifactorial, including thrombocytopenia, hypertension, acute GVHD, VOD, and radiation therapy. Most patients in our series displayed severe thrombocytopenia at the onset of ICH, even though adequate prophylactic platelet transfusions were given. By univariate analysis, cord blood transplantation, acute GVHD, systemic infection, and VOD were related to the incidence of ICH, whereas prior CNS episodes and radiation therapy did not reach statistical significance. A multivariate analysis with logistic regression identified acute GVHD as the only factor that significantly influenced ICH occurrence. Am. J. Hematol. 84:298–301, 2009. © 2009 Wiley-Liss, Inc.

Introduction

HSCT recipients are at high risk for severe neurological complications [1]. These complications arise either from the primary disease for which the patient is undergoing HSCT, or as a consequence of immunosuppressive treatments, infection, or intracranial hemorrhage that may develop during HSCT [2,3]. Although the clinical course of subdural hematoma (SDH) or subarachnoid hemorrhage (SAH) can be relatively benign, intraparenchymal hemorrhage (IPH) has the worst outcome among these complications [4,5]. Pomeranz et al. [6], in a retrospective analysis of the clinical features of ICH, found that while SDH was usually due to a more specific factor such as thrombocytopenia and had a more benign course, IPH was rather sporadic and usually lethal.

This study describes the clinical courses of 21 cases of ICH among 622 allogeneic transplants performed over the last 20 years at a single institution and reviews their clinical outcomes.

Results

Clinical features of post-transplant ICH

Charts and brain CT of 622 allogeneic transplant recipients were retrospectively reviewed for ICH, and 21 patients (3.4%) eventually developed ICH at a median time of 63 days (range, 6–3488 days) after transplantation. Median age at the time of ICH was 42 years (range, 11–66 years) and 11 patients were men (52%). Eleven patients underwent unrelated hematopoietic stem cell transplant with a radiation-containing regimen.

The clinical characteristics of these 21 patients are summarized in Table I. ICH was symptomatic in 14 of the 21 patients and symptoms included loss of consciousness (seven patients), headache (three patients), hemiplegia (three patients), and seizure (one patient). Two asymptomatic patients had ICH which was incidentally found during systemic screening for infection. One patient developed ICH during deep sedation while on mechanical ventilation. The remaining four patients visited another emergency unit at the onset of ICH and, therefore, clinical information relating to their initial symptoms was unavailable. Among the 21 patients with ICH, 15 patients developed IPH, two patients developed SAH, and four patients developed SDH. Median onset of IPH occurred at 122 days (range, 16–3,488 days) after HSCT. In comparison, all patients with SAH or SDH developed their events earlier in the course of HSCT, with a median onset of 22 days (range, 6–38 days) for the SAH patients and 31 days (range, 17–41 days) for the SDH patients (Table I). A previous history of CNS events was present in nine patients including four with reversible encephalopathy syndromes induced by cyclosporine, three patients with leukemic CNS infiltration, one case of fungal infection, and one case of meningitis. Platelet counts at the onset of ICH were extremely low in 14 patients (82%) out of 17 patients whose clinical data was available. Acute GVHD was apparent in 11 patients and three patients displayed active chronic GVHD (two extensive and one limited) at the onset of ICH. Concomitant diseases included hypertension, hyperlipidemia, chronic kidney disease, dia-

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betes mellitus, VOD, and disseminated intravascular coagulation in 10 patients (Table I).

Management, outcome, and risk factor of post-transplant ICH

Treatment options for post-transplant ICH were extremely limited and most cases were not eligible for neurosurgical intervention because of ICH severity, transfusion refractory thrombocytopenia, or poor general condition. Only two patients in our series underwent neurosurgery to avoid immediate death (Cases 2 and 18, Table I).

Post-transplant ICH has a dismal prognosis. According to Kaplan-Meier product-limit estimates, 5-year overall survival was 17.9%, which is much lower compared with patients without ICH (55.8%, $P < 0.00001$), as shown in Fig. 1. In the case of IPH, most patients died soon after the event, with the median survival after IPH of 2 days (range, 0–148 days). In contrast, patients with SAH or SDH had longer survival, and actually no deaths were attributed to SAH or SDH.

We sought to determine which variables were associated with the risk of developing ICH. Univariate and multivariate analyses of the risk factors for ICH are shown in Table II. By univariate analysis, cord blood transplantation, Grade III–IV acute GVHD, systemic infection, and VOD were related to the incidence of ICH, whereas prior CNS episodes and prior radiation did not reach statistical significance. A multivariate analysis with logistic regression identified Grade III–IV acute GVHD as the only factor that significantly influenced ICH occurrence.

Discussion

This study reviews the incidence of ICH among 622 recipients of allogeneic HSCT. Although some patients may have been overlooked due to lack of symptoms, the cumulative incidence of ICH in our series was 3.4%, which is equivalent to the incidence rates reported by others using similar definitions and methods [7]. The incidence of ICH in the setting of post-transplantation, however, was much higher than ICH not associated with HSCT in the general Japanese population, where IPH occurs in 1 per 1,000 patients and SAH occurs in 0.7 per 1,000 patients [8].

The etiology of post-transplant ICH appears to be multifactorial and includes thrombocytopenia, hypertension, acute GVHD, VOD, prior CNS episodes, and radiation therapy. Of particular interest is the finding that most patients in our series displayed severe thrombocytopenia at the onset of ICH, despite adequate prophylactic platelet transfusions which was triggered when a patient's platelet level dropped below 20,000/μl without acute bleeding. Although the precise mechanism of severe thrombocytopenia with refractoriness to platelet transfusion was unknown, cerebro-microvascular endothelial injury could be a possible underlying problem. Our patients with acute GVHD were also more likely to experience ICH, especially those receiving steroids or calcineurin-inhibitors, medications that are known to harm the CNS [9]. In a recent case report, Campbell et al. [10] described several cases of GVHD with cerebral vasculitis resulting in parenchymal hemorrhage. Uckan et al. [7] have also recently reported that life-threatening neurological complications including ICH was more frequently observed in patients carrying severe acute GVHD. In their case series, all patients who developed ICH were complicated with Grade III–IV acute GVHD. In our series, patients with severe acute GVHD (>Grade III) might have an increased risk for ICH on both univariate and multivariate analysis. Although further clarification is warranted, these suggest a possible causal relationship between severe GVHD and ICH. Radiation therapy is also thought

TABLE I. Clinical Characteristics of 21 Patients Who Developed ICH

Case	Age/ Sex	Primary disease	Conditioning regimen	Type of HSCT	ICH								
					Type of ICH	Onset of ICH (days after HSCT)	Platelet counts at the onset ($\times 10^4/\mu l$)	Prior CNS events	Acute GVHD at the onset (grade)	Chronic GVHD at the onset (type)	Concomitant diseases	Survival (days after The onset of ICH)	Outcome/Cause of death
1	56/M	NHL	CA,CY,TBI	UCBSCT	IPH	16	0.5	Leukemic infiltration	Yes (3)	-	HTN	10	Dead/IPH
2	32/F	AML	BU,CY,TLI	UBMT	IPH	42	0.9	No	Yes (3)	-	No	148	Dead/aGVHD
3	47/M	AML	BU,CY,TLI	UBMT	IPH	43	1.6	No	Yes (1)	-	No	2	Dead/IPH
4	30/M	CML	CA,CY,TBI	UBMT	IPH	57	3.3	Fungal infection	Yes (4)	-	No	2	Dead/IPH
5	11/M	ALL	BU,VP,MEL	RBMT	IPH	63	0.1	Leukemic infiltration	Yes (4)	-	VOD,DIC	0	Dead/IPH
6	20/F	AML	BU,CY,VP	RBMT	IPH	88	1.7	No	Yes (1)	-	No	1	Dead/IPH
7	66/M	MDS	FLU,MEL,TBI	UCBSCT	IPH	121	0.5	CyA encephalopathy	No	No	No	10	Dead/infection
8	32/F	CML	BU,CY	RBMT	IPH	122	2.1	Meningitis	No	No	VOD	0	Dead/IPH
9	54/M	NHL	CY,TBI	UBMT	IPH	159	0.7	No	Yes (2)	No	No	5	Dead/IPH
10	31/M	AML	BU,CY,TLI	UBMT	IPH	216	0.7	No	Yes (4)	No	No	2	Dead/IPH
11	36/M	ALL	CA,CY,TBI	RBMT	IPH	235	2.0	CyA encephalopathy	No	Yes (ext.)	CKD	0	Dead/IPH
12	37/M	NHL	CA,CY,TBI	RBMT	IPH	374	1.0	No	No	Yes (lim.)	CKD	0	Dead/IPH
13	44/M	AML	BU,CY	RBMT	IPH	642	N/A	No	No	No	HL	0	Dead/IPH
14	42/F	AML	BU,CY,TLI	UBMT	IPH	1449	N/A	No	No	Yes (ext.)	VOD	8	Dead/IPH
15	39/F	ALL	CA,CY,TBI	RBMT	IPH	3488	N/A	No	Yes (1)	No	CKD	602+	Alive/–
16	53/F	MDS	BU,CY,TLI	RBMT	SAH	6	0.4	No	No	-	No	1199+	Alive/–
17	59/F	MDS	FLU,CY	RPBSCT	SAH	38	2.4	CyA encephalopathy	Yes (4)	-	No	52	Dead/aGVHD
18	23/M	CML	BU,CY	RBMT	SDH	17	N/A	No	No	-	No	5850+	Alive/–
19	43/F	MDS	BU,CY,TLI	UBMT	SDH	29	0.6	CyA encephalopathy	No	-	No	66	Dead/infection
20	50/F	ALL	CA,CY,TBI	UCBSCT	SDH	32	1.5	No	No	-	HTN,DM	1649+	Alive/–
21	45/F	ALL	CA,CY,TBI	UCBSCT	SDH	47	0.3	Leukemic infiltration	Yes (3)	-	VOD	63	Dead/relapse

HSCT, hematopoietic stem cell transplantation; ICH, intracranial hemorrhage; CNS, central nervous system; GVHD, graft-versus-host disease; M, male, F, female; NHL, non-Hodgkin's lymphoma; AML, Acute myelogeneous leukemia; CML, chronic myelogeneous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CA, cytarabine; CY, cyclophosphamide; TBI, total body irradiation; BU, busulfan; TLI, total lymphoid irradiation; VP, VP16; MEL, melphalan; FLU, fludarabine; UCBSCT, unrelated cord blood stem cell transplantation; UBMT, unrelated bone transplantation; RBMT, related bone marrow transplantation; UBMT, unrelated bone marrow transplantation; RPBSCT, related peripheral blood stem cell transplantation; IPH, intraparenchymal hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; N/A, not available; CyA, cyclosporine; ext, extensive; lim, limited; HTN, hypertension; VOD, veno-occlusive disease; DIC, disseminated intravascular coagulation syndrome; CKD, chronic kidney disease; HL, hyperlipidemia; DM, diabetes mellitus.

TABLE II. Univariate and multivariate analysis factors for ICH

	Univariate P^*	Multivariate P^{**}	Hazard ratio (95%CI)
Donor (unrelated/related)	0.120	0.741	0.83 (0.28–2.48)
Radiation containing regimen	0.134	0.443	1.53 (0.51–4.59)
Prior CNS events (yes/no)	0.061	0.312	1.78 (0.58–5.40)
CBSCT (yes/no)	0.006	0.213	1.51 (0.79–2.93)
Acute GVHD grade III-IV (yes/no)	0.006	0.046	1.41 (1.01–1.97)
Systemic infection (yes/no)	0.0069	0.399	1.52 (0.57–4.03)
VOD (yes/no)	0.009	0.125	2.63 (0.77–9.00)

*Univariate analysis with the χ^2 test for categoric variables and the nonparametric Mann-Whitney U test for continuous variables.

**Multivariate analysis with the multiple logistic regression analysis for appropriate variables to evaluate the risk of ICH. Statistical significance was determined at the .05 level. All *P* values were two sided. The statistical data were obtained using the SPSS software package (SPSS 11.0 inc., Chicago, IL).

to contribute to the development of ICH [11], and the majority of our ICH patients received some form of radiation therapy. Laboratory-proven coagulopathies, however, were not evident in our series except for one patient (Case 5) who developed IPH.

Consistent with previous reports, the clinical course of patients with ICH in our series was dismal with a 5-year overall survival rate of only 17.9%. In contrast, among the 601 patients without ICH, the 5-year overall survival was 55.8% (see Fig. 1). In our series, SAH and SDH were observed by Day 50 after allogeneic HSCT and conservative therapy resolved the clinical symptoms in all but one patient, with no death attributed to SAH or SDH. Colosimo et al. [4] reported that 16 of 17 cases of SDH occurred within 60 days after allogeneic HSCT and none were fatal. Pomeranz et al. [6] also reported that all SDH events (13 cases per 471 HSCT cases) were observed within 42 days after HSCT. In contrast, IPH events occurred later, with a wide distribution of onset with a median of 122 days after transplant and a range of 16–3,488 days. Most patients died from their IPH event, especially those whose event occurred early in the course of the HSCT. The cause of this clinical discrepancy remains unclear, but may be due to predisposing factors unique to each disease entity.

Although not statistically significant, patients with VOD also appeared predisposed to developing ICH. This may not be solely due to a side effect of the tissue plasminogen activator administered with antithrombin-III as part of the VOD therapy. On the basis of a recent report, this combination appears to reverse the course of VOD without increased risk of bleeding [12].

This study is limited because of its retrospective nature, and we may have overlooked some patients with ICH, despite detailed database analysis and extensive chart review. Nevertheless, our aim was to review the clinical outcomes of 622 allogeneic transplant patients after ICH over a 20-year period and to provide useful insights into this phenomenon.

Methods

Patient demographics. We retrospectively reviewed 622 patients (370 men, 252 women; median age, 37 years; range, 0–67 years) with various diseases who underwent allogeneic transplantation at our institution. Between September 1986 and December 2006, 499 patients received bone marrow transplantations (264 related, 231 unrelated, four syngenic), 79 received related peripheral blood stem cell transplantations and 44 patients received unrelated cord blood stem cell transplantations. Their underlying diseases included chronic myeloid leukemia (n = 139), acute nonlymphoid leukemia (n = 175), acute lymphoid leukemia (n = 133), myelodysplastic syndrome (n = 83), non-Hodgkin's lymphoma (n = 31), severe aplastic anemia (n = 41), myelofibrosis (n = 5), multiple myeloma (n = 13), and adult T-cell leukemia/lymphoma (n = 2).

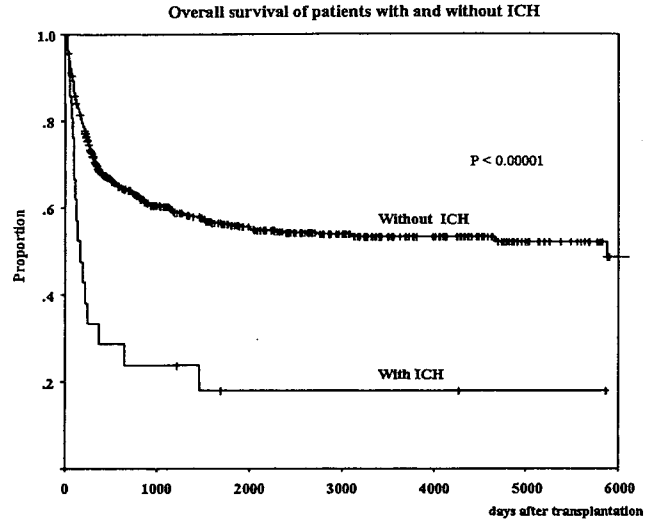

Figure 1. Calculation of overall patient survival with and without ICH, using the Kaplan-Meier method.

Preparative regimen, GVHD prophylaxis, and transfusion policy. Preparative therapy was performed according to the primary disease and type of transplant. Generally, patients with lymphoid malignancy were conditioned using a combination of total body irradiation (TBI) of 12 Gy and chemotherapy, including cytarabine at 8 g/m^2 and cyclophosphamide (CY) at 120 mg/kg. TBI was performed with partial transmission to the anterior–posterior eye with 33% shielding. Conversely, patients with myeloid malignancy were conditioned using a non-TBI containing regimen that included busulfan (BU) at 16 mg/kg and CY at 120 mg/kg. Plasma concentrations of busulfan were not monitored. Total lymphoid irradiation (TLI, 7 Gy) was included in BU/CY regimens in cases with mismatch or unrelated transplantation. Patients with severe aplastic anemia were also conditioned using a TLI-containing regimen. Cyclosporine (CyA) or tacrolimus (FK) plus short-term methotrexate were used for GVHD prophylaxis. FK was used in cases involving either unrelated or mismatched transplantation. Acute and chronic GVHD were diagnosed and graded according to previously established criteria. Prophylactic platelet transfusion was triggered when a patient's platelet level dropped below 20,000/μl without acute bleeding [13].

Definition of ICH and statistical analysis. On the basis of brain computed tomography (CT) findings, ICH was classified as IPH, SAH, or SDH. Ischemic events such as cerebral infarction or transient ischemic attack were not included. Post-traumatic hematoma, meningoencephalitis, or abscess was also excluded. Overall survival and relapse-free survival rate were estimated by Kaplan-Meier product-limit estimates. The log-rank test was used to assess differences between groups of patients with or without ICH. A multivariate analysis was done to determine the risk factors for causing ICH by the logistic regression model.

Acknowledgments

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症例報告

初診時より多発性の巨大髄外形質細胞腫を呈した多発性骨髄腫

澤田武志[1]，名島悠峰[1]，大橋一輝[1]，加藤生真[2]，
宮澤真帆[3]，中野美香子[3]，小林　武[1]，山下卓也[1]，
秋山秀樹[1]，坂巻　壽[1]

症例は58歳，男性。2006年11月より左下腿腫脹が出現し，徐々に歩行不能となった。近医施行のCTにて左鼠径部に巨大腫瘤を認め，2007年4月当院を初診。鼠径部腫瘤の生検にて形質細胞腫の診断，骨髄では形質細胞が5.8%と軽度増加していた。溶骨性病変，腎機能障害や高カルシウム血症はなかったが，軽度貧血のほか血清IgG値は6,387 mg/dlと高値で形質細胞腫を伴う多発性骨髄腫と診断した。CTで全身に多発する巨大腫瘤を認め，傍気管部腫瘤は気道閉塞の危険性が高く気管切開術を施行，左下肢に還流障害をきたす鼠径部腫瘤と脊髄を圧迫する脊柱管内腫瘤に対してそれぞれ放射線照射を施行した。VAD療法3コース施行後，腫瘤は一時縮小しIgG値も低下したが，約3か月後に再燃。ボルテゾミブ療法は奏効せず多臓器不全で死亡した。本例は多数の髄外病変を病初期から認め，急激な経過をたどった多発性骨髄腫と考えられた。(臨床血液 50 (11)：1635～1640，2009)

Key words：Multiple myeloma, Extramedullary plasmacytoma

緒　言

今回，我々は初期病変として骨髄ではなく多発する皮下腫瘤を認め治療抵抗性の経過をたどったmultiple myeloma（MM）の1例を経験したので報告する。

症　例

患　者：58歳　男性

主　訴：左下腿腫脹

既往歴・家族歴：特記すべきことなし

現病歴：2006年11月頃より左下腿浮腫が出現し，徐々に左下肢全体に腫脹が拡大するも放置，2007年4月に歩行困難となり前医受診した。CTで左傍大動脈領域から左鼠径部に巨大な腫瘤を認め，紹介にて同月当科初診，精査加療のため入院となった。

入院時現症：身長169 cm，体重87.0 kg，意識清明，血圧118/54 mmHg，脈拍88/min（整），体温36.6℃，経皮的酸素飽和度98%（室内気）。眼瞼結膜貧血なし，眼球結膜黄疸なし。表在リンパ節は触知せず。胸部聴診所見上心音正常，呼吸音正常，気道狭窄音なし。全身皮下に多発する弾性硬の可動性不良の腫瘤を認めた。左上顎から鼻翼部と左頬部に及ぶ4×4 cm大，左上顎及び左下顎に2×2 cm大の腫瘤，両側頸部に1.5×1.5 cm大，胸骨上部・左胸壁・左鼠径部にそれぞれ3×3 cm，4×5 cm，8×5 cm大の腫瘤を認めた。肝臓・脾臓・腎臓触知せず。左下肢は著明に腫脹し左足背動脈の触知は微弱であった。神経学的所見は左頬部の触覚低下，および臍上部以下の触覚低下と下肢の痺れと対麻痺を認めた。

入院時検査所見（表1）：血算では軽度貧血（血色素11.4 g/dl）を認めた。生化学では総タンパク10.6 g/dlと上昇し，蛋白分画でもγグロブリン分画の上昇（49.9%）を認めた。血清免疫電気泳動ではIgG-κのM蛋白を認めた。血清IgGは6,387 mg/dlと上昇，一方，IgA 137 mg/dl，IgM 167 mg/dlはそれぞれ正常範囲内であった。高カルシウム血症（血清カルシウム9.0 mg/dl）や腎機能障害（尿素窒素10 mg/dl，クレアチニン0.6 mg/dl）は認めなかった。胸壁及び鼠径部腫瘤の生検では異型形質細胞がびまん性に増殖する所見を認めた（図2A）。また，免疫染色では，CD20－，CD3－，CD8－，CD4－，CD5－，CD19－，CD38＋，CD56－，CD79a＋，IgG＋，κ＋，λ－であり形質細胞腫と診断した。骨髄は正形成で異型性のある形質細胞が5.8%と軽

受付：2008年12月22日
受理：2009年7月2日
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[3]がん・感染症センター　薬剤科

表 1　入院時検査成績

〈血算〉

WBC	4,700/μl
Stab	4.0%
Seg	59.0%
Lym	25.0%
Mon	10.0%
Eos	1.0%
Bas	1.0%
RBC	385×10⁴/μl
Hb	11.4 g/dl
Ht	34.0%
Plt	13.3×10⁴/μl
Ret	1.7%

〈凝固〉

PT(INR)	1.10
APTT	31.8 sec
Fib	320 mg/dl
FDP	28.6 μg/ml

〈生化学〉

TP	10.6 g/dl
Alb	3.6 g/dl
Na	136 mEq/l
K	3.7 mEq/l
Cl	103 mEq/l
Ca	9.0 mg/dl
BUN	10 mg/dl
Cr	0.6 mg/dl
AST	21 IU/l
ALT	11 IU/l
LDH	331 IU/l
ALP	132 IU/l
CPK	288 IU/l
CRP	0.4 mg/dl
β2MG	4.3 mg/l

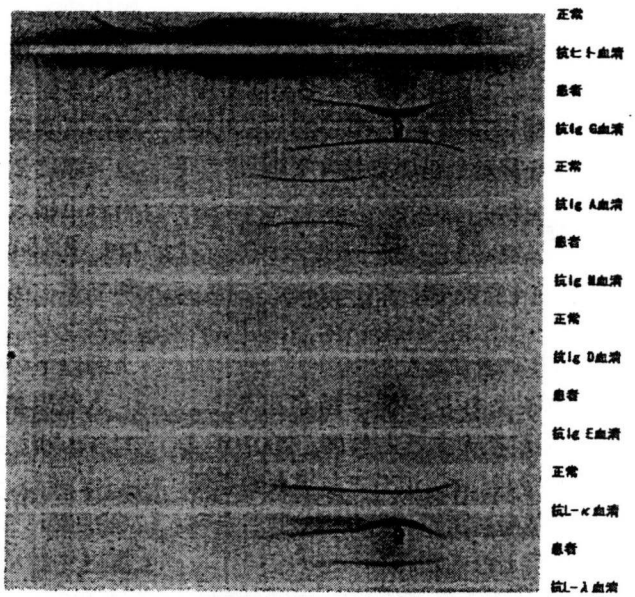
〈血清タンパク分画〉

Albumin	34.5%
α1	2.2%
α2	6.0%
β	7.4%
γ	49.9%

〈免疫グロブリン〉

IgG	6,387 mg/dl
IgA	137 mg/dl
IgM	167 mg/dl

〈免疫電気泳動〉



骨髄

NCC	68,000/μl
G/E	3/1
Mgk	45/μl
Plasma cell	5.8%

〈染色体〉

46XY	20/20

度増加を認めた（図 2B）。染色体解析では 46XY (20/20) と正常核型であった。全身の造影 CT にて，左上顎部に上顎骨を一部破壊する 6×4 cm の腫瘤，甲状軟骨左側周囲に喉頭や気管を右方に強く圧迫する 4×4 cm の腫瘤（図 1A），その他左鎖骨骨頭，左広背筋前方，上縦隔，右腋窩，左季肋部やや前方皮下（図 1B），右腹壁，腹部大動脈と左大腰筋の間，左腸骨動脈領域及び左鼠径部にも腫瘤を認めた。骨盤内左側のものは 10×6 cm（図 1D），鼠径部の腫瘤は 8×5 cm 大の大きさを呈し（図 1E），著明な左下肢の浮腫を伴っていた。第 3～6 胸椎レベルで脊椎左側に腫瘤を認め，また脊柱管内への浸潤も示唆され，MRI では左第 4 胸椎左椎弓から横突起に T2 高信号域及び第 3～4 胸椎レベルの胸髄に中枢神経浸潤を示唆する T2 高信号域を認めた（図 1C）。全身に骨

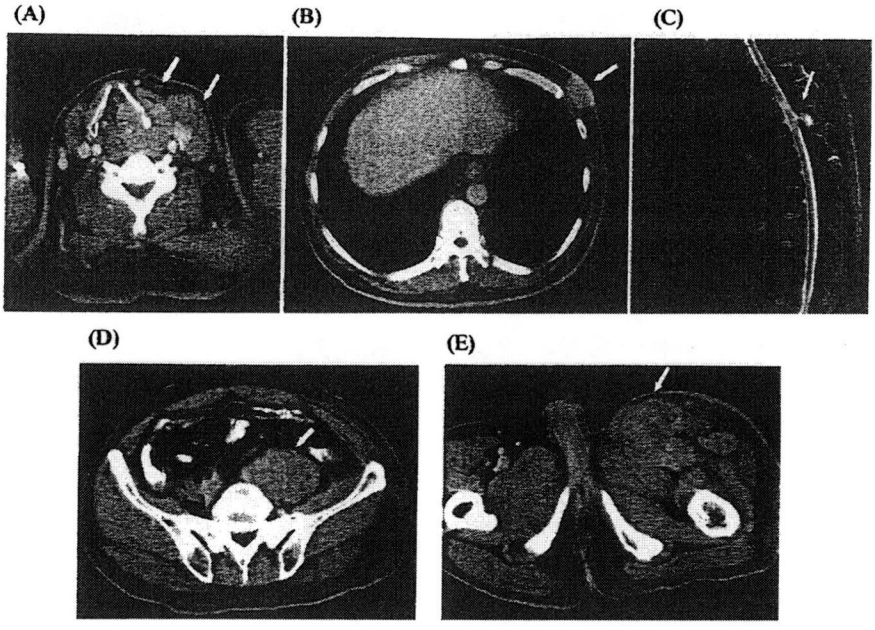


図 1 初診時での頸部～骨盤 CT 検査および胸椎 MRI 検査
(A) 左傍気管支部 (B) 左胸壁 (C) 第3～4 胸椎 (D) 傍大動脈リンパ節
(E) 左鼠径部

病変は認められなかった。

入院後経過：入院後，dexamethasone (DEX) 0.5 mg/kg/day×18 days 先行投与開始の上で胸椎脊柱管内腫瘤および左鼠径部腫瘤に放射線照射を開始，また，気道圧排性の病変による窒息回避のため緊急気管切開術を施行した。照射終了後は vincristine (VCR) 0.4 mg/body/day×4 days 及び doxorubicin (ADR) 9 mg/m^2/day×4 days を追加した (VAD 療法)。VAD 療法2コース終了後に IgG 値は 6,387 mg/d*l* → 1,246 mg/d*l* と低下したが，白血球減少 (1,600/μl) がみられ，血中ガラクトマンナン抗原が陽性化したため G-CSF 100 μg/body/day の投与及び voriconazole (VRCZ) 400 mg/day 経口投与した。VRCZ 投与後に肝障害出現したため itoraconazole 内用液 (200 mg/day) に変更とした。この間 IgG 値は 1,246 mg/d*l* → 2,638 mg/d*l* と再上昇し，腫瘤増大を認め VAD 療法3コース目を施行，その後，自家末梢血幹細胞採取目的も兼ねて cyclophosphamide (CY) 2000 mg/m^2/day を2日間投与した。CY 投与後の骨髄抑制時に胸部に多発結節影が出現，血中ガラクトマンナン抗原も 4.0 と上昇，真菌性肺炎と判断し amphotericin B liposome (200 mg/day) を併用した。採取 CD34 陽性細胞は 0.22×10^6/kg と不十分で自家移植は断念した。その後 IgG 値は 1,166 mg/d*l* と減少し，多発性皮下腫瘤も消退傾向を示した。真菌性肺炎は軽快傾向を示したが，血中ガラクトマンナン抗原は陰性化せず推移した。8月に本人の強い希望で退院し，以降外来にて VCAP 療法 (VCR 1.0 mg/body/day×1day, CY 100 mg/m^2/day×4days, ADR 30 mg/m^2/day×1day, prednisolone 40 mg/m^2/day×4days) を2コース施行したが，左下肢や背部皮下に 新たな腫瘤形成を認め 11 月に再入院した。bortezomib (1.3 mg/m^2/day, day1, 4, 8, 11) 及び間欠的 DEX 20 mg/body (day1, 2, 4, 5, 8, 9, 11, 12) による治療 (VD 療法) 開始後，下腿腫瘤はやや縮小傾向を示したが，背部腫瘤は著変なく残存した。骨髄は正形成で形質細胞の浸潤は僅かであり，κ/λ の2重免疫染色法では monoclonality は見られなかった。VD 療法後に副作用として神経障害 (grade 3) および血小板減少 (grade 4) が見られ，2コース目は 0.7 mg/m^2/day に減量し，一旦退院し外来にて治療継続したが，下腿腫瘤および背部皮下腫瘤は短期間で増大し，IgG 値も 1,218 mg/d*l* → 2,042 mg/d*l* → 3,011 mg/d*l* と漸増した。VD 療法後に血中ガラクトマンナン抗原が 5.0，(1→3) -β-D-グルカン値も 82.7 pg/m*l* と著増した。その後は緩和的医療を継続しつつ徐々に全身状態は悪化，多臓器不全を併発し，初診より約 10 ヶ月の経過で死亡した。

剖検所見では，左下腿の腫瘤のほか，骨髄，脾臓および腹部リンパ節にびまん性に形質細胞浸潤を認め (図 2C, D)，肝臓や精巣の一部にも浸潤を認めた。免疫染色の結果は初診時と同様に CD38，CD79a，IgG-κ が陽性であり IgG-κ に偏りがみられたが，CD56 および cyclin D1 は陰性であった。肺病変からは，真菌は検出されず E.coli が検出された。

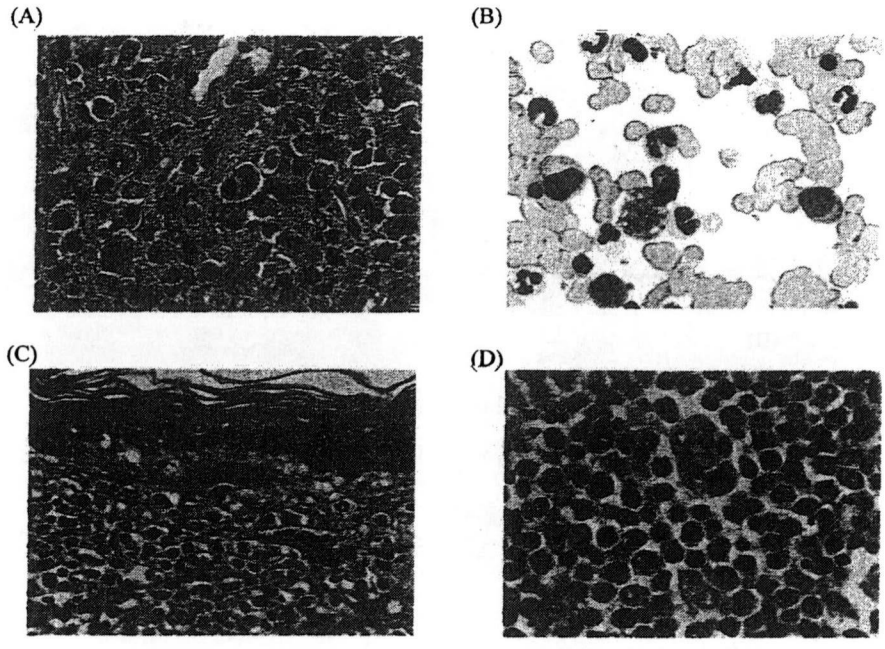


図 2　組織学的所見

A）初診時の胸壁における形質細胞腫（HE 染色，×400）
B）初診時の骨髄穿刺（May-Giemsa 染色，×1000）
C）剖検時の左下腿における形質細胞腫（HE 染色，×400）
D）剖検時の骨髄への広範な形質細胞浸潤（HE 染色，×400）

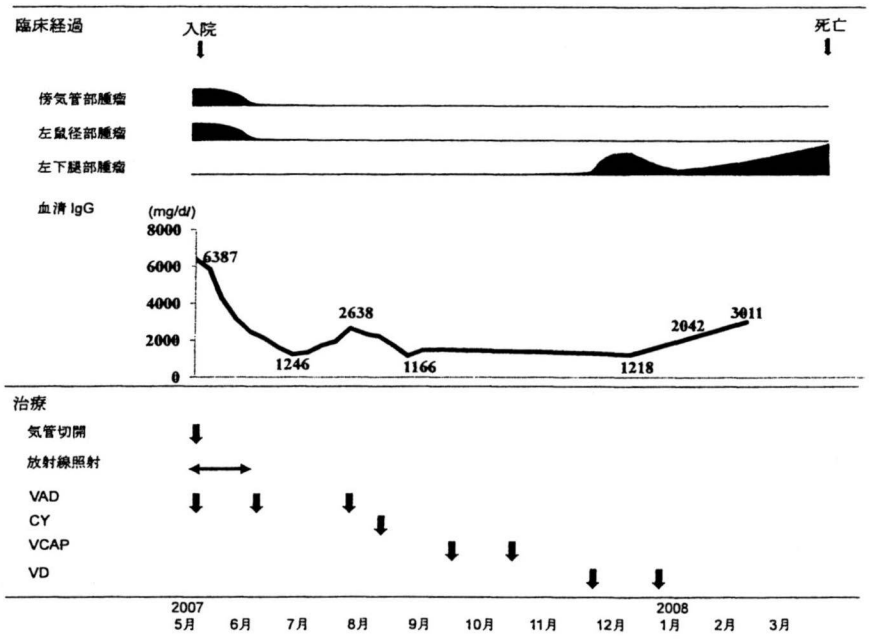


図 3　臨床経過

VAD: vincristine, doxorubicin, dexamethasone, CY: cyclophosphamide, VCAP: vincristine, cyclophosphamide, doxorubicin, prednisolone, VD: bortezomib, dexamethasone, IgG: immunoglobulin G.

考　察

MMは骨髄をその増殖の主体とし，多巣性に全身の骨髄に浸潤し骨溶解性の病変を呈する難治性の造血器疾患である。Mタンパクの産生を伴いInternational Myeloma Working Group（IMWG）の診断基準に示される様な多彩な臓器障害を呈する[1]。初診時の骨髄において形質細胞が10%未満の症例は全体の5%程度といわれており，また多発する髄外の形質細胞腫はMMの進行期にみとめる所見である[1]。一方，約15～20%の症例において，診断時に髄外性形質細胞腫を認めたという報告もある[2]。また，MMの診断基準を満たさない形質細胞腫はWorld Health Organization（WHO）分類により，①extramedullary plasmacytoma（EMP），②solitary plasmacytoma of boneに分類される。これらは通常，孤立性の病変であり，初診時に既に多発性の形質細胞腫が認める場合，EMPとMMの鑑別が臨床上の問題となる[3]。

EMPは全形質細胞腫瘍の約3～5%を占め，その約80%は頭頸部領域に発症する[4]。また，上気道にみられる形質細胞腫の15%の症例で，病変は頚部リンパ節まで進展している[2]。通常は局所放射線治療が奏効し良好な臨床経過をたどるが，約15%の症例においては経過中にMMへ移行するといわれている[4,5]。2001年報告のWHO分類ではEMPとMMを細胞形態学的に鑑別することは困難であるが，最近のKremerらの報告をみてみると，EMPとMMにおいてCD56の発現率は10%（28例中3例）対77%（26例中20例）[p<0.001]，cyclin D1の発現率は0%（28例中0例）対35%（26例中6例）[p<0.001]と大きく異なっており，免疫組織学的に両者の鑑別が可能である[6]。また，Binkらによる EMPの染色体及び遺伝子解析の検討では，MMにみられるIgHの転座や13番染色体欠失などはEMPでも認められるものの，cyclin D1の発現異常を伴うt(11;14)(q13;q32)はEMPでは検出されなかったとしており[7]，cyclin D1の発現の有無も診断上の参考になると考えられる。

本症例は，病初期から多発する髄外の形質細胞腫を認めながらも，骨髄において著明な形質細胞の増多を認めず，また臓器障害も軽微であった。とくに初診時はEMPの好発部位とされる上気道，リンパ節や皮膚に病変が偏っていたが，終末期には繰り返す感染症，高度の貧血などをみとめ，剖検時には全身の骨髄にびまん性の形質細胞浸潤を認めた。また，本症例の形質細胞腫における免疫染色の結果は全経過を通じてcyclin D1およびCD56はいずれも陰性であった。また，本症例では13番染色体のFISH解析は施行していないが，G-banding法を用いた染色体解析においては正常核型であった。これらのことから，本症例はMMとしては非典型的経過をたどった1例であり，その背景としてEMPから急激な経過を辿ってMMへ移行した可能性もあると考えられた。

髄外病変を伴うMMに対する確立した治療戦略はなく，その予後も不良である[8]。Thalidomideによる治療効果は限定的であるが[9,10]，bortezomibは効果的であるとする報告が最近散見される[11～13]。また，単独のEMPに対してもbortezomibが有効である可能性が示唆されている[14]。本症例ではbortezomibの十分な効果を認めなかったが，今後の症例の積み重ねが必要と考えられた。

本症例は病初期より多発する髄外病変と急速に進行する治療抵抗性の経過が興味深い症例と考え報告した。

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