We evaluated the LAC index among patients treated with ICE and DHAP separately. Among the patients treated with ICE, the median OS of high- and low-risk patients was 9.5 months (95% CI 0–21.3) and 63.2 months (95% CI 0.0–140.9), respectively. Among the patients treated with DHAP, the median OS of high- and low-risk patients was 4.7 months (95% CI 3.7–5.8) and 13.8 months (95% CI 13.5–14.2), respectively. There was a significant difference in OS among high- and low-risk patients for patients who were treated with ICE and DHAP (log-rank test; $P = 0.004$ and 0.006, respectively).

Among the patients with all lymphoma, the overall response rate was significantly higher among the low-risk patients than that among the high-risk patients (71.4 versus 28.6%, $P = 0.005$). The complete remission rate was significantly higher among the low-risk patients than that among the high-risk patients (45.2 versus 9.5%, $P = 0.030$). Moreover, among the patients with diffuse large B-cell lymphoma, the overall response rate was significantly higher among the low-risk patients than that among the high-risk patients (81.8 versus 21.4%, $P = 0.001$). The complete remission rate was significantly higher among the low-risk patients than that among the high-risk patients (45.5 versus 7.1%, $P = 0.025$).

Our analysis comparing the LAC index score with well-established factors is shown in Table 4. Multivariate analysis for prognostic factors among the LAC index and well-established prognostic factors demonstrated that the independent prognostic factors for OS were: high risk according to the LAC index (HR 3.604. 95% CI 1.370–10.232; $P = 0.009$), performance status over 1 (HR 3.311. 95% CI 1.072–10.232; $P = 0.038$) and interval from induction therapy to salvage therapy <1 year (HR 9.129. 95% CI 1.948–42.774; $P = 0.005$).

We applied the R-IPI and IPI in our patients. We evaluated the outcome classified by the R-IPI among 29 patients treated with rituximab plus salvage chemotherapy. According to the R-IPI in our patients, the median OS rates of the high-risk, intermediate-risk and low-risk groups were 12.3 months (95% CI 7.5–17.1), not reached, and not reached, respectively. There was a significant difference among the three risk groups (log-rank test; $P = 0.040$, Fig. 3). We evaluated the outcome classified by the IPI among our patients without angioimmunoblastic T-cell lymphoma. According to the IPI in our patients, the median OS rates of high-risk, high-intermediate-risk, low-intermediate-risk and low-risk groups were 12.9 months (95% CI 2.7–23.0), 9.5 months (95% CI 3.0–16.0), not reached, and not reached, respectively. There was not a significant difference among the four risk groups (log-rank test; $P = 0.106$, Fig. 4).

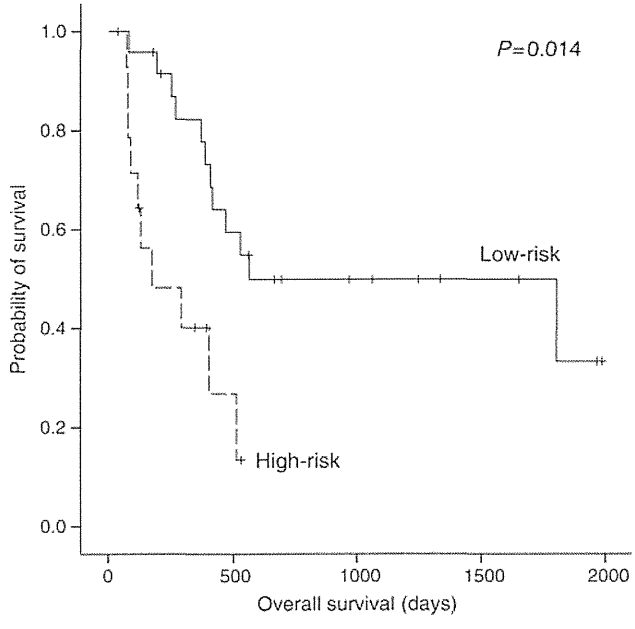

Figure 2. The LAC index among the patients with DLBCL. Among the patients with DLBCL, the median overall survival of high- and low-risk patients was 9.5 months (95% CI 1.3–17.7) and 60.1 months (95% CI 0.0–121.0), respectively. There was a significant difference among high- and low-risk patients for patients with diffuse large B-cell lymphoma (log-rank test; $P = 0.014$).

Correlations Between Five Prognostic Factors in Our Model

According to Pearson's product–moment correlation coefficient, the closer to 1.00 the r value, the stronger correlations become. First, we analyzed the correlation between five laboratory parameters before salvage therapy. There is moderate correlation between CRP and Hb, sIL-2R and Hb, sIL-2R and β2M (correlation coefficient, $r = 0.362$, 0.334, and 0.301, respectively). On the other hand, there is little correlation between LDH and Hb, and LDH and CRP (correlation coefficient, $r = 0.252$, and 0.64, respectively). Secondly, we analyzed the correlation between parameters before salvage therapy and before induction therapy. There is moderate correlation between β2M and sIL-2R before salvage therapy and before induction therapy (correlation coefficient, $r =$

Table 4. The univariate and multivariate analyses of biological index and well-established factors that influence the overall survival

Factors	Cut-off	Univariate	Multivariate	Hazard ratio
LAC index	>1	<0.001	0.009	3.604 (1.370–10.232)
Disease status	Refractory	0.001	0.316	1.663 (.616–4.494)
PS	>1	<0.001	0.038	3.311 (1.072–10.232)
IPI score	>2	0.030	0.989	0.993 (.369–2.674)
Interval	<1 year	<0.001	0.005	9.129 (1.948–42.774)

PS, performance status; Interval, interval from induction therapy to salvage treatment.
[a]Including patients not achieving complete response after the first-line therapy.

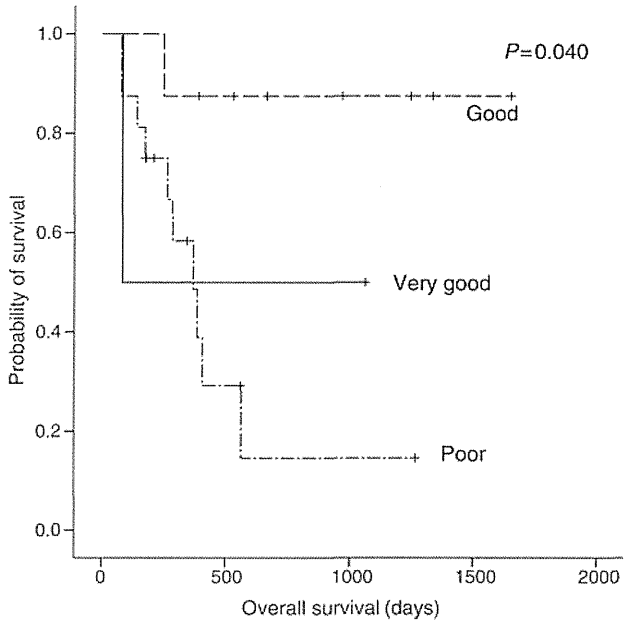

Figure 3. The R-IPI in our patients. According to the R-IPI in our patients, the median overall survival rates of the high-, intermediate- and low-risk groups were 12.3 months (95% CI 7.5–17.1), not reached, and not reached, respectively. There was a significant difference between three risk groups (log-rank test; $P = 0.040$).

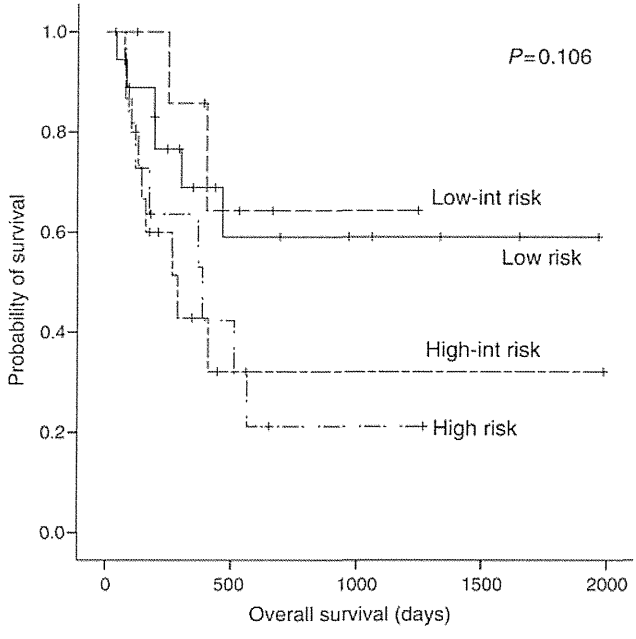

Figure 4. The IPI in our patients. According to the IPI in our patients, the median overall survival rates of high-risk, high-intermediate-risk, low-intermediate-risk and low-risk groups were 12.9 months (95% CI 2.7–23.0), 9.5 months (95% CI 3.0–16.0), not reached, and not reached, respectively. There was not a significant difference among four risk groups (log-rank test; $P = 0.106$).

0.513 and 0.383, respectively). However, there is little correlation between Hb, CRP and LDH before salvage therapy and induction therapy (correlation coefficient, $r = 0.142$, 0.134 and 0.004, respectively).

DISCUSSION

This study suggested that OS after salvage treatment, ICE or DHAP, had started significantly worsened in patients with elevated CRP, elevated LDH and anemia for aggressive malignant lymphoma. Several well-known prognostic predictors for newly diagnosed malignant lymphoma, such as IPI, R-IPI, FLIPI, PIT and IPS, included elevated CRP level, elevated LDH level and anemia (7–11).

CRP is a member of the class of acute-phase reactants, as its level rises dramatically during inflammatory processes occurring in the body. Elevation of serum CRP is due to a rise in the plasma concentration of interleukin-6, which is produced predominantly by macrophages as well as adipocytes. Interleukin-6 is a potent lymphoid growth and differentiation cytokine produced by various types of cells, including benign and malignant B and T lymphocytes. Interleukin-6 is implicated in the pathogenesis of several lymphoproliferative disorders, which has been reported as an independent prognostic factor for complete remission and failure-free survival among diffuse large cell lymphomas (17,18). CRP has been reported to be strongly correlated with the Ann Arbor clinical stages (19).

Serum LDH represents a surrogate quantitative measure for tumor burden. A high serum LDH level is correlated with the progression of disease in non-Hodgkin's lymphoma (20,21). Combined with serum LDH and β2M provides a reliable serologic system for predicting freedom from relapse and survival in large cell lymphoma. Moreover, elevations in both serum LDH and β2M levels predict shortened remission and survival (22).

Anemia is important as a prognostic factor in malignant lymphomas. Its presence is correlated with well-known prognostic factors related to patient and tumor (23). The pathogenesis of anemia in lymphoma is unclear. However, several mechanisms must be considered, such as auto-immune hemolysis, bone marrow involvement and the effects of inflammatory cytokines. Anemia in chronic disease is characterized by bone marrow erythroid hypoplasia, a shortened survival of erythrocytes, and deficient erythropoietin production for the hemoglobin level (24,25). Among patients with lymphomas, anemia may be associated with high inflammatory cytokine production by lymphoma or reactive cells. The inflammatory cytokines, such as interleukin (IL)-1, -6, -10 and tumor necrosis factor-α (TNF-α), reduce erythropoietin production and inhibit the response of erythroid progenitors to erythropoietin *in vitro* (26–29). Elevated TNF-α level is associated with anemia among lymphoma patients (30). On the other hand, hepcidin, an iron-regulated acute-phase protein that is composed of 25 amino acids, has helped to shed light on the relationship of the immune response to iron homeostasis and anemia of chronic disease. Hepcidin expression is induced by lipopolysaccharide and IL-6 (31).

A high serum β2M level is known to be an adverse prognostic factor in lymphoproliferative diseases, being directly related to malignant tumor burden (32), but it also keeps its

adverse prognostic role when other causes, such as renal dysfunction, are the origin of the raised levels. The β2M level is an independent prognostic value in aggressive non-Hodgkin's lymphomas (22,33–35).

A high level of sIL-2R before treatment is associated with tumor burden and poor prognosis among lymphoma patients (36–38). IL-2R is expressed on the cell membrane of lymphocytes and plays important roles in their activation and proliferation (39). A high serum sIL-2R level reflects elevated activity of T cells in the patient's cellular immunity. The serum sIL-2R level reflects the prognosis more obviously in patients with T-cell lymphoma than with B-cell lymphoma because both activated T- and lymphoma cells produce sIL-2R in T-cell lymphoma (40).

We demonstrated that an elevated CRP level, elevated LDH level and anemia were independent prognostic factors for OS among patients with recurrent or refractory aggressive malignant lymphoma. On the other hand, some inflammatory cytokines, such as IL-6 and TNF-α, are related with both anemia and CRP. In our analysis, there is no significant relationship between anemia and CRP because of the result of the correlation between anemia and CRP by Pearson's product–moment correlation coefficient ($P = 0.139$).

We analyzed prognostic factors between the LAC index and well-established prognostic factors such as disease status, interval from induction therapy to salvage treatment (11), international prognostic factor (14,15) and performance status. The LAC index was one of the independent and significant prognostic factors for OS. Moreover, the overall response rate and complete remission rate were significantly higher in the low-risk patients than that in the high-risk patients. The results of OS, overall response and complete remission rates were similar among the patients with both all aggressive lymphoma and diffuse large B-cell lymphoma. The result demonstrates that ICE or DHAP is very effective among the low-risk patients, and new strategies are necessary for the high-risk patients.

Finally, we applied the R-IPI at relapse and IPI at relapse in our patients. There was no significant difference in OS by the R-IPI at relapse and the IPI at relapse in our patients. This may have been due to the small number of patients in our model and the short follow-up time. However, we demonstrate that elevated CRP level, elevated LDH level, anemia and LAC index were strong predictors of poor outcome.

In conclusion, an elevated CRP level, elevated LDH level and anemia were predictive factors for poorer outcomes among patients with recurrent or refractory aggressive lymphoma treated with ICE or DHAP. We classified patients into two groups based on these three predictors, and there was a significant difference in OS among high- and low-risk patients with both all aggressive lymphomas and diffuse large B-cell lymphoma. High-risk by the LAC index was an independent prognostic factor for OS for patients with recurrent or relapsed aggressive lymphoma. However, our sample size is small, and larger scale research would increase our understanding of how best to treat these patients.

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Conflict of interest statement

None declared.

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Original Article

Platinum-based Chemotherapy Plus Cetuximab for the First-line Treatment of Japanese Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck: Results of a Phase II Trial

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Objective: To assess the efficacy and safety of cetuximab in combination with cisplatin and 5-fluorouracil for first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck.

Methods: In this open-label, single-arm, multicenter, Phase II study conducted in Japan, patients with confirmed recurrent and/or metastatic squamous cell carcinoma of the head and neck received weekly cetuximab (week 1, 400 mg/m^2; subsequent weeks, 250 mg/m^2) plus a maximum of six three-weekly cycles of cisplatin (100 mg/m^2, day 1) and 5-fluorouracil (1000 mg/m^2/day, 24-h infusion, days 1–4). The primary endpoint was the best overall response assessed by an independent review committee according to the modified World Health Organization criteria.

Results: In total, 33 patients received treatment. The most frequent primary tumor site was the hypopharynx (42%), and most patients had metastatic disease (85%). The best overall response rate as assessed by the independent review committee was 36% (95% confidence interval: 20, 55) and was significantly greater ($P = 0.002$) than the protocol-specified threshold of 15% at the one-sided 5% level. The disease control rate was 88%. The median progression-free survival and overall survival were 4.1 and 14.1 months, respectively. There were no unexpected safety concerns. Grade 3 or 4 adverse events were experienced by nearly all patients (32, 97%). No adverse events were fatal.

Conclusions: The demonstrated efficacy and safety of cetuximab in combination with cisplatin and 5-fluorouracil for the first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck justify the further use of this combination treatment in this patient population (ClinicalTrials.gov number, NCT00971932).

Key words: cetuximab – chemotherapy – head and neck – squamous cell carcinoma – Phase II trial

INTRODUCTION

Cancer of the head and neck [oral cavity, pharynx (excluding nasopharynx) and larynx] is estimated to represent around 4% of cancers, globally (1). In Japan in 2006, there were 16 351 patients (12 577 males and 3774 females) with oral/pharyngeal or laryngeal cancer, accounting for 2.5% of all cancer cases (2). A total of 7528 deaths due to oral/pharyngeal or laryngeal cancer occurred in Japan in 2009, representing 2.2% of annual cancer deaths (3). Tumors in Japanese patients are most frequently located in the oral cavity (36% of patients), larynx (25%), hypopharynx (16%) and oropharynx (12%); other sites are the nasal cavity/paranasal sinus (7%) and nasopharynx (4%) (4).

Epidermal growth factor receptor (EGFR) is frequently expressed in squamous cell carcinoma of the head and neck (SCCHN) (5–7). Cetuximab (Erbitux®, Merck KGaA, Darmstadt, Germany) is an EGFR-targeting monoclonal antibody which is widely used in the treatment of SCCHN in countries outside Japan.

In the Phase III EXTREME trial, conducted in Europe in patients with recurrent and/or metastatic SCCHN (R/M SCCHN), the addition of cetuximab to platinum/5-fluorouracil (5-FU) in the first-line setting significantly improved overall survival (OS), progression-free survival (PFS) and best overall response rate (ORR) compared with platinum/5-FU alone (8). The median OS time was 7.4 months in the chemotherapy-alone group compared with 10.1 months in the group that received chemotherapy plus cetuximab [hazard ratio for death, 0.80; 95% confidence interval (CI): 0.64, 0.99; $P = 0.04$]. The addition of cetuximab to chemotherapy also prolonged the median PFS time (from 3.3 to 5.6 months; hazard ratio for progression, 0.54, 95% CI: 0.43, 0.67; $P < 0.001$) and increased the best ORR (from 20 to 36%; odds ratio 2.33, 95% CI: 1.50, 3.60, $P < 0.001$). The use of cetuximab plus platinum/5-FU for the first-line treatment of R/M SCCHN is now recommended by a group of European cancer societies (9) and the USA-based National Comprehensive Cancer Network (NCCN) Practice Guidelines (10).

In Japan, cetuximab has not yet been approved for use in head and neck cancers. In other respects, however, the treatment options for R/M SCCHN are not substantially different from those in Europe and the USA. Cisplatin is the mainstay of treatment, and the combination of cisplatin and 5-FU is the most frequently used chemotherapy regimen (11). The dose of cisplatin used in combination with 5-FU at an interval of 3 or 4 weeks is commonly lower in Japan (cisplatin 75–100 mg/m^2 on day 1 plus 5-FU 600–1000 mg/m^2/day for 4–5 days) than in many Western countries (11,12), in keeping with observations from the treatment of different types of cancer, including head and neck cancers, that Japanese patients are generally not able to tolerate the doses of chemotherapy approved for use in Western patients (13,14). However, others have reported that the incidence of high-grade toxicity associated with standard doses of chemotherapy used in Western patients is not substantially higher in Japanese patients (15,16).

The use of cetuximab in combination with radiotherapy for patients with locally advanced SCCHN showed significant benefits over radiotherapy alone in a Phase III trial in Western patients (17), and the efficacy and safety of cetuximab plus radiotherapy has since been demonstrated in a Phase II trial in Japanese patients (18).

The primary objective of the current trial was to assess the antitumor activity of cetuximab when given in combination with cisplatin and 5-FU for the first-line treatment of R/M SCCHN in Japanese patients. Of note, cisplatin was used at a dose of 100 mg/m^2 in line with the dose used in the EXTREME trial. Secondary objectives included the assessment of safety, pharmacokinetic (PK) parameters, biomarkers, pharmacogenomics and the immunogenicity of cetuximab in Japanese patients. This paper reports the efficacy, safety and PK results.

PATIENTS AND METHODS

Patient eligibility criteria and treatment regimens were consistent with those used in the EXTREME trial (8).

Patient Selection

Japanese adults with histologically or cytologically confirmed R/M SCCHN, unsuitable for local therapy, with at least one bidimensionally measurable [computed tomography (CT) scan or magnetic resonance imaging (MRI)] lesion and confirmed expression of EGFR by immunohistochemistry (IHC) were eligible for entry to the trial. The exclusion criteria included nasopharyngeal carcinoma, prior systemic chemotherapy (except as part of multimodal therapy completed >6 months before the trial entry), surgery or irradiation within 4 weeks of trial entry, current or prior cardiac or pulmonary disease, high risk of uncontrolled arrhythmia or cardiac insufficiency and active infection. A written informed consent was provided by all patients taking part in the trial, and additional consent was provided by those also taking part in PK and biomarker analyses.

Trial Design

This was an open-label, single-arm, multicenter, Phase II trial conducted in Japan. Patients received weekly cetuximab (week 1, 400 mg/m^2; subsequent weeks, 250 mg/m^2) plus three-weekly cycles of cisplatin (100 mg/m^2, day 1) and 5-FU (1000 mg/m^2/day, 24-h infusion, day 1–4). Patients could switch to carboplatin (AUC5 on day 1 of each cycle) in the event of non-hematologic toxicities to cisplatin. All drugs were administered by intravenous infusion. Chemotherapy was continued for up to six cycles, or until unacceptable toxicity or progressive disease (PD). Patients received cetuximab until PD or unacceptable toxicity.

Response was assessed every 6 weeks until PD occurred, including in those patients who discontinued treatment before PD. Partial response (PR), complete response (CR) and PD were confirmed with CT or MRI within 4 weeks. Adverse events (AEs) were recorded from the start of treatment until the end of treatment (EOT) visit (30 days after the last trial treatment, or immediately prior to the initiation of any subsequent anticancer treatment). After the EOT visit, patients were followed up every 3 months until death, loss to follow-up or withdrawal of consent.

A PK investigation was carried out in patients enrolled at centers with PK sampling facilities. Blood samples were taken at the following times: days 1, 8 and 15, immediately before and after cetuximab infusion; day 22, directly before and at several time points (up to 168 h) after cetuximab infusion; days 36, 43 and 50, directly before the cetuximab infusion. Serum prepared from each blood sample was divided into two aliquots and stored at −20°C. Samples were analyzed by Celerion, Zurich, Switzerland, for concentrations of cetuximab using a validated enzyme-linked immunosorbent assay (ELISA). PK analysis was monitored and conducted under the supervision of the Institute of Drug Metabolism and Pharmacokinetics, Merck KGaA, Grafing, Germany. The PK parameters of cetuximab after the fourth dose (day 22) were calculated according to the standard non-compartmental methods using the PK software program KINETICA™, version 4.1.1.

Tumor EGFR expression was assessed by SRL medisearch, Tokyo, Japan, using the EGFR pharmDx™ kit (Dako Denmark A/S, Glostrup, Denmark) on archived tumor material or a biopsied specimen collected at the screening visit. EGFR-positive staining was defined as any IHC staining of tumor cell membranes above the background level, whether complete or incomplete circumferential staining. The tumor *KRAS* mutation status was assessed by Merck Serono Ivrea, Colleretto Giacosa (Turin), Italy, by pyrosequencing using the PyroMark Q24 system (developed by QIAGEN Manchester Ltd, Manchester, UK).

The trial protocol was approved by the institutional review boards of each center, and the trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP) (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, the standard stipulated in Articles 14–3 and 80–2 of the Japanese Pharmaceutical Affairs Law, and applicable regulatory requirements.

Endpoints

The primary endpoint was the best overall response (CR or PR) assessed by an independent review committee (IRC) according to the modified World Health Organization (WHO) criteria. The ORR was the proportion of patients with a CR or a PR. The best overall response according to Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.0) criteria was also assessed by the IRC as a secondary efficacy endpoint (19). Other secondary efficacy endpoints were: disease control rate (CR plus PR plus stable disease); duration of response (in patients achieving a CR or PR); time-to-treatment failure (PD assessed by the investigator, discontinuation of treatment due to PD or due to an AE, start of any new anticancer therapy or withdrawal of consent or death within 60 days of the last tumor assessment or first administration of trial treatment); PFS (time from the first administration of trial treatment to the first observation of PD, or death due to any cause when death occurred within 60 days of the last tumor assessment) and OS.

Adverse events were assessed by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE version 3.0). AEs considered to be of special interest in patients receiving cetuximab and based on Medical Dictionary for Regulatory Activities (MedDRA) preferred terms were also investigated: skin reactions and acne-like rash, infusion-related reactions (IRRs) and cardiac events.

Statistics

In the EXTREME trial, patients treated with chemotherapy plus cetuximab achieved a best ORR of 36% (95% CI: 29, 42) compared with 20% (95% CI: 15, 25) for those receiving chemotherapy alone (8). The lower confidence limit in the chemotherapy arm (15%) was considered to be the reference value for this trial, and an exact one-sided test (significance level $\alpha = 5\%$) was used to test the null hypothesis that the response rate was $<15\%$. Assuming a response rate of 35% (similar to that in the EXTREME trial), a patient sample size of 31 was required to achieve a power of $>80\%$.

Efficacy analyses were performed on the intention-to-treat (ITT)/safety population (all patients who received at least one dose of trial medication). Continuous variables were summarized using descriptive statistics; qualitative variables were summarized by means of counts and percentages. Unless otherwise stated, the calculation of proportions included the missing category and CIs were calculated as two-sided with a confidence probability of 95%.

All analyses were performed using SAS® Software version 9.1.

RESULTS

Patient Disposition

In total, 46 patients were enrolled at nine centers in Japan between 22 July 2009 and 3 September 2010. Of these patients, 35 were eligible for the trial and 33 were treated (ITT/safety population). Two patients were not treated due to worsening condition ($n = 1$) and creatinine clearance of <60 ml/min ($n = 1$). At the data cutoff of 14 December 2011, one patient remained on treatment.

Patient Baseline Characteristics

Patients were predominantly male (30, 91%), with good Karnofsky performance status (31, 94% had KPS 90–100), and mainly metastatic (including recurrent) cancer (28, 85%, Table 1). Almost one-third of patients were 65 years or older. All patients had EGFR-positive tumors. The most frequent primary tumor location was the hypopharynx. In one-third of patients ($n = 11$), tumors were reported as non-classifiable, but were specified as tongue ($n = 8$), and maxillary, hard palate and mandibular tumors ($n = 1$, each).

Most patients (30, 91%) had received prior therapy for cancer-related disease: surgery (28, 85%), radiotherapy (11, 33%), chemotherapy (11, 33%) and other types of therapy (10, 30%).

Table 1. Baseline patient and disease characteristics

Characteristic	($n = 33$)
Age (years)	
Median (range, years)	61 (31–71)
<65, *n* (%)	23 (70)
≥65, *n* (%)	10 (30)
Sex, *n* (%)	
Male	30 (91)
Female	3 (9)
Karnofsky performance status, *n* (%)	
100	17 (52)
90	14 (42)
80	2 (6)
Disease duration (from initial diagnosis to informed consent) (months), median (range)	14.3 (0–79)
Frequency of the extent of disease, *n* (%)	
Recurrent, not metastatic	5 (15)
Metastatic, including recurrent	28 (85)
Location of primary tumor, *n* (%)	
Hypopharynx	14 (42)
Larynx[a]	5 (15)
Oropharynx	3 (9)
Non-classifiable[b]	11 (33)
Histology	
Well differentiated	4 (12)
Moderately differentiated	13 (39)
Poorly differentiated	4 (12)
None otherwise specified/unknown/missing	12 (36)
Stage according to UICC at diagnosis, *n* (%)	
Stage I	3 (9)
Stage II	2 (6)
Stage III	4 (12)
Stage IV	24 (73)

UICC, Union for International Cancer Control.
[a]The tumor in one patient was 'non-classifiable' but was specified as 'larynx' and was therefore analyzed as such.
[b]The location of the primary tumor was non-classifiable, but was specified as tongue ($n = 8$), and maxillary, hard palate and mandibular ($n = 1$, each).

Treatment Exposure

All 33 patients received at least one dose of cetuximab, and 29 (88%) patients received cetuximab at a relative dose intensity (RDI) of ≥80%. The median duration of cetuximab treatment was 19 (range 1−98) weeks, the median number of infusions was 18 (range 1–91) and the median cumulative dose was 4650 (range 166–16 877) mg/m^2. In total, 21 (64%) patients received at least one dose of cetuximab monotherapy.

Thirty-two patients (97%) received at least one dose of cisplatin. The median duration of therapy was 11.3 (range 3–23) weeks, and the median cumulative dose was 300 (range 100–600) mg/m^2. RDI was ≥80% in 21 (66%) patients. Seven (21%) patients received two or more doses of carboplatin. The median duration of therapy was 12 (range 6–18) weeks, and the median cumulative dose was 1264 (range 676–2257) mg. Most patients, 32 (97%), received at least one dose of 5-FU. The median duration of therapy was 18.5 (range 3–23) weeks, and the median cumulative dose was 20 000 (range 4000–24 000) mg/m^2. RDI was ≥80% in 19 (59%) patients.

Twenty-seven (82%) patients received post-trial anticancer therapy, comprising chemotherapy (23, 70%), radiotherapy (9, 27%), surgery (2, 6%), immunotherapy (1, 3%) and/or other forms of treatment (2, 6%).

Table 2. Tumor response results

	Response rates, $n = 33$	
Characteristic, *n* (%)	Modified WHO criteria[a]	RECIST criteria[a]
ORR	12 (36)[b]	15 (45)
[95% CI][c]	[20, 55]	[28, 64]
Best overall response		
CR	1 (3)	1 (3)
PR	11 (33)	14 (42)
SD	17 (52)	14 (42)
PD	1 (3)	1 (3)
Not evaluable	3 (9)	3 (9)

CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; WHO, World Health Organization.
[a]Assessed by an Independent Review Committee.
[b]$P = 0.002$ vs. the protocol-specified 15% threshold.
[c]Two-sided Clopper–Pearson.

Efficacy

The best ORR assessed by the IRC according to the modified WHO criteria (primary endpoint) was 36% (95% CI: 20, 55) (Table 2), with a CR in one patient. The ORR was significantly greater than the protocol-specified threshold of 15% ($P = 0.002$). The best ORR assessed by the IRC according to RECIST was 45%, with a CR in one patient (Table 2): three patients with stable disease (SD) according to modified WHO criteria were considered to have a PR according to RECIST.

The median PFS was 4.1 (95% CI: 4.0, 5.5) months (Fig. 1a). The PFS rate was 70% (95% CI: 53, 86) at 3 months and 23% (95% CI: 7, 39) at 6 months. The median OS was 14.1 (95% CI: 10.2, 15.4) months (Fig. 1b). At last follow-up, 24 patients had died due to PD. The OS rates at 3, 6, 9 and 12 months were 100, 85 (95% CI: 73, 97), 67 (95% CI: 51, 83) and 61% (95% CI: 44, 77), respectively. The disease control rate was 88%. The median duration of response (first assessment of CR or PR until PD) was 2.8 (95% CI: 2.8, 5.5), with a median time-to-treatment failure of 4.2 (95% CI: 4.1, 5.6) months.

Safety

The most common AEs reported were decreased appetite (91%), leukopenia (85%), hypomagnesemia (82%), neutropenia (82%) and stomatitis (79%). Grade 3–4 AEs were reported in 32 (97%) patients, and grade 4 events were reported in 21 (64%) patients. Treatment-related grade 3–4 AEs were reported in 32 (97%) patients. Cetuximab-related grade 3–4 AEs were experienced by 20 (61%) patients, and the most frequent of these (≥10% patients) were diarrhea,

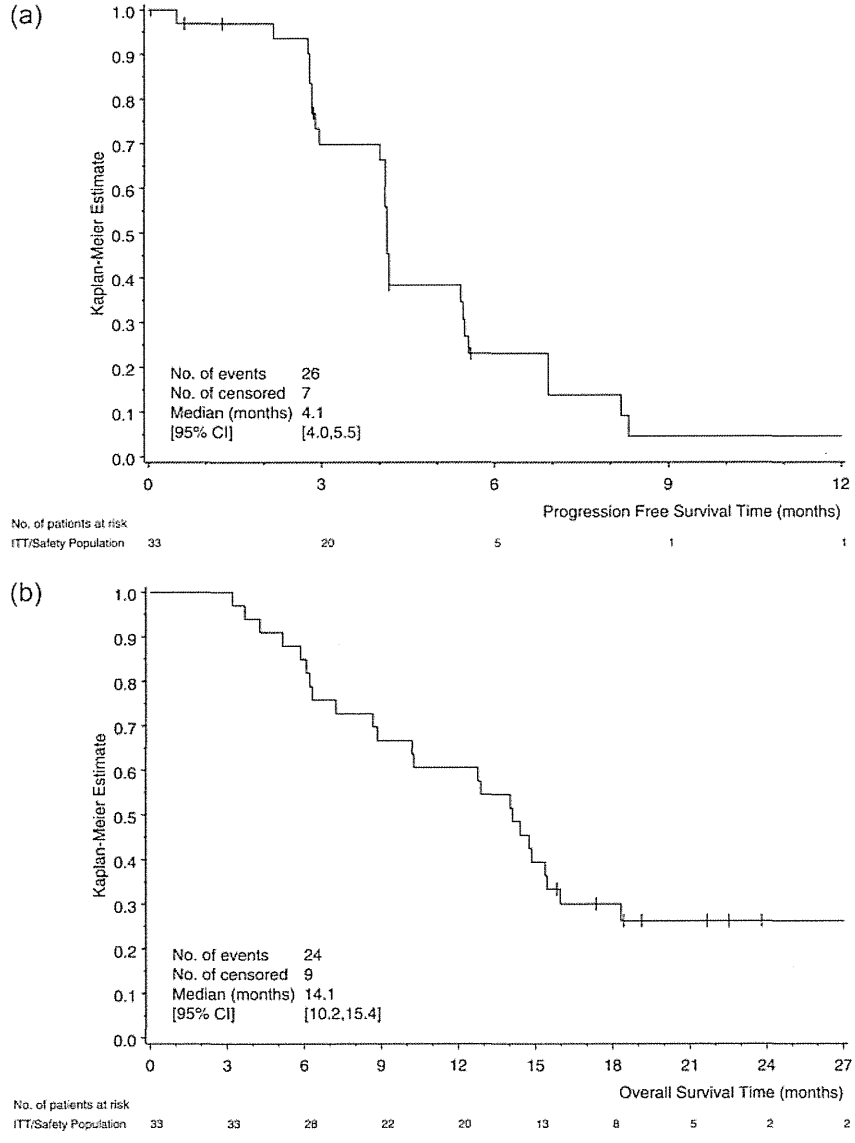

Figure 1. Kaplan–Meier estimates of (a) progression-free survival and (b) overall survival. CI, confidence interval.

hypomagnesemia and neutropenia, each occurring in four (12%) patients. The most common grade 3–4 AEs reported (total and cetuximab-related) are displayed in Table 3.

Among AEs considered to be of special interest, skin reactions and acne-like rash were each reported in 32 (97%) patients. Grade 3 skin reactions were reported in five (15%) patients, and grade 3 acne-like rash in four (12%) patients. There were no grade 4 events. Only two patients experienced an IRR: hot flush (grade 1) and chills and tremor (grade 3); each resolved within the same day. There were seven cardiac events: six grade 1 and one grade 2 event.

Twelve patients experienced serious AEs (SAEs), nine of which were related to treatment: diarrhea, dysphagia, staphylococcal sepsis, septic shock, syncope, intracardiac mass, esophageal fistula, increased C-reactive protein, dehydration, hypercreatininemia and decreased appetite. No AEs were fatal.

Eighteen (55%) patients permanently discontinued either cetuximab or chemotherapy as a result of AEs. The most frequent AEs (occurring in >5% of patients) leading to permanent discontinuation of chemotherapy were toxic nephropathy and neutropenia (three patients, 9% each), and thrombocytopenia (two patients, 6%). Four (12%) patients had AEs leading to permanent discontinuation of cetuximab (hypomagnesemia, IRR, esophageal fistula and septic shock, each in one patient).

Table 3. Most common grade 3–4 adverse events

AE, *n* (%)	All *n* = 33	Cetuximab-related *n* = 33
Any	32 (97)	20 (61)
Neutropenia	21 (64)	4 (12)
Leukopenia	17 (52)	2 (6)
Anemia/hemoglobin decreased	11 (33)	3 (9)
Decreased appetite	7 (21)	0
Lymphopenia	6 (18)	1 (3)
Thrombocytopenia	6 (18)	1 (3)
Diarrhea	5 (15)	4 (12)
Hypomagnesemia	5 (15)	4 (12)
Fatigue	4 (12)	0
Hypokalemia	4 (12)	1 (3)
Hyponatremia	3 (9)	1 (3)
Nausea	3 (9)	0
Syncope	3 (9)	2 (6)
Dermatitis acneiform	2 (6)	2 (6)
Hyperkalemia	2 (6)	2 (6)

Pharmacokinetics

Cetuximab PK parameters were investigated in 12 patients with available samples. All serum cetuximab concentrations after dosing on day 22 were above the lower limit of quantification (0.25 μg/ml) of the bioanalytical assay (Fig. 2). The mean trough concentrations of cetuximab reached around 70 μg/ml after day 36 (Fig. 3). The mean concentration time profile and derived PK parameters were in good agreement with those described previously in Japanese patients receiving cetuximab monotherapy (20).

Tumor *Kras* Mutation Status

Twenty-one patients gave consent for further tumor biomarker testing. Of these, 15 had tumor samples that were evaluable. All 15 patients had *KRAS* wild-type tumors.

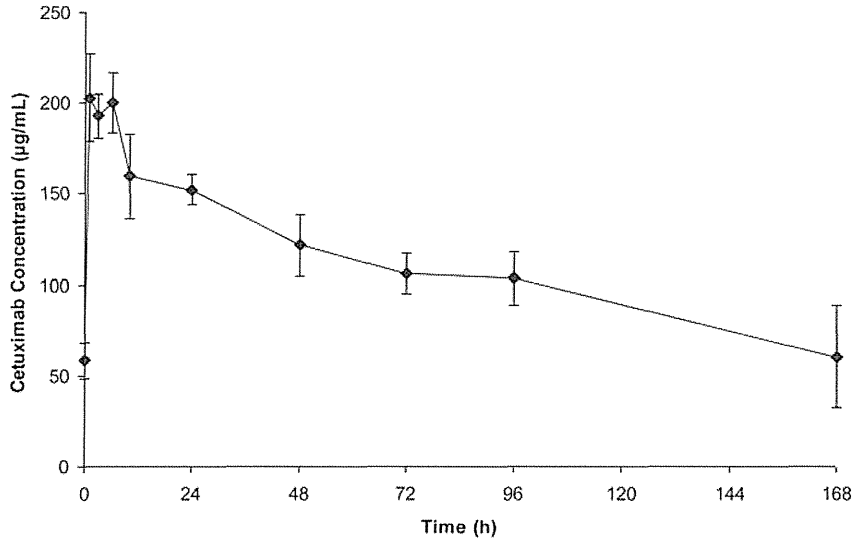

Figure 2. Serum cetuximab concentrations after a dose of 250 mg/m^2 on day 22. Linear plot. Points are mean ± standard deviation.

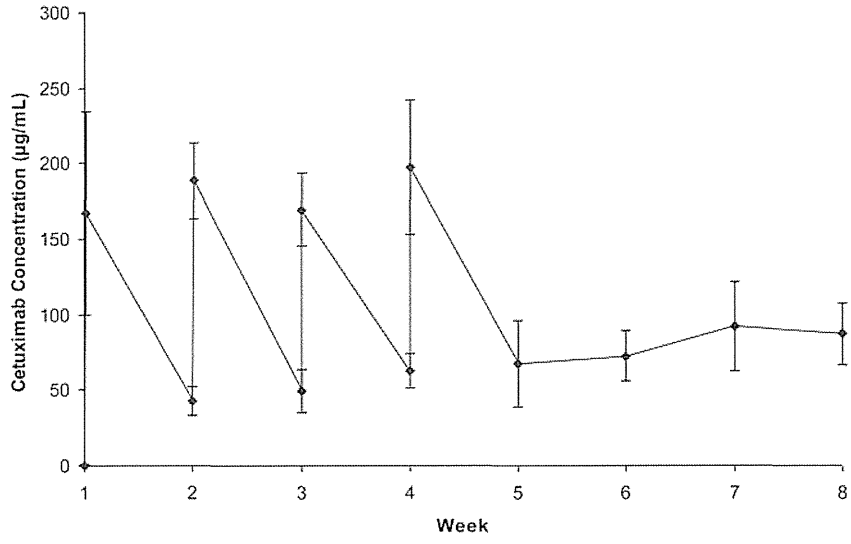

Figure 3. Serum cetuximab peak and trough concentrations.

DISCUSSION

Data from this open-label, multicenter, Phase II trial demonstrated that the combination of platinum-based chemotherapy with cisplatin administered at a dose of 100 mg/m^2, and cetuximab as the first-line treatment for R/M SCCHN was effective and well tolerated in Japanese patients. Furthermore, the efficacy and safety results obtained in the present trial were similar to those obtained in the Phase III EXTREME trial in a Western population (8).

The best ORR achieved (36% assessed by IRC according to modified WHO criteria) was significantly higher than the protocol-specified 15% at the one-sided 5% level, thereby meeting the primary endpoint of the trial. The ORR was equal to that observed for the chemotherapy plus cetuximab arm in the reference EXTREME trial (36%) (8).

The secondary endpoints further supported the efficacy of the combination of chemotherapy and cetuximab in this Japanese patient population. The median OS (14.1 months) was longer than that reported for the platinum/5-FU/cetuximab arm of the EXTREME trial (10.1 months) (8). This may be due to the small number of patients in our trial. In addition, an influence on OS of post-trial anticancer treatment cannot be discounted. The number of patients who received anticancer treatment after the completion of the present trial was higher than in the platinum/5-FU/cetuximab arm of the EXTREME trial [27 patients (82%) vs. 91 patients (41%)]. The apparently shorter median PFS in this trial, compared with the EXTREME trial, is probably due to the small population size. However, given that the 95% CIs of the median PFS in the two trials are overlapping, it may be suggested that the PFS in our trial is similar to that in the platinum/5-FU/cetuximab arm of the EXTREME trial.

In colorectal cancer, the benefits of cetuximab are restricted to patients with *KRAS* wt tumors (21,22). All patients in this trial whose tumors were tested for *KRAS* mutation status had *KRAS* wt tumors, as would be expected, given the low rate of *KRAS* mutations reported previously in head and neck cancers (23–25).

The efficacy reported here is particularly encouraging, given that the patient population in the present trial was older than that in the chemotherapy plus cetuximab arm of the EXTREME trial (30% ≥65 years compared with 18%) and had characteristics indicative of a poorer prognosis, including a higher proportion of patients with recurrent and metastatic primary tumors (85 vs. 47%) and localization of the primary tumor in the hypopharynx (42 vs. 13%). It is also notable that this efficacy was achieved despite dose modifications in platinum therapy made for the management of adverse events, which led to patient exposure to platinum being lower than in the EXTREME trial. For example, 89% of patients in the chemotherapy plus cetuximab arm of the EXTREME trial received ≥80% of RDI of cisplatin compared with 66% of patients in this trial.

The AEs observed in this trial are consistent with the underlying disease, administration of chemotherapy and the known safety profile of cetuximab. No new safety findings were identified in this trial. The overall safety profile observed in the present trial was also similar to that observed in the chemotherapy plus cetuximab arm in the EXTREME trial (8), and it is notable that no AEs had a fatal outcome. However, the incidence of a number of grade 3–4 AEs was higher compared with the EXTREME trial, notably neutropenia, leukopenia, decreased appetite (anorexia) and hypomagnesemia. This might be explained by the poor tolerability of cytotoxic chemotherapy reported for Japanese patients that has been documented previously (13). However, it may also reflect the poorer prognosis of the patient population in the present trial, as discussed briefly in the previous paragraph. The AEs concerned were mostly those known to be chemotherapy related and were manageable by dose adjustments or switches from cisplatin to carboplatin.

In conclusion, the demonstrated efficacy of platinum-based chemotherapy plus cetuximab in Japanese patients with R/M SCCHN, together with a predictable safety profile and PK, justifies the further use of this combination treatment in this patient population.

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Conflict of interest statement

Takayuki Yoshino received honoraria from Chugai, Takeda, Bristol-Myers Squibb, Yakult and Merck Serono, a research grant from Bayer, Taiho, Daiichi-Sankyo and ImClone and consulting fees from Takeda. Makoto Tahara received consulting fees from Merck Serono. Barbara de Blas and Frank Beier are employees of Merck KGaA, Darmstadt, Germany. The other authors declare no conflicts of interest.

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APPENDIX

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IV 乳癌の浸潤・転移

乳癌骨転移の臨床的特徴

Clinical characteristics of bone metastases of breast cancer

高橋俊二

Key words：乳癌，骨転移，ビスホスホネート，RANKL，デノスマブ

はじめに

近年，癌発症率の増加や治療の向上による予後延長に伴い，骨転移の有病率が増加している．特に，進行性の乳癌では65–75％もの高い割合で骨転移が認められる[1]．骨に転移した癌は，生命予後に大きな影響を及ぼさないが，激しい痛みや，病的骨折，脊髄圧迫による麻痺症状，高カルシウム血症，手術などの骨合併症(skeletal-related events: SRE)により患者のQOLが著しく低下し，更には死亡リスクが上昇する場合もある[2]．

ビスホスホネート，抗receptor activator of NFκB ligand(RANKL)抗体デノスマブなどの骨特異的薬剤の開発が進行しており，本稿では薬物治療以外の放射線科的処置，整形外科的処置，interventional radiology(IVR)などとあわせて紹介する．

1 乳癌骨転移の特徴

乳癌における主な遠隔転移部位として肺，肝，骨があげられるが，なかでも骨転移の頻度が高いことが示されている．2000–08年までにがん研化学療法科で治療した進行再発乳癌患者528例の中で，治療開始時に骨転移を認めた患者が

表1 進行再発乳癌の転移部位(がん研化学療法科，2000–08)

		全体	原発進行	再発
患者数		528	128	400
治療開始時の病巣	軟部組織	229(43.4％)	46(35.9％)	183(45.8％)
	骨	263(49.8％)	81(63.3％)	182(45.5％)
	肝	119(22.5％)	40(31.3％)	79(19.8％)
	肺	191(36.2％)	46(35.9％)	145(36.3％)
	脳	8(1.5％)	2(1.6％)	6(1.5％)
	その他	105(19.8％)	20(15.6％)	85(21.3％)
	骨のみ	78(14.8％)	—	77(19.3％)
治療開始時転移臓器の数	1	268(50.8％)	64(50％)	204(51％)
	2	160(30.3％)	32(25％)	128(32％)
	3以上	100(18.9％)	32(25％)	68(17％)

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表2 乳癌骨転移に伴う合併症
(がん研, 1995-98, n=256)

骨 痛	77.5%	骨関連事象(skeletal-related events: SRE) 1-2/人・年
骨 折	39.2%	
神経麻痺	9.8%	
(高カルシウム血症	40.9%)	
骨へのX線照射	60.6%	
骨の手術	1.2%	

49.8%，骨のみの転移であった患者が14.8%であった(表1)[3]．また，乳癌は，腰椎，胸椎，頸椎などの椎骨や，骨盤，肋骨，頭蓋骨，上腕骨，大腿骨などに高い頻度で転移することが示されている．

乳癌の骨転移は高頻度に骨合併症を伴う．がん研化学療法科において1990年代に乳癌骨転移患者256例を1,184日間追跡して調査したところ[4]，骨痛が77.5%，病的骨折が39.2%，麻痺が9.8%，高カルシウム血症が40.9%，骨に対する放射線治療が60.6%の発現率であった(表2)．骨転移は，それ自体が致命的となることは少ないものの，上記の骨合併症によるQOLの低下につながるため，骨転移の発現・進行をいかに防ぐかが重要である．

2 骨転移の機序

骨では，不要な骨を破壊(骨吸収)する破骨細胞と，新しく骨を形成(骨形成)する骨芽細胞が密接に連携して，骨吸収から骨形成の一連の新陳代謝が繰り返し行われている．生理的状況下では，骨破壊と骨吸収のバランスが一定に保たれている．

しかしながら，骨に転移した癌細胞が骨髄に侵入してくると，骨破壊と骨吸収とのバランスが崩れることで骨病変が進行する．癌細胞は副甲状腺ホルモン関連タンパク(parathyroid hormone-related protein: PTHrP)や様々なサイトカインを産生し，骨芽細胞上のRANKLの発現を促進させる．また，RANKLを発現する癌細胞があることが報告されている．RANKLは破骨細胞前駆細胞/破骨細胞上のRANKと結合し，破骨細胞の形成促進・活性化により骨吸収を亢進させる．すると骨から各種増殖因子が放出され，腫瘍細胞の更なる増殖や活性亢進が進行する．このように，癌細胞と癌細胞の転移した骨との間には'悪循環'が成立している(図1)[5]．

がんの骨転移では，破骨細胞による骨吸収が骨転移の成立および進展に重要な役割を果たしており，破骨細胞の機能を抑制することが骨転移の重要な治療戦略として確立されつつある．

3 骨転移の治療の現状

骨転移においては骨合併症を減らして患者のQOLを改善させることが治療の主要な目的となる．適切な薬物療法により骨合併症を減少させること，また疼痛を適切な鎮痛剤の使用によりコントロールすることが重要であるとともに，病的骨折の危険がある部位や神経圧迫による麻痺に対して早期に放射線科的・整形外科的処置などを行うことが必要である．

1) 骨転移の放射線科的治療

骨転移に対する放射線療法は痛みの軽減と病的骨折の予防，麻痺の予防または治療を目的とする．放射線療法は骨痛を軽減する手段として有効性が最も高い(70-80%)．また8-10Gy 1回照射と30Gy 5-10回照射とで疼痛軽減率は変わらず，病的骨折は1回照射で増大するとの報告と不変との報告がある[6]．

最近，有痛性の椎体転移に対してX線・CT下に骨セメントを椎体に注入する経皮的椎体形成術(percutaneous vertebroplasty: PVP)が行われ，50-95%に良好な疼痛コントロールが報告されている[7]．

2) 骨転移の外科療法

長管骨の骨折時にはもちろん整形外科的処置が必要であるが，骨皮質の50%以上の破壊あり・加重時の痛み・大腿骨頸部や上腕骨頸部など荷重のかかる部位などでは骨折予防目的で手術を行う場合がある．椎体骨の手術は神経麻痺，椎体の不安定性とそれによる痛みなどが適応になる．脊髄圧迫の場合，除圧手術を行った方が放射線照射単独より麻痺の改善率が高いとさ

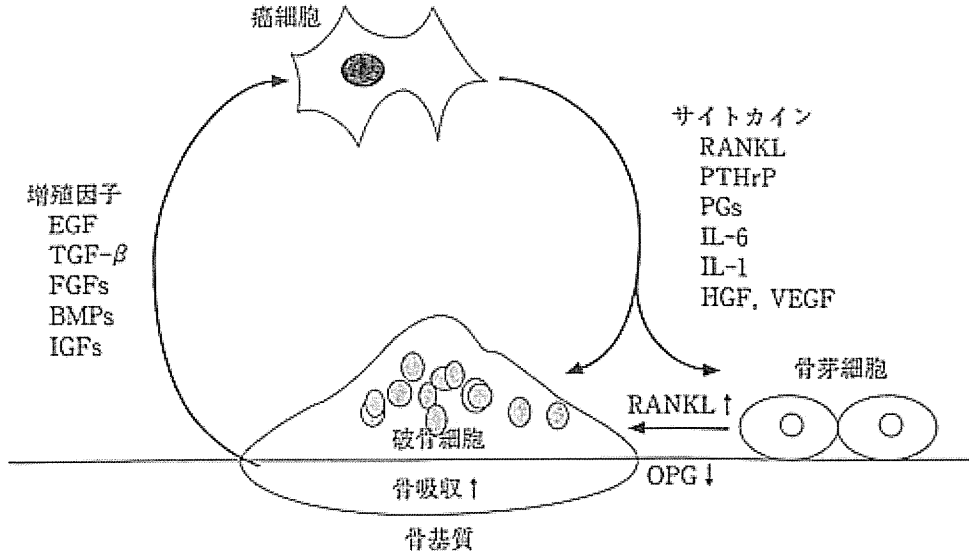

図1 骨転移における癌細胞と骨芽細胞・破骨細胞の相互作用

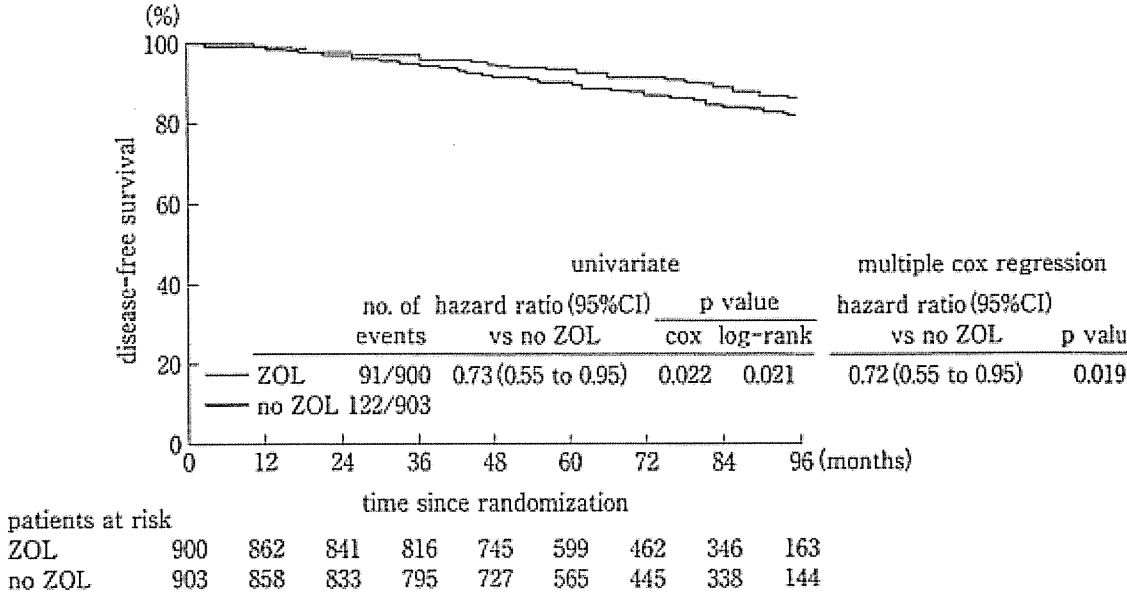

図2 ABCSG-12試験

ゾレドロン酸＋内分泌療法は内分泌療法単独に比して有意に無病生存期間を改善した.

れる.

3）骨転移の薬物療法

骨転移に対しては通常の進行癌の治療と同様に化学療法，内分泌療法を行うが，骨転移に特異的な治療法としてビスホスホネート(bisphosphonates: BP)による抗破骨細胞療法，骨に集中するラジオアイソトープ(^{89}Sr)が用いられている.

a. BPによる骨転移の治療

BPはピロリン酸の類似体で，強力な破骨細胞抑制効果をもつ．BPは骨転移による疼痛に対する緩和的治療として有効であり，また単独治療でも放射線学的な効果が認められている．現在最も活性の高いゾレドロン酸4mg静注投与3-4週ごとは，乳癌骨転移のSREを40％減少させた[8]．骨転移患者の生存期間の改善については明らかなエビデンスはないが，乳癌患者におけるBPの再発予防効果についてはABCSG-12試験において，閉経前乳癌術後患者にホルモン療法にゾレドロン酸(4mg静注投与6カ月

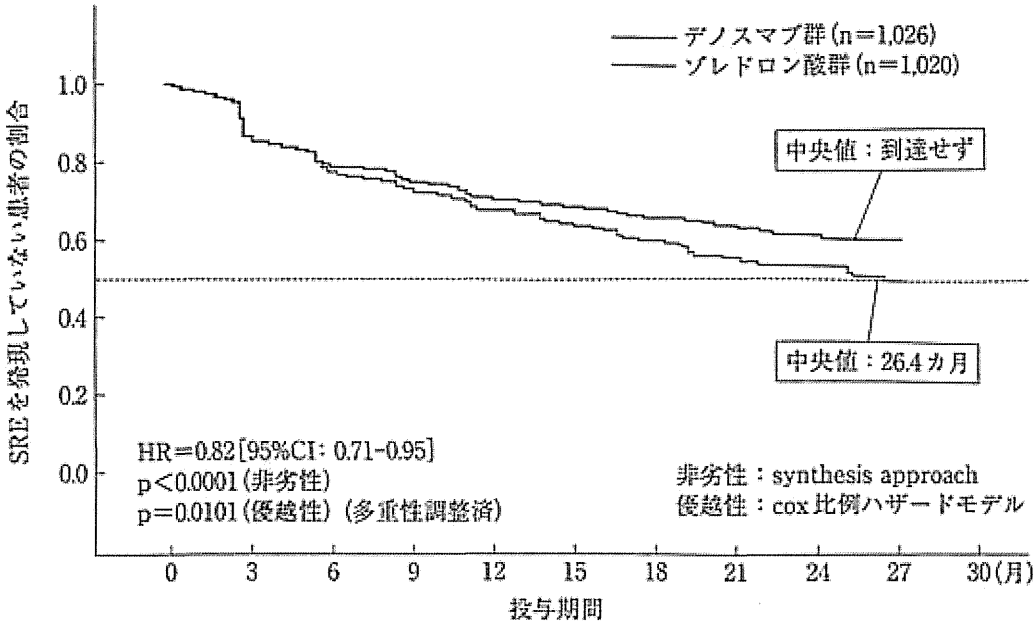

図3 乳癌骨転移患者におけるデノスマブとゾレドロン酸の比較試験
(文献[9]より引用)

ごと)を併用することにより，骨転移のみでなく局所も含めた再発を予防できると報告された(図2)[9]．ほかにもBPを用いた術後補助療法についての大規模試験が行われている．AZURE試験は，Stage II-IIIの乳癌術後患者3,360例を標準的な補助療法を行う群とゾレドロン酸4 mg静注を3-4週ごと6回，3カ月ごと8回，6カ月ごと5回の計5年投与を標準治療に加える群とを比較した．全症例の無病生存期間はhazard ratio(HR) 0.98で全く変わらず，局所再発，遠隔転移，骨転移ともに有意な差はなかったが，閉経後5年以上の患者ではHR 0.76で有意に再発が減少していた．全生存期間はゾレドロン酸がHR 0.85と良い傾向があった(p=0.07)[10]．

BPの副作用としては，特に歯科処置の既往がある患者に長期(1-2年以上)BPを使用したときの顎骨の骨壊死が報告されている．患者の歯科治療必要性の有無を確認するとともに，口腔内の状態を注意深く観察し，口腔内を清潔に保つような指導が必要である[11]．

b. ストロンチウム(^{89}Sr)

骨転移部に集中して取り込まれるラジオアイソトープで，有痛性の骨転移患者の約80％に効果がみられ，1回の注射で6-12カ月間有効とされている．また，BPとの併用により単独治療よりも疼痛コントロールが改善する[12]．

4 新規薬剤

1) 抗RANKL抗体(デノスマブ)

デノスマブは，RANKLに対するヒト型モノクローナル抗体で，RANKLの作用を特異的に阻害し，破骨細胞の骨吸収機能を低下させ，骨転移における癌細胞増殖と骨破壊の悪循環を断ち切り，骨破壊を抑制する．骨転移を有する進行乳癌患者に対するデノスマブ(120 mg皮下注，4週ごと)とゾレドロン酸(4 mg静注，4週ごと)を直接比較したランダム化二重盲検第III相比較試験が136人の日本人被験者を含めて行われた[13]．デノスマブはゾレドロン酸に比べ，SREの初回発現リスクを有意に18％低下させた(p=0.01)(図3)．全生存期間と病勢進行については，両群間で同等の結果を示した．有害事象については，顎骨壊死はデノスマブ群で2.0％，ゾレドロン酸群で1.4％であり，統計学的な有意差はなかった(p=0.39)．腎毒性と関連する可能性のある有害事象の発現率は，デノスマブ群(4.9％)と比較して，ゾレドロン酸群(8.5％)

で高かった(p=0.001).

2) SRC阻害剤

SRCは最も早く分離された癌遺伝子の一つであるが, SRCノックアウトマウスの最も明らかな特徴は骨大理石症であり, SRCは破骨細胞の機能に必須である. 更に癌細胞におけるSRC発現は浸潤・運動能の亢進, EMT(epithelial to mesenchymal transition), VEGF発現などに関与し, また骨転移能が高まるとされている. したがってSRC阻害剤は悪性骨病変に対する治療薬としても期待され, 骨転移患者を対象としたSRC阻害剤の開発が進んでいる. 日本でも固形癌におけるdasatinibの第I相試験が行われ, 骨吸収マーカー低下を認めている[14].

3) c-MET阻害剤

乳癌も含めた多くのがんでhepatocyte growth factor(HGF)-c-METシグナルが増強していることが知られており, 腫瘍細胞の浸潤, 転移, 血管新生などにかかわっていると考えられている. HGF-c-METシグナルの骨における意義はあまり確立していないが, 破骨細胞-骨芽細胞のカップリング因子の一つであり, また骨転移を促進する可能性があるとの報告がある[15]. 最近, VEGFRおよびc-MET阻害剤であるcabozantinibが骨転移に有効であり, 特に骨シンチ所見が早期に改善すると報告された[16]. 機序の詳細は明らかでないが, 最近別のc-MET阻害剤が乳癌骨転移モデルにおいておそらく腫瘍細胞-骨芽細胞の相互作用を抑制することにより骨転移の進行を抑えるとの報告があり[17], 注目されている.

おわりに

骨転移治療は, 1990年代に明らかになってきた破骨細胞形成をはじめとする基礎科学的知見と, BP製剤による破骨細胞を標的とした治療の進展によって飛躍的に発展した. それに加えて, 破骨細胞の分化, 活性化, 生存に対するRANKLの意義が明らかになり, 抗RANKL抗体による新しい治療戦略が生まれ, 更に新たな薬剤が注目されている. 今後も骨特異的な治療薬の進歩と局所的な治療(照射, IVR, 手術)の発展が相まって骨転移のコントロールは進むことが期待される.

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≪肺癌診療にまつわるトータルサポート――治療とケア≫
オンコロジーエマージェンシー

高橋俊二*

要旨

- 悪性腫瘍の経過中で全身状態の悪化を急速にきたし，緊急な治療を必要とする場合をオンコロジーエマージェンシーという．
- これらの病態を理解・診断し，迅速に対応することは臨床腫瘍医にとって重要な資質の一つである．
- オンコロジーエマージェンシーの機序として，①代謝障害(高 Ca 血症，腫瘍崩壊症候群(TLS)，低 Na 血症など)，②構造的障害(頭蓋内圧亢進，脊髄圧迫，心嚢水貯留，上大静脈症候群など)があげられる．
- オンコロジーエマージェンシーを正しく迅速に診断し，放射線科医，外科医などと協力しながら的確な治療を行う．

オンコロジーエマージェンシーとは悪性腫瘍のために緊急な対応が必要となる症状の総称であり，Table 1 のような事態が列挙される．内科的治療で対応できるものと外科的・放射線的治療が必要なものとがあり，本稿では肺癌でよくみられ，内科的・薬剤治療で対処する事態を中心に紹介する．

代謝障害○

1．高 Ca 血症

1）病態，症状：悪性腫瘍による高 Ca 血症の機序としては，腫瘍から分泌される副甲状腺ホルモン関連蛋白(parathyroid hormone-related protein：PTHrP)による腫瘍随伴体液性高 Ca 血症(humoral hypercalcemia of malignancy：HHM，扁平上皮癌で多い)と，広範な骨転移に伴う局所性骨溶解性高 Ca 血症(local osteolytic hypercalcemia)に分類される．一般に HHM のほうが治療抵抗性である．

2）治　療

a）細胞外液の補充と利尿：高 Ca 血症は食欲不振と利尿をきたし，脱水状態とそれによる腎機能不全を伴い，これがさらに高 Ca 血症を悪化させるという vicious cycle に入っていることが多い．したがって，輸液により細胞外液を補充し，尿への Ca 排泄を促進することが重要である．なお，乳酸 Ringer 液，高カロリー輸液製剤の多くは大量の Ca を含んでいること，またサイアザイド

キーワード：オンコロジーエマージェンシー，高 Ca 血症．

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Table 1. オンコロジーエマージェンシー

1．代謝性(metabolic)
- 悪性高 Ca 血症(hypercalcemia of malignancy：HCM)
- 腫瘍崩壊症候群(tumor lysis syndrome：TLS)
- 低 Na 血症(hyponatremia)

2．構造性(structural)
- 神経系：頭蓋内圧亢進(intracranial hypertension)，脊髄圧迫(spinal cord compression)
- 心血管系：上大静脈症候群(superior vena cava (SVC) syndrome)，心嚢水貯留(心タンポナーデ)(pericardial effusion (cardiac tamponade))
- 呼吸器系：気道閉塞(airway obstruction)，血胸(haemothorax)
- 消化器系：腸閉塞(ileus)，穿孔(perforation)，出血(bleeding)
- 泌尿器系：水腎症(hydronephrosis)

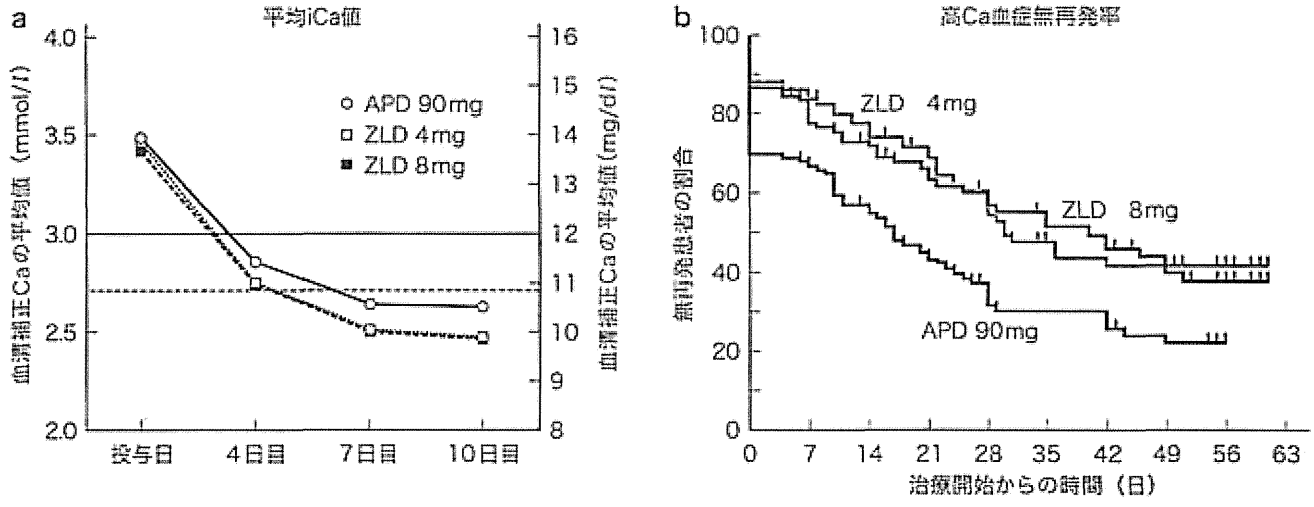

Fig. 1. 高 Ca 血症に対する zoledronic acid(ZLD)と pamidronate(APD)の比較試験
[Major P et al：J Clin Oncol 19(2)：558, 2001 より引用，改変]

系利尿薬は Ca 排泄を抑制することに注意が必要である．

b）ビスホスホネート製剤：強力な破骨細胞抑制効果をもち，また副作用が少ない．現在はもっとも効力の高い zoledronic acid が使われている(Fig. 1)．zoledronic acid は 4 mg を生理食塩水，または 5% glucose 500 m*l* に溶解し，15 分で点滴する．血清 Ca は 2 日後から低下し始め，6～10 日で最低となる．副作用としては，発熱・感冒様症状を 10～20% に認めるが，とくに処置が必要な場合はまれである．最近は zoledronic acid または抗 RANKL 抗体(denosumab)が骨転移の合併症(骨関連事象)を減少させる目的で使用され，骨転移に伴う高 Ca 血症の頻度は明らかに減少している．

c）カルシトニン製剤：生理的な骨吸収抑制ホルモンであり，Ca 利尿作用もある．副作用がほとんどなく，また数時間で効果があるが 2～3 日で不応性となる．急速に Ca を低下させる必要がある緊急時にはビスホスホネート製剤と併用される．elcatonin 40 単位を生理食塩水 50 m*l* で点滴静注，または筋注で 1 日 2 回投与する．

d）ステロイド：血液腫瘍による高 Ca 血症に有用で，通常 prednisolone 20～50 mg/day の経口投与，または点滴静注を行う．