| 副作用名 | 特定使用成績調査 | | | | 国内第Ⅱ相臨床試験 | | | |
|---|---|---|---|---|---|---|---|---|
| | 副作用 | | 重篤な副作用 | | 副作用 | | 重篤な副作用 | |
| | 例数 | 発現症例率 | 例数 | 発現症例率 | 例数 | 発現症例率 | 例数 | 発現症例率 |
| ヘモグロビン増加 | 0 | — | 0 | — | 1 | 0.76% | 0 | — |
| 心拍数増加 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| ＩＮＲ減少 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 眼圧上昇 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| ロイシンアミノペプチダーゼ上昇 | 1 | 0.04% | 1 | 0.04% | 0 | — | 0 | — |
| リパーゼ増加 | 322 | 13.38% | 11 | 0.46% | 73 | 55.73% | 2 | 1.53% |
| 肝機能検査異常 | 2 | 0.08% | 1 | 0.04% | 0 | — | 0 | — |
| リンパ球数減少 | 15 | 0.62% | 4 | 0.17% | 7 | 5.34% | 0 | — |
| リンパ球数増加 | 3 | 0.12% | 0 | — | 0 | — | 0 | — |
| 好中球数減少 | 8 | 0.33% | 3 | 0.12% | 2 | 1.53% | 0 | — |
| 好中球数増加 | 3 | 0.12% | 2 | 0.08% | 0 | — | 0 | — |
| 血小板数減少 | 134 | 5.57% | 41 | 1.70% | 3 | 2.29% | 2 | 1.53% |
| 総蛋白減少 | 2 | 0.08% | 1 | 0.04% | 0 | — | 0 | — |
| 総蛋白増加 | 6 | 0.25% | 0 | — | 0 | — | 0 | — |
| 尿蛋白 | 10 | 0.42% | 0 | — | 0 | — | 0 | — |
| プロトロンビン量増加 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| プロトロンビン時間延長 | 3 | 0.12% | 0 | — | 2 | 1.53% | 1 | 0.76% |
| 赤血球数減少 | 3 | 0.12% | 0 | — | 1 | 0.76% | 0 | — |
| 赤血球数増加 | 2 | 0.08% | 0 | — | 1 | 0.76% | 0 | — |
| トリヨードチロニン減少 | 2 | 0.08% | 0 | — | 0 | — | 0 | — |
| 体重減少 | 12 | 0.50% | 1 | 0.04% | 13 | 9.92% | 0 | — |
| 体重増加 | 0 | — | 0 | — | 2 | 1.53% | 1 | 0.76% |
| 白血球数減少 | 46 | 1.91% | 9 | 0.37% | 2 | 1.53% | 1 | 0.76% |
| 白血球数増加 | 9 | 0.37% | 2 | 0.08% | 0 | — | 0 | — |
| 血中リン減少 | 18 | 0.75% | 0 | — | 2 | 1.53% | 0 | — |
| 血中リン増加 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 駆出率減少 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 尿中ビリルビン増加 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 心電図異常Q波 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 血小板数増加 | 3 | 0.12% | 0 | — | 0 | — | 0 | — |
| 尿中蛋白陽性 | 13 | 0.54% | 0 | — | 0 | — | 0 | — |
| 脳性ナトリウム利尿ペプチド増加 | 1 | 0.04% | 1 | 0.04% | 0 | — | 0 | — |
| 遊離サイロキシン増加 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 血中アルカリホスファターゼ増加 | 20 | 0.83% | 2 | 0.08% | 11 | 8.40% | 0 | — |
| 肝酵素上昇 | 8 | 0.33% | 3 | 0.12% | 0 | — | 0 | — |
| 腎機能検査異常 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 便潜血 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 膵酵素増加 | 40 | 1.66% | 0 | — | 0 | — | 0 | — |
| 免疫抑制剤濃度増加 | 1 | 0.04% | 1 | 0.04% | 0 | — | 0 | — |
| 凝固検査異常 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 血中トリプシン増加 | 0 | — | 0 | — | 25 | 19.08% | 0 | — |
| 尿中ウロビリノーゲン増加 | 2 | 0.08% | 0 | — | 0 | — | 0 | — |
| 傷害、中毒および処置合併症 | 7 | 0.29% | 5 | 0.21% | 1 | 0.76% | 0 | — |
| 大腿骨頚部骨折 | 1 | 0.04% | 1 | 0.04% | 0 | — | 0 | — |
| 放射線胃腸炎 | 2 | 0.08% | 2 | 0.08% | 0 | — | 0 | — |
| 外傷性血腫 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 創し開 | 1 | 0.04% | 0 | — | 0 | — | 0 | — |
| 擦過傷 | 0 | — | 0 | — | 1 | 0.76% | 0 | — |
| 創傷出血 | 1 | 0.04% | 1 | 0.04% | 0 | — | 0 | — |
| 気管出血 | 1 | 0.04% | 1 | 0.04% | 0 | — | 0 | — |

※副作用名はMedDRAの器官別大分類(SOC)および基本語(PT)で集計(MedDRA/J ver14.0)。
同一症例中に同一副作用が複数件発現した場合は、1例として計算した。

弊社製品情報サイトNexavar.jp(http://www.nexavar.jp/)をご参照ください

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資材番号 NER-11-9600

II. 研究成果の刊行に関する一覧表

雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| Hamada S, Hinotsu S, Hori K, Furuse H, Oikawa T, Kawakami J, Ozono S, Akaza H, Kawakami K | The cost of antiemetic therapy for chemotherapy-induced nausea and vomiting in patients receiving platinum-containing regimens in daily practice in Japan: a retrospective study | Support Care Cancer | 20(4) | 813-20 | 2012 |
| Escudier B, Osanto S, Ljungberg B, Porta C, Wagstaff J, Mulders P, Gore M, Bex A, Bellmunt J, Bracarda S, Franklin A, Honore PH, Ravaud A, Steijn JV, Aziz Z, Akaza H | Multidisciplinary management of metastatic renalcell carcinoma in the era of targeted therapies | Cancer Treat Rev | 38(2) | 127-32 | 2012 |
| Akaza H, Carroll P, Cooperberg MR, Hinotsu S | Fifth Joint Meeting of J-CaP and CaPSURE: Advancing the Global Understanding of Prostate Cancer and Its Management | Jpn J Clin Oncol | 42(3) | 226-36 | 2012 |
| Tsuji H, Moriyama K, Nomoto K, Akaza H | Identification of an Enzyme System for Daidzein-to-Equol Conversion in Slackia sp. Strain NATTS | Appl Environ Microbiol | 78(4) | 1228-36 | 2012 |
| Miyanaga N, Akaza H, Hinotsu S, Fujioka T, Naito S, Namiki M, Takahashi S, Hirao Y, Horie S, Tsukamoto T, Mori M, Tsuji H | Prostate cancerchemoprevention study: an investigative randomized control study using purified isoflavones in men with rising prostate-specific antigen | Cancer Sci | 103(1) | 125-30 | 2012 |
| Naito S, Tsukamoto T, Murai M, Fukino K, Akaza H | Overall survival and good tolerability of long-term use of sorafenib after cytokine treatment: final results of a phase II trial of sorafenib in Japanese patients with metastatic renal cell carcinoma | BJU Int | 108(11) | 1813-9 | 2011 |

| | | | | | |
|---|---|---|---|---|---|
| Brausi M, Witjes JA, Lamm D, Persad R, Palou J, Colombel M, Buckley R, Soloway M, Akaza H, Bohle A | A review of current guidelines and best practice recommendations for the management of nonmuscle invasive bladder cancer by the international bladder cancer group | J Urol | 186(6) | 2158-67 | 2011 |
| Miyazaki J, Kawai K, Kojima T, Oikawa T, Joraku A, Shimazui T, Nakaya A, Yano I, Nakamura T, Harashima H, Akaza H | The liposome-incorporating cell wall skeleton of Mycobacterium bovis bacillus Calmette-Guein can directly enhance the susceptibility of cancer cells to lymphokine-activated killer cells through up-regulation of natural-killer group 2, member D ligands | BJU Int | 108(9) | 1520-6 | 2011 |
| Tomita Y, Uemura H, Fujimoto H, Kanayama HO, Shinohara N, Nakazawa H, Imai K, Umeyama Y, Ozono S, Naito S, Akaza H | Japan Axitinib Phase II Study Group, Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: A phase II study in Japanese patients with cytokine-refractory metastatic renal cell Carcinoma | Eur J Cancer | 47(17) | 2592-602 | 2011 |
| Algaba F, Akaza H, Lopez-Beltran A, Martignoni G, Moch H, Montironi R, Reuter V | Current pathology keys of renal cell carcinoma | Eur Urol | 60(4) | 634-43 | 2011 |
| Akaza H, Tsukamoto T, Fujioka T, Tomita Y, Kitamura T, Ozono S, Miki T, Naito S, Zembutsu H, Nakamura Y | Combined immunotherapy with low-dose IL-2 plus IFN-alpha for metastatic renal cell carcinoma: survival benefit for selected patients with lung metastasis and serum sodium level | Jpn J Clin Oncol | 41(8) | 1023-30 | 2011 |
| Zennami K, Yoshikawa K, Kondo E, Nakamura K, Upsilonamada Y, De Velasco MA, Tanaka M, Uemura H, Shimazui T, Akaza H, Saga S, Ueda R, Honda N | A new molecular targeted therapeutic approach for renal cell carcinoma with a p16 functional peptide using a novel transporter system | Oncol Rep | 26(2) | 327-33 | 2011 |

| | | | | | |
|---|---|---|---|---|---|
| Hinotsu S, Akaza H, Naito S, Ozono S, Sumiyoshi Y, Noguchi S, Yamaguchi A, Nagamori S, Terai A, Nasu Y, Kume H, Tomita Y, Tanaka Y, Samma S, Uemura H, Koga H, Tsushima T | Maintenance therapy with bacillus Calmette-Guerin Connaught strain clearly prolongs recurrence-free survival following transurethral resection of bladder tumour for non-muscle-invasive bladder cancer | BJU Int | 108(2) | 187-95 | 2011 |
| Miyazaki J, Nishiyama H, Yano I, Nakaya A, Kohama H, Kawai K, Joraku A, Nakamura T, Harashima H, Akaza H | The therapeutic effects of R8-liposome-BCG-CWS on BBN-induced rat urinary bladder carcinoma | Anticancer Res | 31(6) | 2065-71 | 2011 |
| Kawahara N, Roh JK, Akaza H, Inoue H, Shibuya K, Iwasaki M, Tsuji T, Nishiyama M, Nakagawara A, Watanabe K, Nozaki S, Inoue M, Sugimura H, Miyake J, Li F | The 7th Asia Cancer Forum: from the perspective of human security, how can we collaborate as Asians in order to place cancer on the global health agenda? How can we fill in the gaps that exist among us? | Jpn J Clin Oncol | 41(6) | 825-31 | 2011 |
| Kawahara N, Sugimura H, Nakagawara A, Masui T, Miyake J, Akiyama M, Wahid IA, Hao X, Akaza H | The 6th Asia cancer forum: What should we do to place cancer on the global health agenda? Sharing information leads to human security | Jpn J Clin Oncol | 41(5) | 723-9 | 2011 |
| Noguchi M, Uemura H, Naito S, Akaza H, Yamada A, Itoh K | A phase I study of personalized peptide vaccination using 14 kinds of vaccine in combination with low-doseestramustine in HLA-A24-positive patients with castration-resistant prostate cancer | Prostate | 71(5) | 470-9 | 2011 |

| | | | | | |
|---|---|---|---|---|---|
| Kuroiwa K, Shiraishi T, Naito S; Clinicopathological Research Group for Localized Prostate Cancer Investigators. Collaborators: Akaza H, Arai Y, Baba S, Egawa S, Hirao Y, Kagawa S, Kanetake H, Murai M, Nose Y, Ogawa O, Ohori M, Ohshima S, Okuyama A, Tsukamoto T, Usami M, Yamanaka H, Goto K, Koga H | Gleason score correlation between biopsy and prostatectomy specimens and prediction of high-grade Gleason patterns: significance of central pathologic review | Urology | 77(2) | 407-11 | 2011 |
| Akaza H | Combined androgen blockade for prostate cancer: review of efficacy, safety and cost-effectiveness | Cancer Sci | 102(1) | 51-6 | 2011 |
| Tsukamoto T, Shinohara N, Tsuchiya N, Hamamoto Y, Maruoka M, Fujimoto H, Niwakawa M, Uemura H, Usami M, Terai A, Kanayama HO, Sumiyoshi Y, Eto M, Akaza H | Phase III trial of everolimus in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from RECORD-1 | Jpn J Clin Oncol | 41(1) | 17-24 | 2011 |
| Behjati R, Kawai K, Inadome Y, Kano J, Akaza H, Noguchi M | APAF-1 is related to an undifferentiated state in the testicular germ cell tumor pathway | Cancer Sci | 102(1) | 267-74 | 2011 |
| Mori M, Masumori N, Fukuta F, Nagata Y, Sonoda T, Miyanaga N, Akaza H, Tsukamoto T | Weight gain and family history of prostate or breast cancers as risk f actors for prostate cancer: results of a case-control study in Japan | Asian Pac J Cancer Prev | 12(3) | 743-7 | 2011 |
| Akaza H, Kanetake H, Tsukamoto T, Miyanaga N, Sakai H, Masumori N, Nakatsu H, Sagiyama K, Sakamoto S, Endo Y, Yamanouchi T; REDUCE Study Group | Efficacy and Safety of Dutasteride on Prostate Cancer Risk Reduction in Asian Men: The Results from the REDUCE Study | Jpn J Clin Oncol | 41(3) | 417-23 | 2011 |

# III. 研究成果の刊行物・別刷

Support Care Cancer (2012) 20:813–820
DOI 10.1007/s00520-011-1155-3

ORIGINAL ARTICLE

# The cost of antiemetic therapy for chemotherapy-induced nausea and vomiting in patients receiving platinum-containing regimens in daily practice in Japan: a retrospective study

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**Abstract**
*Purpose* The objective of this study was to estimate the cost of antiemetic therapy for chemotherapy-induced nausea and vomiting (CINV) in daily practice in Japan.

*Methods* This was a retrospective observational study using medical records. Eligible patients were those with bladder or testicular cancer receiving platinum-containing highly emetogenic chemotherapy. The incidence of CINV on days 1–5 in single-day chemotherapy and on days 1–9 in multiple-day chemotherapy, and the costs of antiemetic therapy directly associated with the administration of antiemetics were estimated. The analysis of costs was performed from a hospital perspective.

*Results* A total of 54 patients or 169 chemotherapy courses were included. In all chemotherapy courses 5-$HT_3$ receptor antagonists were used on the day(s) that platinum-containing agents were administered and frequently used on subsequent days. In contrast, the use of corticosteroids was infrequent. Acute CINV in single-day chemotherapy was well controlled, but the incidences of delayed CINV in single-day chemotherapy and CINV in multiple-day chemotherapy were relatively high. The costs for antiemetic therapy were $484.65 in courses with CINV and $318.56 in courses without CINV, and the difference was approximately $170 per chemotherapy course, which was considered to be mainly imputable to the prevalence of CINV.

*Conclusions* The cost of antiemetic therapy for CINV is substantial in Japan as well as in other countries, and it is suggested that the onset of CINV is a possible cost driver. The improvements in antiemetic therapy may contribute not only to improved patient well-being but also to a reduction of economic burden.

**Keywords** Chemotherapy-induced nausea and vomiting · Emesis · Cost of illness · Health economics · Pharmacoeconomics

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**Abbreviations**
CINV Chemotherapy-induced nausea and vomiting

## Introduction

Chemotherapy-induced nausea and vomiting (CINV) is common and the most distressing side effect for patients receiving cancer chemotherapy [1–3]. Patients developing CINV may occasionally be forced to discontinue or postpone their chemotherapy, resulting in a loss of optimal clinical outcomes. The specified risk factors for CINV are, for example, female gender, younger age, dose, and intrinsic emetogenicity of chemotherapeutic agents given, history of low alcohol consumption, and pretreatment expectation of severe nausea [4]. Regarding the severity of emetogenicity, chemotherapeutic agents are generally placed in one of four risk categories—minimal, low, moderate, and high—according to the expected frequency of emesis in the absence of effective antiemetic prophylaxis [5].

In research into CINV, chemotherapy regimens have been classified according to the dosing schedule of chemotherapeutic agents: single-day or multiple-day chemotherapy. Although the introduction of 5-$HT_3$ receptor antagonists has dramatically improved the control of acute CINV (occurring within 24 h of chemotherapy) in patients receiving single-day chemotherapy, the control of delayed CINV (occurring more than 24 h after chemotherapy) remains a significant problem [6, 7]. Multiple-day chemotherapy is given to patients with germ cell cancer, sarcoma, leukemia, and non-Hodgkin's lymphoma, such as the 5-day fractionated administration of cisplatin to patients with testicular cancer, and nearly half of patients continue to experience emesis despite prophylaxis with 5-$HT_3$ receptor antagonists and corticosteroids [8].

Recently, several studies have demonstrated that CINV not only has clinical consequences but also has an economic impact [6, 9–11]. The costs of CINV including direct and/or indirect ones imputable to CINV were estimated in these studies, but such costs cannot be extrapolated directly to the setting of another country because of the differences in commonly used antiemetic therapies, drug pricing, and personnel costs. Several studies evaluating CINV-associated costs have been performed in Japan [12, 13], but the cost of antiemetic therapy for CINV itself has not yet been clarified. In general, the economic evaluations of medicine are limited in Japan, compared to research conducted in the United States or Europe [14]. The purpose of the present study was to estimate the cost of antiemetic therapy for CINV and the impact of the onset of CINV on the cost in daily practice in Japan.

## Patients and methods

### Study design and setting

This was a retrospective observational study. The measurements were extracted from the medical records at two National University Hospitals (Hamamatsu University School of Medicine, University Hospital, Hamamatsu, Japan and Tsukuba University Hospital, Tsukuba, Japan).

### Patients

Platinum-containing compounds such as cisplatin and carboplatin are chemotherapeutic agents widely used for the treatment of malignancies, including head and neck, lung, ovarian, bladder, and testicular cancer. Cisplatin and carboplatin have relatively high emetogenicity, and are listed as high and moderate risks when used as single agents, respectively, in emetogenic schema [5]. Some of us are urologists with a great deal of experience in chemotherapy, and so we decided in this study to focus on patients with bladder or testicular cancer receiving platinum-containing highly emetogenic chemotherapy in a hospital setting between January 2005 and December 2007. Chemotherapy regimens included in the study were as follows: MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), GC (gemcitabine and cisplatin or carboplatin), and ITP (ifosfamide, paclitaxel, and cisplatin) for bladder cancer, and BEP (bleomycin, etoposide, and cisplatin), EP (etoposide and cisplatin), TIP (paclitaxel, ifosfamide, and cisplatin), and VIP (vinblastine, ifosfamide, and cisplatin) for testicular cancer. The standard doses of cisplatin in the hospitals were 70 mg/$m^2$ for the regimens for bladder cancer, and 100 mg/$m^2$ as single-day chemotherapy and 20 mg/$m^2$/day as a 5-day fractionated multiple-day chemotherapy for the regimens for testicular cancer. These regimens are conventional rather than experimental [15, 16]. All of the chemotherapeutic agents in combination with platinum-containing agents are listed as minimal to moderate risks in the emetogenic schema [5]. The combination of gemcitabine plus carboplatin corresponded to a high risk of emetogenicity according to the algorithm proposed by Hesketh et al. [17]. Consequently, all chemotherapy regimens included in this study were regarded as highly emetogenic. In addition, platinum-containing agents might be the main contributors to the onset of CINV since the emetogenicity of platinum is high compared to the other agents used concomitantly.

Patients were included regardless of their experience of chemotherapy. Patients who were previously diagnosed as having malignancies located in the central nervous system or gastrointestinal tract and patients with metastasis of

cancer in these organs were excluded because the onset of CINV might be affected by these conditions.

The research protocol was approved by the ethical review boards at Kyoto University, Hamamatsu University School of Medicine, and Tsukuba University. This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research in Japan.

### Data collection

Data were obtained by a structured chart review. We extracted the following information from the medical records: age, sex, chemotherapy setting (inpatient or outpatient), dates of admission and discharge, type of cancer, histopathological diagnosis, grade of tumor, presence and location of metastasis, previous treatment (chemotherapy, surgery, and radiation), chemotherapeutic agents and antiemetics (dose, route, and time and date of administration of agents), and episodes of nausea and vomiting. No information on the use of benzodiazepines was collected because drugs in this class were not used as antiemetics in the two hospitals. The day or the initial day on which platinum-containing agents were administered was set as day 1.

### Incidence of CINV

In this study, nausea and vomiting on days 1–5 in single-day chemotherapy and on days 1–9 in multiple-day chemotherapy were defined as chemotherapy-induced. All episodes of nausea and vomiting in this period were collected per chemotherapy course regardless of the intensity or number of episodes. The incidences of nausea, vomiting, nausea and vomiting, or neither were estimated on day 1 (the acute phase), and on days 2–5 (the delayed phase) for single-day chemotherapy, and on days 1–5 (the acute phase) and on days 6–9 (the delayed phase) in multiple-day chemotherapy. For the purpose of the following cost analysis, chemotherapy courses were classified into those with at least one episode of nausea and/or vomiting and ones without any episodes.

### Cost of CINV

All patients scheduled to receive highly emetogenic chemotherapy were given predetermined antiemetic therapy, standardized within each hospital, for the purpose of prevention of CINV. This type of antiemetic therapy was referred to as routine prophylaxis in this study. Routine prophylaxis was basically set before emetogenic chemotherapy, and occasionally until a few days after chemotherapy. In addition to routine prophylaxis, antiemetic therapy was conducted in certain other situations, such as cases where the patient was considered to be susceptible to CINV because of the onset of CINV in a previous course or having actually developed CINV. These types of antiemetic therapy were referred to as additional medication in this study. The overall costs of antiemetic therapy were divided into the two categories—routine prophylaxis and additional medication—and calculated separately.

The cost of antiemetic therapy for CINV per chemotherapy course was calculated by summing the following costs associated with the administration of antiemetics directly: drug, administration device, and staff time to prepare and administer antiemetics. We calculated the costs of antiemetic therapy using drug prices in 2007, and the costs of administration devices and personnel costs reported by Ishimaru et al. [12]. The unit cost for an administration device was added to the cost of routine prophylaxis and/or additional medication when the device was used for each intended purpose at least once, irrespective of the number of administration devices used. Personnel cost was added depending on the number of times the antiemetics were administered.

A prospective payment system based on the diagnostic procedure combination was implemented with a partly inherited fee for service system in Japan in 2003 [14]. Hospitals cover the economic burden in acute inpatient care for all cancer-related treatments including the cost of antiemetic therapy for CINV. Therefore, the analysis of costs in this study was performed from a hospital perspective.

All costs (Japanese yen) were converted to US dollars using the mean currency exchange rate in 2007 ($1=\113.15 yen).

### Statistical analysis

JMP, version 8.0.1 (SAS Institute, Cary, NC, USA) [18] was used for statistical analysis. For cost analysis, mean, standard deviation, median, and range were calculated as descriptive statistics because costs were expected not to be normally distributed and to be highly variable due to differences in chemotherapeutic and antiemetic regimens.

## Results

### Description of patients and chemotherapy regimens

The characteristics of patients and chemotherapy regimens are summarized in Table 1. A total of 54 patients or 169 chemotherapy courses were included in this study. The median age was 57.5 years, and patients with bladder cancer were older than those with testicular cancer. The majority of the patients were male. Approximately one third

**Table 1** Patient characteristics and chemotherapy regimens

| Characteristics | | Bladder cancer | Testicular cancer | All patients |
|---|---|---|---|---|
| No. of patients | | 31 | 23 | 54 |
| Age (years), median (range) | | 64 (50–81) | 36 (22–81) | 57.5 (22–70) |
| Sex | Male | 25 | 23 | 48 |
| | Female | 6 | 0 | 6 |
| Presence of metastasis, *n* (%) | | 11 (35) | 8 (35) | 19 (35) |
| Previous chemotherapy, *n* (%) | | 12 (39) | 5 (22) | 17 (31) |
| No. of chemotherapy courses | | 90 | 79 | 169 |
| Single-day chemotherapy | | MVAC 55 | BEP 40 | 141 |
| | | GC 28 | EP 11 | |
| | | ITP 7 | | |
| Multiple-day chemotherapy | | | BEP 9 | 28 |
| | | | EP 1 | |
| | | | TIP 18 | |

*M* methotrexate, *V* vinblastine, *A* doxorubicin, *C* cisplatin (or carboplatin in 24 courses of GC), *G* gemcitabine, *I* ifosfamide, *T* paclitaxel, *P* cisplatin, *B* bleomycin, *E* etoposide

of the patients had metastasis or had received chemotherapy prior to the series of chemotherapy courses included in this study. Four patients were excluded because of brain metastasis of bladder cancer (one patient), brain metastasis of testicular cancer (two patients), and a history of primary brain cancer (one patient). Approximately 80% of the chemotherapy regimens were single-day chemotherapy and the remainder was multiple-day chemotherapy, or 5-day fractionated administration of cisplatin. The mean (daily) dosages of cisplatin in single-day and multiple-day chemotherapy were 137.4 and 34.1 mg, respectively, approximately 80 and 20 mg/m$^2$ in terms of a body surface area of 1.73 m$^2$. The mean dosage of carboplatin was 341.6 mg or approximately 200 mg/m$^2$.

## Usage of antiemetics

Antiemetics used on the day(s) of administration of platinum-containing agents and from the subsequent day to the end of the chemotherapy course are listed in Table 2. The specific drug names and standard doses per administration included in each drug class and those used in this study were as follows: granisetron (3 mg, i.v.), ramosetron (0.3 mg, i.v.), azasetron (10 mg, i.v.), tropisetron (5 mg, oral), and ondansetron (4 mg, oral) in 5-HT$_3$ receptor antagonists, methylprednisolone (125 or 250 mg, i.v.) in corticosteroids, domperidone (5 or 10 mg, oral, or 30 or 60 mg, rectal), and prochlorperazine (5 mg, oral) in dopamine D2 receptor antagonists, and hydroxyzine (25 or 50 mg, oral) in anti-histamines. In all chemotherapy courses 5-HT$_3$ receptor antagonists were used on day 1 in single-day chemotherapy and on days 1–5 in multiple-day chemotherapy, and this class of drugs was used frequently on subsequent days. In contrast, corticosteroids were used infrequently from day 2 in single-day chemotherapy and rarely in multiple-day chemotherapy. In addition to these classes of drugs, metoclopramide was used in more than half of the courses.

According to the classification for cost estimation, routine prophylaxis consisted of 5-HT$_3$ receptor antagonists and corticosteroids on the day(s) of administration of platinum agents, and partly of 5-HT$_3$ receptor antagonists

**Table 2** Usage of antiemetics

| Chemotherapy regimen | Single-day (*n*=141) | | | | Multiple-day (*n*=28) | | | |
|---|---|---|---|---|---|---|---|---|
| | Day 1 | | Days 2+ | | Days 1–5 | | Days 6+ | |
| Drug class | Number | Percentage | Number | Percentage | Number | Percentage | Number | Percentage |
| 5-HT$_3$ receptor antagonists | 141 | (100) | 86 | (57) | 28 | (100) | 7 | (25) |
| Corticosteroids | 98 | (70) | 35 | (25) | 1 | (4) | 0 | (0) |
| Metoclopramide | 27 | (19) | 75 | (53) | 15 | (54) | 10 | (36) |
| Dopamine D2 receptor antagonists | 3 | (2) | 7 | (5) | 3 | (11) | 7 | (25) |
| Antihistamines | 2 | (1) | 17 | (12) | 0 | (0) | 0 | (0) |

from day 2 in single-day chemotherapy, and of metoclopramide. The other antiemetics were used as additional medication.

Incidence of CINV

The incidences of CINV per chemotherapy course are shown in Table 3. Acute CINV in single-day chemotherapy was controlled in more than 80% of courses. The incidences of delayed CINV in single-day chemotherapy and CINV in multiple-day chemotherapy were about 70% to 90%, and approximately half of the courses with nausea were accompanied with vomiting. Although the exact times of the onset of CINV were not available in some cases, the date on which the episodes developed could at least be specified.

Cost of CINV

There were 44 chemotherapy courses without CINV and 125 courses with CINV. The overall costs of antiemetic therapy for CINV and its components are presented in Table 4. The majority of expenses were drug costs; the cost of administration devices and personnel costs were low compared to drug cost. The overall costs (i.e., routine prophylaxis plus additional medication) were $484.65 in the courses with CINV and $318.56 in the courses without CINV, and the difference was approximately $170 per chemotherapy course. The cost of routine prophylaxis in the courses with CINV was similar to or a little bit higher than that of courses without CINV. On the other hand, the cost of additional medication in the courses with CINV was nearly twice as high as that in the courses without CINV.

## Discussion

In this study, we investigated the usage of antiemetics and estimated the incidence of CINV and the cost of antiemetic therapy for CINV in patients receiving platinum-containing highly emetogenic chemotherapy in daily practice. Patients with bladder or testicular cancer were included to grasp current situations associated with CINV in multiple-day chemotherapy as well as single-day chemotherapy. As far as we know, this was the first study to estimate the cost of antiemetic therapy for CINV itself and the impact of the onset of CINV on the cost of therapy in Japan.

The use of antiemetics for the prophylaxis of CINV was highly correlated with the onset of CINV. Acute CINV in single-day chemotherapy was well controlled by 5-$HT_3$ receptor antagonist-based prophylaxis in the present study as well as in other studies [6, 7, 9, 10]. It should be noted that the use of corticosteroids was infrequent or even rare

**Table 3** Incidence of chemotherapy-induced nausea and vomiting per chemotherapy course

| Chemotherapy regimen | Single-day ($n$=141) | | | | | | Multiple-day ($n$=28) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 1 (Acute phase) | | Days 2–5 (delayed phase) | | Days 1–5 (overall) | | Days 1–5 (acute phase) | | Days 6–9 (delayed phase) | | Days 1–9 (overall) | |
| Episode | Number | Percentage | Number | Percentage | Number | Percentage | Number | Percentage | Number | Percentage | Number | Percentage |
| Nausea | 18 | (13) | 44 | (31) | 45 | (32) | 12 | (43) | 6 | (21) | 9 | (32) |
| Vomiting | 4 | (3) | 9 | (6) | 6 | (4) | 0 | (0) | 4 | (14) | 1 | (4) |
| Nausea and vomiting | 2 | (1) | 46 | (33) | 49 | (35) | 11 | (39) | 7 | (25) | 15 | (54) |
| None | 117 | (83) | 42 | (30) | 41 | (29) | 5 | (18) | 11 | (39) | 3 | (11) |

The sum of the proportions may not equal 100% due to rounding

**Table 4** Cost of chemotherapy-induced nausea and vomiting per chemotherapy course

| Type of cost | Courses without CINV ($n$=44) | | Courses with CINV ($n$=125) | |
|---|---|---|---|---|
| Routine prophylaxis | | | | |
| Drug | 146.11±166.25 | [85.95; 60.03–685.21] | 168.05±157.10 | [87.64; 63.43–685.21] |
| Administration device[a] | 6.81±2.27 | [5.21; 4.26–9.47] | 7.52±2.38 | [9.47; 4.26–9.47] |
| Staff time (personnel cost)[b] | 1.03±1.53 | [0.57; 0.09–5.83] | 1.58±1.29 | [1.06; 0.18–5.83] |
| Subtotal | 153.95±167.20 | [94.30; 64.77–695.31] | 177.16±157.04 | [97.30; 68.17–695.31] |
| Additional medication | | | | |
| Drug | 161.87±235.45 | [0; 0–570.86] | 300.15±261.66 | [209.80; 0–1105.39] |
| Administration device[a] | 1.71±2.19 | [0; 0–5.21] | 3.81±2.05 | [4.26; 0–9.47] |
| Staff time (personnel cost)[b] | 1.03±1.60 | [0; 0–4.37] | 3.53±3.37 | [2.92; 0–17.98] |
| Subtotal | 164.61±238.72 | [0; 0–579.50] | 307.50±265.33 | [217.95; 0–1122.78] |
| Total | 318.56±275.15 | [189.12; 64.77–783.99] | 484.65±271.38 | [425.45; 93.17–1225.32] |

All costs (in dollars) are presented as mean±SD [median; range]

[a] For main route, $5.2; for subroute, $4.3

[b] For main route, $0.088; for subroute, $0.49

from day 2 in single-day chemotherapy and in the overall observational period in multiple-day chemotherapy, but the use of 5-$HT_3$ receptor antagonists was relatively frequent. This is despite the guidelines available at that time recommending dexamethasone-based antiemetic therapy against delayed emesis induced by high doses (≥50 mg/$m^2$) of cisplatin [19] or the combination of 5-$HT_3$ receptor antagonists plus dexamethasone against emesis induced by multiple-day chemotherapy [20]. This was considered to be one of the possible reasons for a tendency toward a higher incidence of delayed CINV in single-day chemotherapy in the present study compared to studies performed in other countries [6, 7, 9, 10]. Sato et al. reported a similar situation in another hospital in Japan, where 5-$HT_3$ receptor antagonists tended to be used frequently instead of corticosteroids in patients receiving moderately emetogenic chemotherapy [13]. Although available data on the use of antiemetics in emetogenic chemotherapy are limited, antiemetic therapy in Japan could be improved by the appropriate application of guidelines formulated in Japan and overseas. The first antiemetic guideline in Japan was published in May 2010 [21]. On the other hand, it was reported that about half of the patients receiving multiple-day chemotherapy achieved a complete response (no vomiting and no rescue medication) [8], and the incidence of chemotherapy-induced vomiting in patients with or without additional medications in the present study was comparable with other studies despite the rare use of corticosteroids. This result does not contradict recommendations to use corticosteroids because our study was observational, with a limited sample size, and was not designed to evaluate the efficacy of antiemetic therapy.

When the costs of antiemetic therapy for CINV directly associated with the administration of antiemetics were estimated, we divided antiemetic therapy into routine prophylaxis, which all patients received, and additional medication, which some patients received depending on their situation. As expected, the costs of antiemetic therapy were highly varied. Since there had been no antiemetic guideline in Japan until the first one was published, antiemetic therapies were basically standardized only within each hospital and the physicians could change the regimens at their manuals in the hospitals included in this study. These were considered major reasons why the variations of costs for routine prophylaxis and additional medication were wide. The overall costs of antiemetic therapy of the courses with or without CINV were $484.65 or $318.56, respectively, and the difference of approximately $170 between courses with and without CINV was principally attributed to the additional medication. Namely, this incremental cost was considered to be mainly imputable to the prevalence of CINV in previous or current chemotherapy courses. Several studies have reported on the costs of CINV per patient per chemotherapy course: costs incurred by third-party payers and hospital providers were €49 and €48, respectively, in Germany [6], and incremental costs in courses with CINV were CAN $61 in Canada [9] and €36 in Italy [10]. The overall costs and incremental costs estimated in the present study were higher than those in the above mentioned studies partly because of the frequent use of 5-$HT_3$ receptor antagonists instead of corticosteroids, the use of brand-name drugs despite generic drugs existing, and the calculation of costs using retail rather than wholesale prices. The use of 5-$HT_3$ receptor

antagonists more than 24 h after chemotherapy for prevention of delayed emesis has not been justified in terms of clinical efficacy or cost-effectiveness [22]. The use of not only corticosteroids but also metoclopramide and dopamine D2 receptor antagonists could be considered for the prophylaxis of delayed emesis or rescue medication in cases where patients have developed CINV despite prophylactic use of 5-$HT_3$ receptor antagonists. The improved control of CINV and the adjusted cost of antiemetic therapy for CINV might also be achieved as a result.

Two major limitations existed in this study. First, detailed data were limited in the study because of its retrospective nature. The incidence of CINV might be underestimated if all episodes are not reported in the medical records. In addition, quality of life or discomfort of the patients could not be predicted although the incidence of CINV was estimated. Although the costs of drugs, administration devices, and personnel directly associated with the administration of antiemetics were included in the present study, CINV actually affects not only these direct costs but also other costs. From the patient or social perspective, the other direct costs (e.g., transportation, over-the-counter drugs, and alternative medication) and indirect costs (i.e., loss of productivity in patients and caregivers) should be included when considering the cost of CINV. Taking into account the results of studies from other countries [6, 9, 10], these direct costs seem to be relatively low, and the indirect costs were highly variable according to the calculation methods.

The other limitation was a possible selection bias. The patients included in the study well reflected the characteristics of bladder and testicular cancer patients in Japan. Complementary studies, however, are needed to be performed in more extended patient groups with other types of cancer or chemotherapy to achieve a more accurate estimate of incidence and cost.

Most recently, two novel antiemetics, aprepitant, and palonosetron, were approved in Japan. These agents were approved in the United States in 2003. Aprepitant is a member of the family of neurokinin-1 receptor antagonists and selectively blocks the neurokinin-1 receptor, which is the binding site of substance P [23]. The Japanese antiemetic guideline [21] recommends the use of aprepitant for the prophylaxis of acute and delayed emesis in patients receiving single-day highly emetogenic chemotherapy as well as the MASCC guideline [5]. In addition, the Japanese guideline suggests that aprepitant may contribute to the improvement of the quality of life of patients receiving multiple-day chemotherapy despite the evidences of this drug limited to the cases in single-day chemotherapy. Palonosetron is a second-generation 5-$HT_3$ receptor antagonist with a longer half-life and greater receptor-binding affinity than first-generation 5-$HT_3$ receptor antagonists [23]. Although the effectiveness of replacing the first-generation drugs with palonosetron has not been fully clarified, palonosetron has been shown to have improved efficacy in the prophylaxis of delayed emesis induced by moderately [24, 25] and highly [26] emetogenic chemotherapy. The improved control of CINV, particularly delayed CINV in single-day chemotherapy and CINV in multiple-day chemotherapy, possibly can be achieved by optimizing antiemetic therapy with these new agents and the existing drugs. The cost of antiemetic regimens that include these new agents might be higher than the current therapy. However, there is also the possibility that the overall cost of antiemetic therapy for CINV decreases by preventing the onset of CINV because the present study suggested that the onset of CINV might increase the cost of antiemetic therapy. It should be noted that the cost of antiemetic therapy for CINV in this study did not include all costs associated with CINV, and patient discomfort was not taken into account.

In conclusion, the cost of antiemetic therapy for CINV is substantial in Japan as well as in other countries, and it is suggested that the onset of CINV is a possible cost driver. Although the goal of antiemetic therapy is to prevent the onset of CINV completely, current antiemetic therapy does not fulfill this ultimate goal. There is much room for improving antiemetic therapy, such as the use of corticosteroids, and other existing and/or new agents. The improved practice of antiemetic therapy may contribute not only to an improvement in patient well-being but also to a reduction of economic burden.

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**Conflict of interest** No conflict of interest is declared.

## References

1. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, van Beurden V, Stoter G, Verweij J (1997) Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 76:1055–1061
2. Hickok JT, Roscoe JA, Morrow GR, King DK, Atkins JN, Fitch TR (2003) Nausea and emesis remain significant problems of chemotherapy despite prophylaxis with 5-hydroxytryptamine-3 antiemetics: a University of Rochester James P. Wilmot Cancer Center Community Clinical Oncology Program Study of 360 cancer patients treated in the community. Cancer 97:2880–2886
3. Sun CC, Bodurka DC, Weaver CB, Rasu R, Wolf JK, Bevers MW, Smith JA, Wharton JT, Rubenstein EB (2005) Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. Support Care Cancer 13:219–227
4. Hesketh PJ (2008) Chemotherapy-induced nausea and vomiting. N Engl J Med 358:2482–2494

5. Roila F, Hesketh PJ, Herrstedt J, Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (2006) Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol 17:20–28
6. Ihbe-Heffinger A, Ehlken B, Bernard R, Berger K, Peschel C, Eichler HG, Deuson R, Thödtmann J, Lordick F (2004) The impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centers. Ann Oncol 15:526–536
7. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H (2007) Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. Support Care Cancer 15:497–503
8. Navari RM (2007) Prevention of emesis from multiple-day and high-dose chemotherapy regimens. J Natl Compr Canc Netw 5:51–59
9. Lachaine J, Yelle L, Kaizer L, Dufour A, Hopkins S, Deuson R (2005) Chemotherapy-induced emesis: quality of life and economic impact in the context of current practice in Canada. Support Cancer Ther 2:181–187
10. Ballatori E, Roila F, Ruggeri B, Porrozzi S, Iannopollo M, Soru G, Cruciani G, Daniele B, Locatelli MC, Pellissier J, Deuson R (2007) The cost of chemotherapy-induced nausea and vomiting in Italy. Support Care Cancer 15:31–38
11. Tina Shih YC, Xu Y, Elting LS (2007) Costs of uncontrolled chemotherapy-induced nausea and vomiting among working-age cancer patients receiving highly or moderately emetogenic chemotherapy. Cancer 110:678–685
12. Ishimaru H, Takayama S, Shiokawa M, Inoue T (2008) Cost-effectiveness analysis of 5-$HT_3$ receptor antagonist drugs in cancer chemotherapy. Gan To Kagaku Ryoho 35:619–623 (in Japanese)
13. Sato J, Terui K, Souma A, Fujita S, Hayakari M (2007) Survey on antiemetic therapy in ambulatory cancer chemotherapy and medical economics for standardization. Gan To Kagaku Ryoho 34:1637–1642 (in Japanese)
14. Tarn YH, Hu S, Kamae I, Yang BM, Li SC, Tangcharoensathien V, Teerawattananon Y, Limwattananon S, Hameed A, Aljunid SM, Bapna JS (2008) Health-care systems and pharmacoeconomic research in Asia-Pacific region. Value Health 11:S137–S155
15. Pectasides D, Pectasides M, Economopoulos T (2006) Systemic chemotherapy in locally advanced and/or metastatic bladder cancer. Cancer Treat Rev 32:456–470
16. Kondagunta GV, Motzer RJ (2006) Chemotherapy for advanced germ cell tumors. J Clin Oncol 24:5493–5502
17. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM (1997) Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 15:103–109
18. SASInstitute (2000) JMP statistics and graphic guide. SAS Institute, Cary
19. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC) (1998) Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. Ann Oncol 9:811–819
20. Einhorn LH, Rapoport B, Koeller L, Grunberg SM, Feyer P, Rittenberg C, Aapro M (2005) Antiemetic therapy for multiple-day chemotherapy and high-dose chemotherapy with stem cell transplant: review and consensus statement. Support Care Cancer 13:112–116
21. Japan Society of Clinical Oncology (2010) Seitoyaku tekiseishiyou guideline. Kanehara Shuppan, Tokyo, in Japanese
22. Geling O, Eichler HG (2005) Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. J Clin Oncol 23:1289–1294
23. Oo TH, Hesketh PJ (2005) Drug insight: new antiemetics in the management of chemotherapy-induced nausea and vomiting. Nat Clin Pract Oncol 2:196–201
24. Gralla R, Lichinitser M, Van Der Vegt S, Sleeboom H, Mezger J, Peschel C, Tonini G, Labianca R, Macciocchi A, Aapro M (2003) Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 14:1570–1577
25. Eisenberg P, Figueroa-Vadillo J, Zamora R, Charu V, Hajdenberg J, Cartmell A, Macciocchi A, Grunberg S, 99–04 Palonosetron Study Group (2003) Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a phaemacologically novel 5-$HT_3$ receptor antagonist: results of a phase III, single-dose trial versus dolasetron. Cancer 98:2473–2482
26. Saito M, Aogi K, Sekine I, Yoshizawa H, Yanagita Y, Sakai H, Inoue K, Kitagawa C, Ogura T, Mitsuhashi S (2009) Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomized, comparative phase III trial. Lancet Oncol 10:115–124

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Anti-Tumour Treatment

# Multidisciplinary management of metastatic renal cell carcinoma in the era of targeted therapies

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ABSTRACT

The use of targeted agents to treat metastatic renal cell carcinoma (mRCC) has significantly extended progression-free and overall survival but raises issues relating to the long-term delivery of care and the sustained monitoring of efficacy and toxicities, certain of which have not previously been experienced. In this paper, an expert group of medical oncologists, urologists and oncology nurses and pharmacists review and make informal recommendations on the multidisciplinary management of mRCC in the light of progress made and problems that have arisen. Decentralisation of care, with a shift in emphasis from large to small hospitals and possibly to the community, may offer advantages of cost and convenience. However, the major responsibility for care should continue to lie with clinicians (either medical oncologists or urologists) with extensive experience in mRCC, assisted by specialist nurses, and working in centres with facilities adequate to monitor efficacy and manage toxicities. That said, the extended survival of patients emphasises the importance of compliance and the long-term prevention, detection and management of side effects. Much of this will take place in the community. There is therefore a need for multidisciplinary working to extend beyond specialist centres to include general practitioners, community

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nurses and pharmacists. Although this paper focuses on mRCC, many of the considerations discussed are also relevant to the management of more common solid tumours in the era of targeted therapy.


## Introduction

Renal cell cancer (RCC) is the tenth most common malignancy in Europe: in the enlarged European Union in 2006, 63,000 new cases were diagnosed and 26,000 people died from the disease.[1] However, although the associated mortality and morbidity are considerable, RCC accounts for only 2–3% of cancers and is therefore relatively infrequent when compared, for example, with those of the breast, bowel and lung.

The management of RCC has traditionally been the province of urologists, and surgery continues to play a large and frequently curative role in the primary therapy of localised disease.[2] Even when patients present with metastases, nephrectomy (at least for patients who subsequently undergo cytokine treatment) is beneficial, as – in selected cases – is metastasectomy.[2,3]

Although only a small proportion of patients with metastatic RCC (mRCC) respond to cytokines, the prospects for systemic therapy have been substantially improved by the introduction of novel, small molecule and antibody inhibitors of signalling within and around the tumour cell.[4] There are now many options for the drug therapy of mRCC. To date, large controlled studies have shown significant benefit in progression-free or overall survival (or both) with six drugs: the oral tyrosine kinase inhibitors (TKIs) sunitinib (Sutent), sorafenib (Nexavar) and pazopanib (Votrient); the anti-angiogenic monoclonal antibody bevacizumab (Avastin) given with interferon; and the inhibitors of the mammalian target of rapamycin (mTOR) temsirolimus (Torisel) and everolimus (Afinitor).[3]

However, significant clinical benefit is accompanied by toxicities (including diarrhoea, fatigue and rash) which may be chronic and require adjustment of treatment regimen, as is exemplified in three of the pivotal trials. In the sunitinib registration study, 38% of patients randomised to the drug had a dose interruption because of adverse events, and dose reduction was necessary in 32%.[5] In the pivotal sorafenib trial, the comparable figures were 21% and 13%.[6] In the key temsirolimus study (which, unlike the sunitinib and sorafenib trials, involved poor-prognosis patients), 66% of patients had a delay in dosing on at least one occasion, and 23% required one or more dose reductions.[7] Patients treated outside the context of major studies are more likely than trial subjects to have significant comorbidities and to be elderly, raising the possibility that adverse event rates in routine practice will be higher than those reported in the trial literature.[8]

The exact role (or roles) recommended for each targeted agent depend on several patient- or tumour-related factors. One important consideration is the risk status of the patient, usually defined by Memorial Sloan-Kettering Cancer Center (MSKCC) criteria.[9] Others are history of prior therapy (if any), and disease histology (principally clear cell versus non-clear cell).[3] Clinical trial data provide only an incomplete guide to choice of agent in these varying circumstances. However, it is clear that for many patients combination therapy or several lines of sequential treatment can be envisaged.

According to final analysis of the recent AVOREN (Avastin and Roferon in Renal Cell Carcinoma) trial of first-line bevacizumab and/or interferon, median overall survival (OS) exceeded 21 months in both arms of the study, and more than 55% of patients had at least one post-protocol anti-tumour regimen.[10] In the similar Cancer and Leukemia Group B phase III study, the median OS in the 26% of patients who were in the good-risk category according to Memorial Sloan-Kettering criteria was longer than 33 months.[11] Given extended periods of survival, drugs may be given for years, patients will spend long periods in the community, and issues of compliance and long-term tolerability come to the fore.

RCC is a relatively rare malignancy. It is likely that community oncologists not specialised in this tumour will see relatively few patients (compared with those with cancers of the breast, bowel and lung) and find it more difficult to keep up with developments. RCC is amenable to treatment involving medical and surgical modalities. Such treatment involves many options, may be long-term, and carries a risk of significant toxicities, some of which will be unfamiliar to most clinicians. All of these considerations suggest that the care of patients with mRCC should be in the hands of those who are both individually expert and, collectively, open to collaboration across disciplines both within hospital and outside.

There has recently been a great expansion in the reporting of high-quality studies relating to the management of mRCC. However, the published literature on multidisciplinary working in cancer in general and RCC in particular is sparse. This paper presents a perspective on multidisciplinary management covering the role of urologists, medical oncologists, nurses and pharmacists – including their potential in managing patients in the community. In the absence of information from controlled studies, the evidence discussed derives principally from the personal experience of the authors and that of their colleagues and institutions.

The informal recommendations made reflect an emerging consensus on both clinical and organisational aspects of care. Throughout, the main consideration is the aim of prolonging survival while maintaining quality of life, i.e. of achieving the optimum balance between efficacy and toxicity in the individual patient.

## Issues arising from the introduction of targeted agents

The introduction of novel, targeted agents has significantly extended progression-free and overall survival for many patients with locally advanced and metastatic RCC. However, their introduction has raised new questions and brought fresh challenges. One area of debate is whether there should be restrictions on who can prescribe targeted agents – defined either by specialty or by relevant experience. Another is whether care of mRCC should be confined to large centres seeing a critical mass of patients.

### *Who should prescribe novel agents, and where?*

Compared with the era of cytokines, the advent of novel drugs (and especially those that are taken orally) opens up the possibility of decentralisation of care, with a shift from large to small hospitals, and from hospitals to the community. Delivery of care close to the patient has clear advantages: less time is lost through disruption in daily life and travel, and healthcare providers may benefit from reduced costs.

However, any push towards decentralisation is opposed by the pull towards specialisation. Given that the disease is infrequent, each small local hospital is likely to see few patients with RCC. Our consensus is that the major responsibility for care of mRCC should continue to be taken by specialised centres with experienced staff and the facilities needed to monitor the efficacy and toxicity of treatment. The following points define more precisely the elements contributing to expertise in managing mRCC: an adequate understanding of disease stage and heterogeneity;

familiarity with the level I evidence for the efficacy of available treatments; and knowledge of how to recognise and manage toxicities. Where such centralisation of care is not possible, expert regional or national frameworks should provide guidance on dosing and toxicity management.

Maintaining centralisation of care has the additional advantage of facilitating accrual to the phase III clinical trials which continue to be vital if standards of treatment are to be further improved.

As far as the prescribing of novel agents by individual clinicians is concerned, expertise in RCC and its systemic treatment – and perhaps having a minimum annual workload of patients – are more important factors than whether a clinician is a urologist or a medical oncologist by specialty. There is no consensus on the number of mRCC patients that would constitute a minimum annual workload, but a figure of around fifteen would be a reasonable suggestion.

*The management of unfamiliar and/or chronic toxicities*

New drugs have brought new toxicities. Certain of these toxicities – such as hand/foot syndrome and hypothyroidism – pose problems which many clinicians (especially urologists) will not be familiar with. Others, such as hypertension and impaired ejection fraction, are more familiar but have the ability significantly to complicate the treatment of mRCC, especially in the many patients who have relevant cardiovascular comorbidities.[8] A particular concern is that the desire to avoid toxicities and uncertainty about their management may lead less experienced clinicians to prescribe a lower than optimal dose of targeted agents or to reduce dose unnecessarily. Maintaining adequate dose intensity (which requires that treatment-related adverse events are well managed or prevented) is likely to be crucial to efficacy. It is already clear, for example, that exposure to sunitinib (measured by AUC) is correlated with clinical activity.[12]

The fact that many patients are now on long-term drug treatment for mRCC also has implications for tolerability. With side-effects such as diarrhoea, fatigue and hand–foot syndrome, even a relatively low grade of toxicity may be unacceptable when experienced over prolonged periods. Ongoing support for patients on long-term therapy becomes a priority. This will involve education of all concerned in the need for and effects of drug treatment, the importance of good compliance (simple regimens should help in this regard), and the prevention of toxicities (by good hand and foot care, for example).

The long-term drug treatment of mRCC is a reality. If agents active in mRCC also prove beneficial in the adjuvant setting, tolerability and the prevention of delayed as well as short-term toxicities will assume still greater importance. Providing advice on the prevention and management of specific treatment-related toxicities is not the purpose of this paper. Certain guidance has been published,[13–15] and other comprehensive reviews are in preparation.

## Multidisciplinary working in the new context

*The role of individual specialties*

Urologists have primary responsibility for the diagnosis of RCC, and for initial surgery and follow-up. They may also take the lead in cancer registration and the bio-banking of tissue and blood. Patients with resectable mRCC should not be started on targeted agents until surgical options, which can provide a durable complete response or "cure", have been explored. In mRCC patients treated with cytokines, nephrectomy confers a clear survival advantage.[16] A recent retrospective analysis suggests that this is also the case in patients treated with vascular endothelial growth factor-targeted therapy, but this remains to be confirmed by ongoing prospective trials since many biases could account for this putative benefit.[17]

Urologists have a clear interest in there being effective adjuvant therapy since 50% of nephrectomized patients with locally aggressive disease (as indicated by nodal involvement and/or vascular invasion) experience disease recurrence and die within 5 years.[18–20] However, there is as yet no adjuvant systemic treatment of proven benefit.

In locally advanced disease where neoadjuvant therapy offers the possibility of downstaging, urologists and medical oncologists act in partnership, and have the responsibility to conduct good clinical trials. Urologists, medical oncologists and radiologists have a joint role in the assessment and management of local recurrence or oligometastatic disease that may be amenable to complete surgical resection following downstaging.

In the systemic treatment of metastatic disease, oncologists in many centres are likely to take the lead in supervising therapy, frequently assisted by nurses specialised not only in oncology but specifically in RCC. Their knowledge is likely to encompass the natural history of the disease, the prevention, detection and monitoring of drug toxicity (perhaps through use of checklists and diaries), its grading and management, and the promotion of patient adherence to treatment.[21]

Nurses may be more accessible to patients than medical oncologists or urologists, generally have more time to spend with them, and can act as a bridge between doctor and patient. Since they are less subject to job rotation, nurses provide stability, enjoy a sustained caring relationship with patients, and are able to act as a reliable channel allowing two-way exchange of information between patient and health professionals. The European Oncology Nursing Society, which since its inception in 1984 has firmly established the prominence of this nursing speciality, devoted a session of its 2010 meeting to discussion of targeted agents. Recent publications in the nursing literature demonstrate a commitment to patient education, monitoring and early reporting as ways of optimising adverse event management and patient compliance with TKI and mTOR inhibitor therapy in RCC.[14,15]

Oncology pharmacists now also have a specialist professional society (the European Society of Oncology Pharmacy), which operates under the auspices of the European Cancer Organisation.[22] As well as having a duty to safely prepare and accurately dispense oncology drugs, the hospital pharmacist offers expert knowledge of drug interactions at the prescribing stage and during long-term treatment. Pharmacists may contribute towards the effective management of cancer-related pain, nausea and emesis. In relation to targeted agents, they have a potential role in informing patients about the prevention of toxicities and in advising on their management.[23]

*Multidisciplinary teams in hospitals*

Multidisciplinary teams (MDTs) are only one aspect of multidisciplinary working. However, their formal adoption has been an increasing part of oncology practice in specialist centres. Discussion between co-authors established that in-hospital MDTs for the management of RCC are now in place in several large centres. Such teams are likely to be selective in the cases they consider. A urologist would not generally refer to an MDT a patient with a small localised tumour, for example. Nevertheless, both urologists and medical oncologists have a clear interest in patients with mRCC. MDTs are seen as particularly valuable in cases which fall outside guidelines operative in the institution concerned. Given the heterogeneity of RCC, such cases are common.

Where needed, the MDT can seek the help of other specialists (such as those in endocrinology or dermatology) on an ad hoc

basis. When the side effects are both relatively common and potentially life-threatening, as they are with the cardiotoxicity of certain agents, there may be case for involving other specialists more routinely in decisions on treatment and monitoring. Lenihan and colleagues at the MD Anderson Cancer Center have already described the potential cardiotoxicity of novel agents as a factor that should strengthen the concept of team working in oncology.[24–26] As well as making joint decisions regarding management, hospital MDTs should have a role in professional education by allowing participants to challenge each other's practice.

In half the hospitals we represent, nurse specialists in systemic therapy are part of the mRCC team. However, there is considerable difference between countries in the prominence of clinical nurse specialists, who concentrate on the management of a specific disease, and in whether or not there are "nurse practitioners", who are able to prescribe in their own right. The important role of research nurses, however, is widely accepted, along with their value in passing on their expertise with novel agents. Although it is likely that the knowledge and skill of research nurses would help patients avoid toxicity, there are as yet no controlled data showing this is the case, nor that their involvement reduces the costs associated with adverse events.

The factors considered above suggest a need for multidisciplinary working in the hospital treatment of mRCC, at least in cases that are complex or uncertain. There is a dearth of evidence from controlled trials in cancer in general, but a persuasive case can be found in the narratives of both clinicians and patients.[27–30] A related question is whether multidisciplinary collaboration should be extended into the community.

*Multidisciplinary working that extends into the community*

It is unlikely that formal multidisciplinary teams for treating mRCC will span the hospital and the community. On the other hand, if patients are to be encouraged and monitored over years of disease-stabilising therapy, much of the day-to-day responsibility will devolve to those involved in primary care, notably the doctors and nurses working in general practice, and community pharmacists.

For general practitioners, the key enabling skills will be an understanding of the benefits and toxicities of novel agents, the knowledge needed to prescribe any other drugs required without risk of adverse interactions, and the confidence to help manage common side effects such as hypertension. In helping to avoid potential adverse drug interactions, there is a case for having a single record which provides a comprehensive account of the medication being taken by each patient. However, any distributed health information system designed to facilitate shared care raises issues of security and confidentiality.[31] There may be a case for any such records to be held by patients themselves, perhaps in the form of an electronic card.

The community-based approach may be helpful in the palliative care of cancer patients. There is recent evidence of benefit from integrating a nurse with advanced palliative care skills into a community oncology centre.[32] There is also evidence that community pharmacists make use of and value an internet-based programme in palliative cancer care which they can access at a time of their choosing.[32] Although the incidence of mRCC itself is low, there is an overlap with other cancers in the use of targeted drugs; and there may be potential in training community-based nurses and pharmacists in the efficacy and side-effects of these drugs.

Hospital pharmacists have expressed an enthusiasm to help their colleagues in the community to understand more about the benefits and risks of these novel drugs.[22] Community pharmacists may have a role in motivating patients and encouraging compliance, which can be poor with long-term therapy even for a highly malignant disease. They are more accessible than general practitioners, are likely to have regular contact with patients between hospital visits, and should be able to advise on possible drug interactions. This role is likely to be particularly critical in elderly patients who very commonly are taking many different drugs. Community pharmacists can also play a role in preventing, monitoring and managing toxicity. In relation to the targeted agents under discussion, helpful activities might range from the regular taking of blood pressure to advice on topical emollient creams in the case of hand–foot syndrome, and oral hygiene, avoidance of alcohol and choice of toothbrush in stomatitis.[23]

**Table 1**
Recommendations for systemic therapy in mRCC. The table combines the updated 2010 recommendations from the EAU and from ESMO:[33,34] these are compatible in substance but differ slightly in presentation.

| Histology | Treatment setting and risk | | Recommended agents | Options |
|---|---|---|---|---|
| Clear cell | 1st Line | Good/ intermediate | Sunitinib | Cytokines |
| | | | Bevacizumab + IFN alpha | |
| | | | Pazopanib | |
| | Poor risk | | Temsirolimus | Sunitinib |
| | Prior cytokine | | Sorafenib | Sunitnib |
| | | | Pazopanib | |
| | Prior VEGFR agent | | Everolimus | |
| Non-clear | | | | Temsirolimus |
| | | | | Sunitinib |
| | | | | Sorafenib |

For many patients, entry into a clinical trial would be a good option.

*Multidisciplinary working in the establishment of guidelines*

In addition to national guidelines, four pan-European organisations have written guidelines or recommendations relevant to mRCC.[2,8,34,35] In 2009, a genito-urinary interest group of the European Organisation for Research and Treatment of Cancer (EORTC) published an "expert opinion" on mRCC,[2] and a taskforce of the International Society of Geriatric Oncology (SIOG) published a "position paper" on treatment of the disease in the elderly.[8] The 2010 guidelines of the European Association of Urology (EAU)[34,36] and the 2010 update from the Guidelines Working Group of the European Society for Medical Oncology (ESMO)[35] are the most recent and comprehensive, and Table 1 is based on their recommendations. In relation to such guidelines, it is important to note that there are significant ethnic differences in both efficacy and toxicity profile between Asian and Western RCC patients treated with molecularly targeted drugs.[37] The Japanese Urological Association has developed its own guidelines;[38] and there is also an Asian Consensus Group statement.[39]

The extent to which such guidelines influence clinical practice varies from one country to another, depending at least in part on the reimbursement policies of governments and health insurers. However, when based on thorough research and established rules for evaluating evidence, they can be expected to have at least a moral authority. In the treatment of mRCC of clear cell histology, there is broad consensus among these documents on the choice of first- and second-line agents for patients in the different Memorial Sloan-Kettering prognostic groups.

In the current context, it is interesting to note that the contributors to the SIOG and ESMO documents were all medical oncologists, while the EAU guidelines were written exclusively by urologists. Only in the case of the EORTC-GU group were both specialties represented; and none of the guideline committees had members drawn from related professions such as nursing.

Therefore it is perhaps not surprising that multidisciplinary management does not feature as a recommendation in any of these publications.

It is our view – even though there are no controlled studies in support of this claim – that mRCC patients should be cared for by multidisciplinary teams made up from representatives of specialities key to the successful treatment of this particular pathology. Hopefully in the future, guidelines developed jointly by medical oncologists and urologists will become available. Consideration might also be given to integrating the recommendations of the various interest groups.

## Looking to the future

Current limitations in the efficacy of drug treatment for mRCC are most obvious in the fact that while we can prolong life and provide palliation we still cannot generally cure the disease. There is no reason in principle why this should not become possible, as it has with testicular tumours, although we are clearly some distance from that goal.

Among the factors holding us back is a lack of useful biomarkers predictive of tumour response or resistance to therapy and limitations in tumour imaging. Functional MRI and PET may offer helpful information, and determining whether this is the case will require the involvement of radiologists in relevant studies. In predicting tumour sensitivity to specific agents, genomics holds the key and will inform the clinical trials needed to extend our understanding of the optimal sequencing and combination of novel agents with each other and possibly also with cytokines. Tailoring therapy to the patient as well as the tumour will be assisted by pharmacokinetic and pharmacogenomic data that predict the balance of efficacy and toxicity in individual cases. All of this work will require multidisciplinary cooperation.

Much of the above discussion relates to multidisciplinary efforts to prevent, monitor and manage the toxicities associated with kinase inhibitors that are relatively non-selective in their targeting. In mRCC generally, despite the advance represented by novel agents when compared with cytokines, there has been a lack of well tolerated drugs, especially in poor performance status and elderly populations and those with comorbidities. Hence dose reduction and interruption are relatively common: in the sunitinib expanded access programme, for example, a third of patients started at 50 mg daily (on the four-weeks on/two off regimen) had their dose reduced to 37.5 mg.[40] The introduction of agents which have equivalent activity but fewer side effects would facilitate treatment. Pazopanib, the most recently approved of the drugs used to treat mRCC, may be one such agent.[41] However, this hypothesis can be confirmed only by head-to-head trials. Provided that toxicities are non-overlapping, an increased range of available drugs would also enhance the overall tolerability of combination therapy. But this will not diminish the need for multidisciplinary working to optimise care for the individual patient.

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## References

1. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;**18**:581–92.
2. de Reijke TM, Bellmunt J, van Poppel H, et al. EORTC-GU group expert opinion on metastatic renal cell cancer. *Eur J Cancer* 2009;**45**:765–73.
3. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Kidney Cancer version 1, 2011. Accessed 28.1.2011.
4. Vogelzang NJ. Treatment options in metastatic renal carcinoma: an embarrassment of riches. *J Clin Oncol* 2006;**24**:1–2.
5. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;**356**:115–24.
6. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;**356**:125–34.
7. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon-alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;**356**:2271–81.
8. Bellmunt J, Negrier S, Escudier B, et al. The medical treatment of metastatic renal cell carcinoma: position paper of a SIOG Taskforce. *Crit Rev Oncol Hematol* 2009;**69**:64–72.
9. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously-treated patients with metastatic renal cell carcinoma. *J Clin Oncol* 2004;**22**:454–63.
10. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol* 2010;**28**:2144–50.
11. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol* 2010;**28**:2137–43.
12. Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic pharmacodynamic meta-analysis. *Cancer Chemother Pharmacol* 2010;**66**:357–71.
13. Gruenwald V, Kalanovic D, Merseburger AS. Management of sunitinib-related adverse events: an evidence- and expert-based consensus approach. *World J Urol* 2010;**28**:343–51.
14. Edmonds K, Spencer-Shaw A. Managing adverse events associated with sorafenib in renal cell carcinoma. *Br J Nurs* 2010;**19**:58–60.
15. Creel PA. Management of mTOR inhibitor side effects. *Clin J Oncol Nurs* 2009;**13**(Supp):19–23.
16. Flanigan RC, Mickisch C, Sylvester R, et al. Cytoreductive nephrectomy in patients with metastatic renal cell cancer: a combined analysis. *J Urol* 2004;**171**:1071–6.
17. Choueiri TK, Xie W, Kollmansberger CK et al. The impact of cytoreductive nephrectomy in patients with metastatic renal carcinoma treated with VEGF-targeted therapy. Proc ASCO Genitourinary Cancers Symposium 2010, Abs 311.
18. Belldegrun AS, Klatte T, Shuch B, et al. Cancer-specific survival outcomes among patients treated during the cytokine era of kidney cancer (1989–2005): a benchmark for emerging targeted cancer therapies. *Cancer* 2008;**113**:2457–63.
19. Zisman A, Wieder JA, Pantuck AJ, et al. Renal cell carcinoma with tumor thrombus extension: biology, role of nephrectomy and response to immunotherapy. *J Urol* 2003;**169**:909–16.
20. Ljungberg B, Stenling R, Osterdahl B, et al. Vein invasion in renal cell carcinoma: impact on metastatic behavior and survival. *J Urol* 1995;**154**:1681–4.
21. Wood LS. New therapeutic strategies for renal cell carcinoma. *Urologic Nursing* 2010;**30**:40–54.
22. Maier K. Our capability needs a goal–patients need our competence. *Eur J Oncology Pharmacy* 2009;**3**:3.
23. Negrier S. Best use of targeted agents for the treatment of advanced renal cell carcinoma. *Eur J Oncology Pharmacy* 2009;**3**:8–12.
24. Lenihan DJ. Tyrosine kinase inhibitors: can promising new therapy associated with cardiac toxicity strengthen the concept of teamwork? *J Clin Oncol* 2008;**32**:5154–5.
25. Ewer MS, Lenihan DJ, Khakoo AY. Sunitinib-related cardiotoxicity: an interdisciplinary issue. *Nature Reviews Cardiology* 2008;**5**:364–5.
26. Khakoo AY, Kassiotis CM, Tannir N, et al. Heart failure associated with sunitinib malate: a multitargeted tyrosine kinase inhibitor. *Cancer* 2008;**112**:2500–8.
27. Taylor C, Munro AJ, Glynne-Jones R, et al. Multidisciplinary team working in cancer: what is the evidence? *Br Med J* 2010;**340**:c951.
28. Fleissig A, Jenkins V, Catt S, Fallowfield L. Multidisciplinary teams in cancer care: are they effective in the UK? *Lancet Oncol* 2006;**7**:886–8.
29. Samuel DG. MDT=Multidisciplinary teaching. Br Med J 2010; Rapid response 7 April.
30. Blennerhassett M. Patient narratives hold the evidence for MDTs. Br Med J 2010; rapid response 25 March.
31. Blobel B, Pharow P. Results of European projects improving security of distributed health information systems. *Stud Health Technol Inform* 1998;**52**:1119–23.
32. Prince-Paul M, Burant CJ, Saltzman JN, et al. The effects of integrating an advanced practice palliative care nurse in a community oncology center: a pilot study. *J Support Oncol* 2010;**8**:21–7.
33. Hussainy SY, Marriott JL, Beattie J, et al. A palliative care flexible education program of Australian community pharmacists. *Am J Pharm Educ* 2010;**74**:24.