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The correlation between the response to progestogen treatment and the expression of progesterone receptor B and 17β-hydroxysteroid dehydrogenase type 2 in human endometrial carcinoma

Hiroki Utsunomiya*, Takashi Suzuki†, Kiyoshi Ito*, Takuya Moriya†, Ryo Konno*, Shinji Sato*, Nobuo Yaegashi*, Kunihiro Okamura* and Hironobu Sasano†

*Departments of *Obstetrics and Gynecology †Pathology, Tohoku University School of Medicine, Sendai, Japan*

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Summary

OBJECTIVE ***In situ*** **metabolism and synthesis of oestrogens are considered to play important roles in the pathogenesis and development of human endometrial endometrioid adenocarcinoma. Approximately 3–5% of patients with these neoplasms are under age 40, some of whom have been treated with progestogen alone as a primary therapy for both atypical endometrial hyperplasia and adenocarcinoma in order to preserve their fertility. Medroxyprogesterone acetate (MPA) has been used extensively in the treatment of both breast and endometrial disorders as an endocrine therapy. However, details of the alterations of *in situ* oestrogen metabolism following progestogen treatment have yet to be fully elucidated.**

DESIGN, PATIENTS AND MEASUREMENTS **In this study we examined the immunolocalization of 17β-hydroxysteroid dehydrogenase (17β-HSD) types 1 and 2, oestrogen receptor (ER), progesterone receptor (PR)A + PRB, PRB, and Ki67 in progestogen-treated endometrial endometrioid adenocarcinoma (16 cases). We compared our findings both prior to and following treatment. These findings were then correlated with the treatment outcome of individual patients in order to elucidate factors associated with the response to treatment.**

RESULTS **17β-HSD type 2 immunoreactivity was detected in 8/16 cases examined, whereas 17β-HSD type 1 immunoreactivity was undetected in all cases examined. 17β-HSD type 2 positive immunostaining, PRA + PRB labelling index (LI), and PRB/PRA + PRB ratio were all significantly higher in cases responding to the treatment than in those not responding. There were no significant correlations between responsive and nonresponsive cases for positive 17β-HSD type 1 immunostaining, Ki67 LI, ER LI and age. There were no significant differences in the positive immunostaining for 17β-HSD types 1 and 2, Ki67 LI, ER LI, PRA + PRB LI, age and PRB/PRA + PRB ratio between specimens taken prior to and following progestogen treatment.**

CONCLUSION **These results suggest that *in situ* abundance of 17β-HSD type 2 and PR, especially PRB, can predict the possible response of patients with endometrial carcinoma to progestogen treatment.**

Endometrial endometrioid adenocarcinoma is one of the most frequently occurring gynaecological neoplasms in developed countries and its incidence has recently increased (Parker *et al.*, 1996). Approximately 3–5% of these patients are under age 40 (Gallup & Stock, 1984). The standard therapy for early endometrial carcinoma is established as staging laparotomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy, which deprives these patients of any potential for fertility. Therefore, a more conservative medical treatment is desirable in young patients who wish to preserve their fertility. A number of patients have been treated with progestin, especially medroxyprogesterone acetate (MPA), alone as a primary endocrine therapy for both atypical endometrial hyperplasia and adenocarcinoma. This approach is by no means a standard therapy, but has been supported by isolated reports of successful treatment in patients desiring fertility (Gallup & Stock, 1984; Thornton *et al.*, 1985; Kim *et al.*, 1997; Randall & Kurman, 1997). However, it is important to determine which subsets of patients may respond to this mode of therapy, because of the possible side-effects of MPA treatment (Roberts *et al.*, 1990; Izuo *et al.*, 1981).

In endometrial endometrioid adenocarcinoma, *in situ* oestradiol-17β (E2) availability has been demonstrated to contribute to

Correspondence: Hiroki Utsunomiya, Department of Obstetrics and Gynecology, Tohoku University Hospital, 1–1 Seiryo-machi, Aoba-ku, Sendai 980–8574, Japan. Tel: +81 22 717 7253; Fax: +81 22 717 7258. E-mail: H-Utsu@ob-gy.med.tohoku.ac.jp

the pathogenesis and development of endometrial proliferative disorders, including endometrial hyperplasia and adenocarcinoma (Lippman & Swain, 1992). The enzyme, 17β-hydroxysteroid dehydrogenase (17β-HSD) catalyses the reversible interconversion of oestrone (E1) and E2. Six isozymes encoded by distinctive genes have been identified in human (Peltoketo *et al.*, 1999), of which 17β-HSD types 1 and 2 are mainly involved in *in situ* oestrogen metabolism in the human endometrium (Miettinen *et al.*, 1996; Labrie *et al.*, 1997). 17β-HSD type 1 catalyses the 17β-reduction of biologically inactive E1 to E2 (Peltoketo *et al.*, 1998), whereas 17β-HSD type 2 isozyme preferentially catalyses the oxidation of E2 to E1 (Wu *et al.*, 1993). Both 17β-HSD types 1 and 2 regulate the local tissue levels of E2 and modulate oestrogenic actions in oestrogen target tissues, such as the endometrium.

The presence of the progesterone receptor (PR) is well-known as a prerequisite for progesterone actions. To date, two PR isoforms have been identified, PRA and PRB (Horwitz & Alexander, 1983; Savouret *et al.*, 1990). PRB is a 114-kDa protein, whereas PRA is a 94-kDa protein that lacks 164 amino acids from the N-terminus (Kastner *et al.*, 1990). PRA and PRB are products of a single gene and are translated from individual messenger ribonucleic acid species under the control of distinct promotors (Kastner *et al.*, 1990). The magnitude of transcriptional activation of PRB can be significantly greater than that of PRA (Meyer *et al.*, 1990; Kumar *et al.*, 1998). In addition, PRA can act as a dominant repressor of PRB activation of progestogen-sensitive reporter genes (Giangrande *et al.*, 1997; Tung *et al.*, 1993; Vegeto *et al.*, 1993), and similarly it can inhibit the transcriptional activity of receptors for oestrogens, androgens, glucocorticoids and mineralocorticoids (Vegeto *et al.*, 1993; McDonnell *et al.*, 1994). Several studies have demonstrated that the differences between these isoforms are not only promoter-specific, but also cell-specific (Meyer *et al.*, 1990; Turcotte *et al.*, 1991; Tung *et al.*, 1993; Vegeto *et al.*, 1993). Therefore, alterations in the ratio of PRA to PRB in a certain target tissue may modify the overall progesterone actions via differential regulation of specific progesterone-responsive genes.

Therefore, in this study, we examined the immunolocalization of 17β-HSD types 1 and 2, oestrogen receptor (ER), PRA + PRB, PRB and Ki67 in progestogen-treated endometrial carcinoma and then correlated these findings with the treatment outcome of individual patients. We also compared our findings in these patients both prior to and following progestogen therapy in order to examine the changes caused by this steroid therapy.

Materials and methods

Tissue preparation

Sixteen endometrial endometrioid adenocarcinomas (well-differentiated type, FIGO stage Ia) all treated with MPA were obtained from surgical pathology files at Tohoku University Hospital, Sendai, Japan between 1994 and 2001. All patients examined had received neither irradiation nor chemotherapy prior to hormonal therapy. Prior to the therapy, whole-wall endometrial curretage was performed. After the patients gave informed consent of the treatment, they started receiving continuous MPA therapy (600 mg/day). Their lesions were evaluated via hysteroscopy and whole-wall endometrial curretage under anaesthesia every 3 months following the start of therapy. Patients were interpreted as having been regressed or responsive to treatment if the endometrial biopsy specimens demonstrated a normal endometrium or hyperplasia without atypia. On the other hand, patients were interpreted as persistent or treatment failure if the biopsy specimens demonstrated atypical hyperplasia or adenocarcinoma. This treatment continued for at least 6 months. The median length of treatment required for regression was 7 months, with a range of 3–12 months. All available histological slides from endometrial curretage were re-evaluated. Histopathological classification in each specimen was also re-evaluated according to the 1988 FIGO histological grading system for endometrial adenocarcinoma (International Federation of Gynecology, 1989). The criteria of Kurman & Norris (1982) were used to distinguish between atypical endometrial hyperplasia and well-differentiated adenocarcinoma. The protocol in this study was approved by the Ethical Committee at Tohoku University School of Medicine. In this protocol, all patients survived and three of them delivered full-term babies. They had no evidence of recurrence 50, 39 and 6 months after conservative treatment, respectively.

The specimens were all processed routinely (10% formalin fixed for 24–48 h), paraffin embedded and thin sectioned (3 μm).

Antibodies

17β-HSD type 1 antibody was a rabbit polyclonal antibody against the enzyme purified from human placenta (Poutanen *et al.*, 1992), and was kindly provided by Dr MH Poutanen (University of Oulu, Oulu, Finland). The monoclonal antibody for 17β-HSD type 2, mAb-C2–12, was produced by immunizing mice with a synthetic carboxyl-terminal peptide corresponding to amino acids 375–387 of 17β-HSD type 2 (Moghrabi *et al.*, 1997), and was kindly provided by Dr S. Andersson (University of Texas Southwestern Medical Center, Dallas, TX, USA). Monoclonal antibodies for Ki67 (M1B1), ER (ER1D5), PRA + B and PRB were purchased from Immunotech (Marseille, France), Immunotech, Neo Markers (CA, USA) and Neo Markers, respectively (Clarke *et al.*, 1987; Mote *et al.*, 1999). Autoclave treatment was used as an antigen retrieval except for immunostain of 17β-HSD type 1. Utilization of these antibodies for immunohistochemistry has been reported previously (Takeyama *et al.*, 1998).

Immunohistochemistry

Immunohistochemical analyses were performed employing the streptavidin–biotin amplification method using a Histofine Kit (Nichirei, Tokyo, Japan), and have been previously described in detail (Takeyama *et al.*, 1998). The antigen–antibody complex was visualized with 3·3′-diaminobenzidine (DAB) solution [1 mM DAB, 50 mM Tris–HCl buffer (pH 7·6), and 0·006% H_2O_2], and counterstained with haematoxylin. Tissue sections from full-term placentae were used as positive controls for 17β-HSD types 1 and 2 (Takeyama *et al.*, 1998). As negative controls, normal rabbit or mouse IgG was used instead of primary antibodies. No specific immunoreactivity was detected in these tissue sections.

Scoring of immunoreactivity

Evaluation of 17β-HSD types 1 and 2, ER, PRA + PRB, PRB, and Ki67 in gland or carcinoma cells was performed on high power fields (×400) using a standard light microscope. Two of the authors (HU and TS) simultaneously searched the entire tissue sections and determined the most representative areas using double-headed light microscope. In all cases examined, a total of more than 500 glandular or carcinoma cells from three different representative fields were counted independently by the same two authors above, and the percentage of immunoreactivity, i.e. labelling index (LI), was determined. After completely reviewing the immunostained sections of each lesion, two of the authors (HU and TS) independently divided the cases into the following three groups: ++, more than 50% positive cells; +, 5–50% positive cells; and –, less than 5% positive cells. Cases with disconcordant results (interobserver differences with more than 5%) were simultaneously re-evaluated by the same two authors above using double-headed light microscope. In this study, interobserver differences were less than 5%.

Statistical analyses

Values for PRB/PRA + PRB ratio and LIs of 17β-HSD types 1 and 2, ER, PRA + PRB, and Ki67 were summarized as a mean ± 95% confidence interval (95% CI). Association between responsive and nonresponsive cases, or between pre- and post-treatment cases were evaluated using a Welch's *t*-test. In this study, *P*-values less than 0·05 were considered significant.

Results

Eleven of 16 patients demonstrated an initial response to MPA treatment based on the results of biopsy specimens, but five of 16 patients were associated with persistent lesions. Details of these patients are summarized in Table 1. 17β-HSD type 2 immunoreactivity was detected in the cytoplasm of carcinomatous cells, but not in stromal cells (Fig. 1a and b). 17β-HSD type 1 immunoreactivity was not detected in any of the cases examined. ER, PRA + PRB (Fig. 2a and b), PRB (Fig. 3a and b) and Ki67 were detected in the nuclei of carcinomatous cells and/or stromal cells in all the cases examined, respectively.

Comparison between responsive and nonresponsive cases

Results are summarized in Table 2. 17β-HSD type 2 immunopositivity, PRA + PRB LI and PRB/PRA + PRB ratio in

Table 1 Patient summaries

Patient	Age	MPA treatment	Treatment period (months)	17β-HSD type 2 expression	PRA + PRB expression
1	38	Responsive	6	+	+
2	37	Responsive	6	++	++
3	34	Responsive	6	+	++
4	31	Responsive	6	+	+
5	29	Responsive	9	++	+
6	29	Responsive	6	+	++
7	29	Responsive	12	–	+
8	29	Responsive	6	+	+
9	28	Responsive	6	–	+
10	27	Responsive	9	–	–
11	26	Responsive	6	+	++
12	38	Nonresponsive	9	–	–
13	36	Nonresponsive	12	–	–
14	29	Nonresponsive	6	–	+
15	26	Nonresponsive	6	–	+
16	26	Nonresponsive	6	–	+

++, more than 50% positive cells; +, 5–55% positive cells; –, less than 5% positive cells.

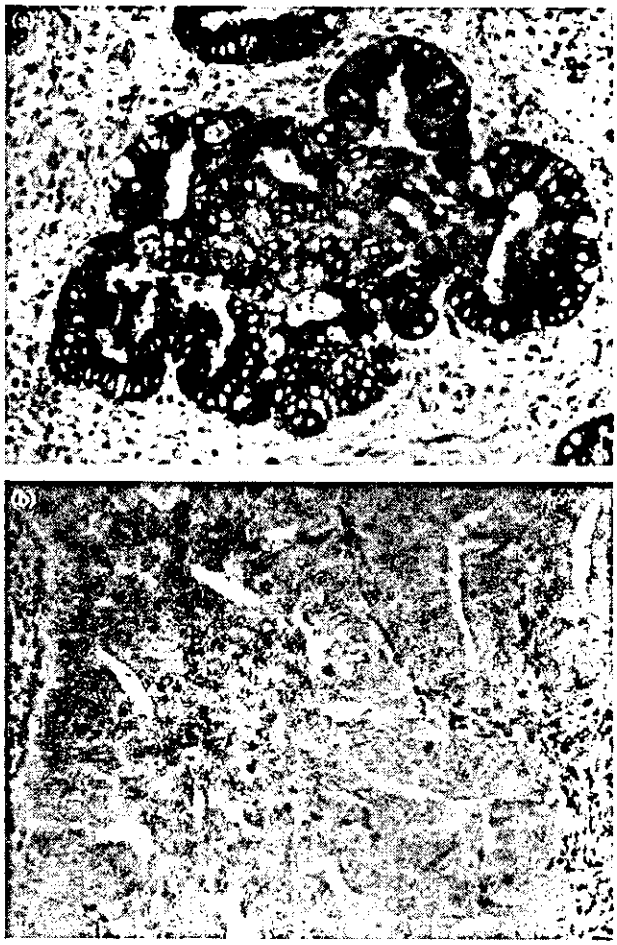

Fig. 1 Immunohistochemistry for 17β-HSD type 2 in a responsive case (a) and a nonresponsive case (b). Original magnification ×200.

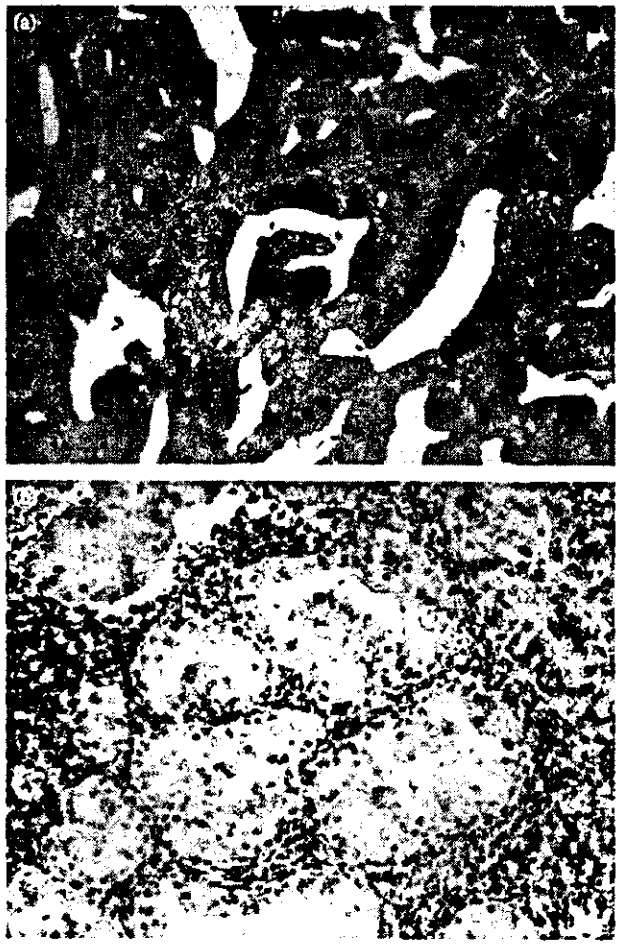

Fig. 2 Immunohistochemistry for PRA + PRB in a responsive case (a) and a nonresponsive case (b). Original magnification ×200.

responsive pretreatment cases were significantly higher than those in nonresponsive pretreatment cases, 17β-HSD type 2 LI ($P < 0{\cdot}01$; $26{\cdot}3 \pm 20{\cdot}7$ *vs.* $0{\cdot}8 \pm 2{\cdot}0$), PRA + PRB LI ($P < 0{\cdot}05$; $40{\cdot}7 \pm 16{\cdot}8$ *vs.* $17{\cdot}3 \pm 6{\cdot}7$), or PRB/PRA + PRB ratio ($P < 0{\cdot}02$; $0{\cdot}52 \pm 0{\cdot}15$ *vs.* $0{\cdot}32 \pm 0{\cdot}12$). There was no significant correlation in 17β-HSD type 1 LI, Ki67 LI, ER LI and age between responsive and nonresponsive pretreatment cases.

Comparison prior to and following treatment

Results are summarized in Table 3. 17β-HSD types 1 and 2 immunopositivity, Ki67 LI, ER LI, PRA + PRB LI and PRB/PRA + PRB ratio were not significantly different prior to and following progestogen therapy.

Discussion

Oestrogens, especially E2, have been demonstrated to contribute greatly to the development and progression of a great majority of endometrial endometrioid adenocarcinomas (Thomas, 1984). Endometrial endometrioid adenocarcinoma in premenopausal women accounts for approximately 5% of all cancer cases. Many of these patients have also been shown to have irregular menstrual cycles, chronic anovulation and infertility, as well as some clinical symptoms of polycystic ovarian syndrome (Gallup & Stock, 1984). These findings suggest that prolonged unopposed oestrogen exposure may induce endometrial hyperplasia progressing to endometrial carcinoma in these premenopausal patients with endometrial endometrioid adenocarcinoma (Ferenczy & Gelfand, 1989). Therefore, it is very important to study the details of these unopposed oestrogenic effects in these patients. 17β-HSD isozymes catalyse the interconversion

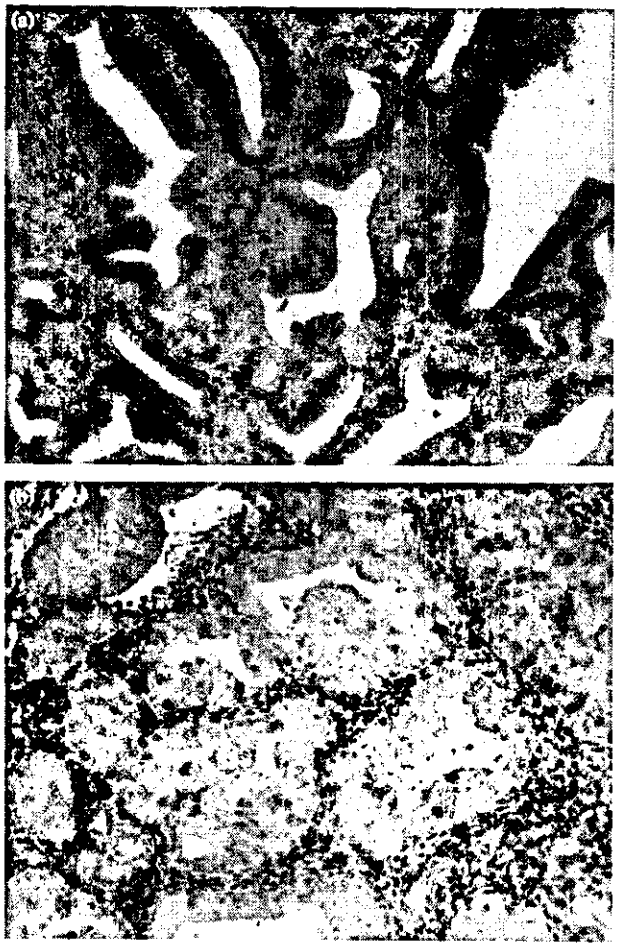

Fig. 3 Immunohistochemistry for PRB in a responsive case (a) and a nonresponsive case (b). Original magnification ×200.

Table 2 Correlation between responsive and nonresponsive pretreatment cases

	Responsive cases	Nonresponsive cases	*P*-value
17β-HSD type 2 LI	26·3 ± 20·7	0·8 ± 2·0	< 0·01
17β-HSD type 1 LI	0·9 ± 1·9	0·8 ± 2·0	NS
Ki67 LI	19·1 ± 13·2	19·2 ± 14·3	NS
ER LI	23·3 ± 19·1	10·3 ± 5·3	NS
PRA + PRB LI	40·7 ± 16·8	17·3 ± 6·7	< 0·05
PRB/PRA + PRB ratio	0·52 ± 0·15	0·32 ± 0·12	< 0·02
Age	30·4 ± 3·2	31·0 ± 6·2	NS

All data are presented as mean ± 95% confidence interval (95% CI).

Table 3 Correlation between pretreatment and post-treatment cases

	Pretreatment	Post-treatment	*P*-value
17β-HSD type 2 LI	18·1 ± 18·8	20·0 ± 24.1	NS
17β-HSD type 1 LI	0·5 ± 1·5	1·0 ± 2·1	NS
Ki67 LI	22·4 ± 13·2	16·2 ± 12·0	NS
ER LI	18·7 ± 18·5	20·5 ± 16·7	NS
PRA + PRB LI	32·0 ± 17·5	35·2 ± 20·2	NS
PRB/PRA + PRB ratio	0·43 ± 0·18	0·46 ± 0·15	NS

All data are presented as mean ± 95% confidence interval (95% CI).

of E2 and E1, and thereby serve to modulate the tissue levels of bioactive E2. 17β-HSD type 1 catalyses the 17β-reduction of biologically inactive E1 to E2 (Peltoketo *et al.*, 1998), whereas 17β-HSD type 2 preferentially catalyses the oxidation of E2 to E1 (Wu *et al.*, 1993). Therefore, the expression of 17β-HSD type 2 in proliferative glandular cells of endometrial disorders may also represent one of the *in situ* defensive mechanisms in modulating unopposed oestrogenic effects.

Progesterone has been demonstrated to exert antioestrogenic effects upon oestrogenic stimuli in the human endometrium, which may also indicate the possibility for progesterone therapy in endometrial proliferative disorders (Clarke & Sutherland, 1990; Delingdisch, 1993; Ace & Okulicz, 1995). MPA treatment has been proposed to be useful for the prevention of the development and progression in some patients with oestrogen-related endometrial proliferative disorders (Niwa *et al.*, 1995). Therefore, MPA has been occasionally administrated to patients with atypical endometrial hyperplasia and endometrioid adenocarcinoma of the well-differentiated type (Ferenczy & Gelfand, 1989; Kim *et al.*, 1997; Randall & Kurman, 1997).

Treatment of complex hyperplasia with or without atypia using progestogens is a relatively well-established treatment and has been administrated to many premenopausal patients with these disorders (Ferenczy & Gelfand, 1989). However, MPA treatment in patients diagnosed with endometrial endometrioid adenocarcinoma has been associated with a much lower rate of success than that of hyperplasia, although these cases demonstrated PR positivity (Randall & Kurman, 1997). Therefore, additional factors may contribute to the prediction of treatment outcome and possible selection of patients. In this study, there was a statistically significant correlation in the response to MPA treatment of patients not only in PR, but also in 17β-HSD type 2 immunoreactive protein expression. These findings suggest that the presence of not only PR but also 17β-HSD type 2 may function as possible indicators of MPA treatment in these patients. 17β-HSD type 2 immunoreactivity has been reported in 75% of endometrial hyperplasia and 37% of carcinoma cases, but not 17β-HSD type 1 (Utsunomiya *et al.*, 2001). Results from this study were also consistent with those reported above.

Progestogens have been reported to increase the rates of conversion of 17β-oestradiol to oestrone and sulphurylate oestrogens within the endometrium (Pack *et al.*, 1979). Therefore, the increase in 17β-HSD type 2 expression during the secretory phase may be caused by increased serum progesterone levels following ovulation. Progestogens may therefore exert a potent antioestrogenic effect in the endometrium by inducing 17β-HSD type 2 and thereby promoting the regression of endometrial proliferative disease.

It is also important to examine PR subsets when evaluating progesterone effects, because hormonal effects through PRA and PRB can be different. In this study, there was a statistically significant correlation between responsive and nonresponsive cases in PRA + PRB LI and PRB/PRA + PRB ratio. Results of recent studies investigating the expression of PR isoforms in human breast carcinoma demonstrated that PRA was more frequently expressed than PRB in 76% of the cases (Graham *et al.*, 1995). Low level PRB expression is considered to cause decreased transcriptional activity of progesterone-responsive genes including those responsible for cell differentiation, thereby concentrating unopposed oestrogen stimulation. Kumar *et al.* (1998) reported that low PRB expression is associated with endometrial cancer cell lines with poor response to progestogen therapy. Therefore, abundant PRB expression in carcinoma cells may be a necessary prerequisite for successful MPA treatment. However, it is also true that the loss of PRA has been reported to result in decreased dominant negative inhibitory activity of ER and oestrogen-dependent cell proliferation (Vegeto *et al.*, 1993; McDonnell *et al.*, 1994), which suggests the involvement of PRA in antagonistic effects of progesterone toward unopposed oestrogen stimuli. These results suggest that MPA exerts its effects through both PRA and PRB, possibly more predominantly through PRB. Further investigations are required to clarify these complex sex steroid interactions and their role in steroid-mediated pathogenesis.

Oestrogen replacement therapy has been linked to the development of endometrial endometrioid adenocarcinoma, and is considered a risk factor, especially with long-term use (Hulka *et al.*, 1980; Genazzani, 1998). Whitehead and associates reported that, if they added progestogens with the oestrogen therapy in menopausal women, they could reduce significantly the risk of the development of cystic or atypical hyperplasia of the endometrium (Whitehead *et al.*, 1981). Therefore, progestogens may exert an antioestrogenic effect on the endometrium. However, the combined oestrogen–progestogen regimen is associated with greater increases in breast cancer risk than oestrogen alone (Schairer *et al.*, 2000). In endometrial endometrioid adenocarcinoma, 17β-HSD type 1 expression and activity were not detected, (Utsunomiya *et al.*, 2001) but nearly half of the cases of breast cancer demonstrated 17β-HSD type 1 expression in carcinoma cells, whereas 17β-HSD type 2 was not expressed (Poutanen *et al.*, 1992; Sasano *et al.*, 1996). 17β-HSD type 2 in the endometrium has been suggested to be induced by progesterone secreted from the corpus luteum during the secretory phase via PR-mediated actions (Gurpide *et al.*, 1977; Satyaswaroop *et al.*, 1982). 17β-HSD type 1 was also induced by progesterone in the breast, predominantly catalysing the conversion of the less potent E1 to the more potent E2 (Poutanen *et al.*, 1995). Therefore, different responses of the combined oestrogen–progestogen regimen between breast and endometrial carcinoma may be related to different patterns of 17β-HSD isozyme expression.

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Docetaxel: an alternative taxane in ovarian cancer

N Katsumata[1,*]

[1]*Department of Medical Oncology, National Cancer Centre Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*

The taxanes paclitaxel and docetaxel are potent chemotherapeutic agents that block tubulin depolymerisation, leading to the inhibition of microtubule dynamics and cell cycle arrest. Although docetaxel and paclitaxel share a mutual tubulin binding site, mechanistic and pharmacological differences exist between these agents. For example, docetaxel has increased potency and an improved therapeutic index compared with paclitaxel, and its short 1-h infusion offers a substantial clinical advantage over the prolonged infusion durations required with paclitaxel. In clinical studies, docetaxel monotherapy demonstrated good response rates and an acceptable toxicity profile in both paclitaxel- and platinum-refractory ovarian cancer patients. In particular, neurotoxicity — a dominant side effect with both paclitaxel and cisplatin — occurs at a low incidence with docetaxel, making docetaxel a promising agent for combining cisplatin and other platinum compounds. In Phase II studies, the combination of docetaxel with either cisplatin or carboplatin has yielded impressive response rates of 69–74 and 81–87%, respectively. Furthermore, Phase III data suggest that docetaxel–carboplatin and paclitaxel–carboplatin are similarly efficacious with respect to progression-free survival and clinical response, although neurotoxicity occurs more frequently with the paclitaxel regimen. While paclitaxel–carboplatin remains the standard treatment for the management of advanced ovarian cancer, docetaxel–carboplatin appears to be a promising alternative, particularly in terms of minimising the incidence and severity of peripheral neuropathy.
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Ovarian cancer accounts for nearly 4% of cancers among women and is the leading cause of gynaecological cancer death in the USA (American Cancer Society, 2003). Indeed, the American Cancer Society estimates that during 2003 a total of 25 400 new cases of ovarian cancer will be diagnosed in the USA, and that almost 14 300 US women will die from this disease (American Cancer Society, 2003). Platinum-based chemotherapy has been the cornerstone of therapy for advanced ovarian carcinomas since the activity — in the early 1980s — of cisplatin-based regimens in ovarian cancer was first reported (Decker *et al*, 1982; Lambert and Berry, 1985; Kaye, 2000). Subsequently, platinum-based combination therapies have been shown to achieve higher clinical response rates and longer progression-free intervals than alkylating agents alone, or nonplatinum regimens, although the evidence for overall survival benefit with such regimens — in cases of advanced ovarian cancer — is less compelling (Aabo *et al*, 1998). More recently, two large randomised trials, one conducted by the Gynecologic Oncology Group (GOG) and the other by the European Organisation for Research and Treatment of Cancer (EORTC), have shown that administration of the taxane paclitaxel in combination with cisplatin significantly improves the duration of progression-free survival and overall survival in women with advanced epithelial ovarian cancer compared with cisplatin–cyclophosphamide therapy (McGuire *et al*, 1996; Piccart *et al*, 2000). Paclitaxel–platinum combinations are therefore replacing platinum-alkylating agent regimens as standard first-line therapy in advanced ovarian cancer (Kaye, 2000). However, since both paclitaxel and cisplatin are neurotoxic, such combinations are associated with a high degree of neuropathy. Two recently published large randomised trials have shown that paclitaxel–carboplatin achieved comparable efficacy and less toxicity compared with paclitaxel–cisplatin (du Bois *et al*, 2003; Ozols *et al*, 2003). It would therefore appear that paclitaxel–carboplatin may provide another first-line chemotherapy regimen for the treatment of advanced ovarian cancer.

Docetaxel is a newer member of the taxoid family, derived by a semisynthetic process from the needles of the European Yew tree *Taxus baccata* (Denis *et al*, 1990). This agent has shown significant activity in a variety of cancers including breast, lung, ovarian, head and neck, and gastric cancers. Like paclitaxel, docetaxel acts as a spindle poison, promoting microtubulin assembly and stabilising the polymers against depolymerisation, leading to the inhibition of microtubule dynamics and cell cycle arrest (Ringel and Horwitz, 1991). Although docetaxel and paclitaxel share a mutual tubulin binding site, mechanistic and pharmacological differences exist. For example, preclinical studies have shown that — compared with paclitaxel — docetaxel is a stronger promoter of tubulin polymerisation *in vitro*, has a longer intracellular half-life and demonstrates greater activity in some tumour models (Barasoain *et al*, 1991; Ringel and Horwitz, 1991; Bissery *et al*, 1995).

Docetaxel has demonstrated potent *in vitro* and *in vivo* cytotoxic activity against a range of tumour types, particularly ovarian cancer. Indeed, docetaxel was found to be 1.2–2.6 times more cytotoxic than paclitaxel and over 1000 times more cytotoxic than cisplatin or etoposide in ovarian carcinoma cell lines (Kelland and Abel, 1992; Engblom *et al*, 1997). Docetaxel has also been shown to act synergistically with cisplatin and carboplatin in epithelial ovarian cancer *in vitro*, and to have potent cytotoxic activity in

*Correspondence: Dr N Katsumata; E-mail: nkatsuma@ncc.go.jp

ovarian cell lines that are resistant to these agents (Kelland and Abel, 1992). Furthermore, there is incomplete cross-resistance between paclitaxel and docetaxel in a range of *in vitro* human tumour cell lines (including ovarian) (Hanauske *et al*, 1992); and in clinical trials, docetaxel 75 or 100 mg m^{-2} every 3 weeks has been found to be an active second-line agent in patients refractory to paclitaxel-based regimens (Verschraegen *et al*, 2000).

Docetaxel and paclitaxel also have substantially different toxicity profiles. Of particular note, docetaxel is associated with only minimal neurotoxicity, which has prompted interest in the use of this agent as an alternative to paclitaxel for inclusion in platinum-based regimens for the management of advanced ovarian cancer (Markman *et al*, 2001; Vasey on behalf of the Scottish Gynaecological Cancer Trials Group, 2002). In the light of these observations, this paper examines clinical experience to date with docetaxel and discusses the potential of this drug as an alternative to paclitaxel in the management of ovarian cancer.

DOCETAXEL MONOTHERAPY

Phase I trials

The clinical efficacy of docetaxel was first reported in Phase I studies in patients with a range of solid tumours (including ovarian cancer) resistant to standard chemotherapy in use at the time of these early trials (Cortes and Pazdur, 1995). These studies identified a short 1-h infusion as the optimal means of delivering docetaxel (Aapro *et al*, 1992; Bissett *et al*, 1993; Extra *et al*, 1993; Cortes and Pazdur, 1995) — offering a substantial clinical advantage over paclitaxel, which requires longer infusion times (3 or 24 h). Neutropenia was the major toxicity reported with docetaxel in Phase I trials; this was dose- but not schedule-dependent (Cortes and Pazdur, 1995). Other side effects included mucositis, hypersensitivity reactions, asthenia and fluid retention, although fluid retention is now routinely prevented by the prophylactic administration of steroids (Cortes and Pazdur, 1995; Kaye *et al*, 1997; Piccart *et al*, 1997).

Phase II trials

The safety and efficacy of docetaxel 100 mg m^{-2} administered every 3 weeks as a 1-h intravenous infusion have been evaluated in four Phase II trials in women with platinum-refractory advanced ovarian cancer. Two of these studies were multicentre European trials conducted by the Early Clinical Trials Group (ECTG) and the Clinical Screening Group (CSG) of the EORTC, and two were single-centre trials conducted in the USA by the MD Anderson Cancer Center (MDACC) and the Memorial Sloan-Kettering Cancer Center (MSKCC) (Aapro *et al*, 1994; Francis *et al*, 1994; Piccart *et al*, 1995; Kavanagh *et al*, 1996). A total of 340 patients were included, all of whom had been previously treated with cisplatin or carboplatin and had recurrent or progressive disease. A summary of the characteristics of the patients enrolled in these trials and their response to docetaxel therapy are provided in Table 1.

Overall response rates across the four individual trials ranged from 26 to 40% (Kaye *et al*, 1997). When response data from the four trials were pooled, there were 14 complete responses and 79 partial responses among the 315 evaluable patients, giving an overall response rate of 30% (95% confidence intervals (CI): 19–36%) (Kaye *et al*, 1997). Importantly, docetaxel maintained this high response rate even in the most platinum-refractory patients, with an overall response rate of 28% (95% CI: 19–36%) in the 155 patients with a treatment-free interval of less than 4 months. The median duration of response and the median survival in the four individual trials ranged from 4.5 to 6.7 months and from 8 to 10.4 months, respectively. The overall response rates obtained with docetaxel in these four Phase II studies compare favourably with the 22% response rate reported with paclitaxel in a large population-based study in women with platinum-refractory disease (Trimble *et al*, 1993).

The toxicity profile of docetaxel was similar across the four trials and reflected observations made in the Phase I studies. Neutropenia was the most frequently reported grade III–IV toxicity (90–96% of patients) and was followed by severe fluid retention, which was experienced by 8–12% of patients. However, none of these studies included steroid prophylaxis, which has since been shown to reduce significantly the incidence and severity of fluid retention, and also the frequency of treatment discontinuation due to this adverse event. Consequently, routine premedication with a steroid (e.g. dexamethasone) has been incorporated in subsequent docetaxel studies. Other grade III–IV toxicities reported in the four Phase II trials in advanced ovarian cancer included acute hypersensitivity (7–10% of patients), diarrhoea (6–10%),

Table 1 Efficacy of docetaxel 100 mg m^{-2} every 3 weeks in women with recurrent or progressive ovarian cancer previously treated with platinum compounds: results from four Phase II studies (adapted from Kaye *et al*, 1997)

	Study			
	ECTG	**CSG**	**MDACC**	**MSKCC**
Patient characteristics				
No. of patients				
Treated	132	124	59	25
Evaluable for efficacy	116	121	55	23
Median age range] (years)	54 30–75]	57 35–76]	58 26–70]	59 36–73]
Interval since prior platinum therapy (% of patients)				
0–4 months	30	38	100	83
4–12 months	35	62	—	17
>12 months	35	—	—	—
Response to therapy (evaluable population)				
Response rates (% of patients)				
Complete response	3	7	5	0
Partial response	25	19	35	35
No change	41	36	38	43
Median response duration range] (months)	6.7 4.1–17.4]	5.8 1.4–13.5]	4.5 1–12]	5.0 3–9]
Median survival (months)	8.4	10.4	10	8

CSG = Clinical Screening Group; ECTG = Early Clinical Trials Group; MDACC = MD Anderson Cancer Center; MSKCC = Memorial Sloan–Kettering Cancer Center.

dermatitis (4–8%) and stomatitis (0–5%). From these Phase II studies, it can be concluded that docetaxel demonstrates significant clinical activity against advanced ovarian cancer and has a different spectrum of toxicity to paclitaxel, which is commonly associated with neuropathy and myalgia.

Phase II trials using low-dose docetaxel

As an alternative to administering prophylactic steroids to reduce the degree of fluid retention, Japanese studies have tended to use lower doses of docetaxel than those used in European and American trials. In a Phase I study conducted in Japan in patients with solid tumours, the maximum tolerated dose of docetaxel without premedication ranged between 70 and 90 mg m^{-2} (Taguchi *et al*, 1994). On this basis, the Japanese Phase II programme for docetaxel was initiated at a dose of 60 mg m^{-2}. However, while this dose generated good response rates in women with breast cancer, results in ovarian cancer were disappointing (only one partial response and no complete responses in 36 evaluable patients) (Noda *et al*, 1994). In a subsequent Phase II pilot study, the dose of docetaxel was increased to 70 mg m^{-2} every 3 weeks in Japanese women with platinum-pretreated advanced ovarian cancer. This resulted in an acceptable tolerability profile and delivered a response rate of 24% in the 25 evaluable patients (Fujiwara *et al*, 1999).

The clinical efficacy and tolerability of docetaxel 70 mg m^{-2} every 3 weeks in advanced ovarian cancer have since been confirmed in a larger Phase II study in Japan (Katsumata *et al*, 2000). Here, 60 women previously treated with platinum-based therapies received a median of four courses of docetaxel, 98% of which were given without the need for dose reduction. Response was achieved in 25% of platinum-refractory patients (within 0–6 months of the platinum-free interval) and 33% of platinum-sensitive patients (within 6 and more months of the platinum-free interval); the overall response rate was 28% for all patients combined. Haematological effects were the main toxicities associated with therapy and were recorded at frequencies similar to those observed in European and US Phase II programmes. However, nonhaematological toxicities tended to be milder than had been reported with higher docetaxel dosages. In particular, there was a low incidence of severe hypersensitivity reactions or fluid retention, despite the fact that steroid prophylaxis was not given in this or any other Japanese Phase II trial. Given that the response rates achieved in this trial were similar to those achieved in the higher-dose European and US trials, reducing the docetaxel dosage to 70 mg m^{-2} may be the preferred chemotherapeutic approach in patients for whom steroid premedication is inappropriate.

DOCETAXEL–PLATINUM: AN ALTERNATIVE FIRST-LINE THERAPY

Overview of docetaxel–cisplatin trials

As mentioned previously, the superiority of paclitaxel–cisplatin regimens as first-line chemotherapy over cisplatin–cyclophosphamide therapy (the previous standard of care) has been established in two large randomised trials in women with advanced epithelial ovarian cancer (McGuire *et al*, 1996; Piccart *et al*, 2000). One of the major limitations of this combination is that both paclitaxel and cisplatin are neurotoxic, and co-administration of these two agents can result in a high incidence of peripheral neuropathy. This has led several groups, including the French Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), the Russian RAMS group and the Scottish Gynaecological Clinical Trials Group (SGCTG), to evaluate the potential of docetaxel as an alternative taxoid to paclitaxel for use in combination with cisplatin in this patient population (Guastalla *et al*, 1999; Vasey *et al*, 1999; Gorbounova *et al*, 2000). In each of these studies, docetaxel 75 mg m^{-2} and cisplatin 75 mg m^{-2} were administered every 3 weeks for six courses with routine steroid premedication.

In an interim analysis of the Russian RAMS study, the overall rate of clinical response to docetaxel–cisplatin among the 38 evaluable patients was 73.6%, of which 42.1% were complete responses and 31.5% partial responses (Gorbounova *et al*, 2000); four patients experienced a pathological complete response. In the GINECO trial, docetaxel–cisplatin was associated with a pathological complete response in 21% of the 43 evaluable patients, and a disease-free survival of 16 months after a median 16 months follow-up (Guastalla *et al*, 1999). In both trials, docetaxel–cisplatin had an acceptable tolerability profile. No unexpected toxicities were reported (neutropenia was the most common adverse event) and the rates of neurological toxicity and fluid retention were low.

The SGCTG trial differed from the RAMS and GINECO studies in that patients were divided into two treatment cohorts: one receiving cisplatin 75 mg m^{-2} plus docetaxel 75 mg m^{-2} ($n=49$), the other receiving cisplatin 75 mg m^{-2} plus docetaxel 85 mg m^{-2} ($n=51$) (Vasey *et al*, 1999). In addition, the study was designed primarily to assess the toxicity of the docetaxel–cisplatin combination, its primary end point being the proportion of patients who discontinued therapy because of fluid retention. Only two-thirds of patients completed the full six courses of therapy, with half of all patient withdrawals being attributed to treatment-related toxicity. However, no patients withdrew because of fluid retention and only 14 patients (14%) developed peripheral oedema requiring diuretics, which confirmed previous reports that premedication with a 5-day course of corticosteroids reduces the severity of this adverse event. The incidence of moderate to severe peripheral neuropathy was low (6% grade III). Among the 39 patients who were available for assessment of clinical response after three or six cycles of chemotherapy, 38% had a complete response and 31% a partial response.

Overview of docetaxel–carboplatin trials

There is now a large body of evidence to suggest that in patients with ovarian cancer, carboplatin provides comparable antitumour activity to cisplatin, but with significantly less toxicity when given as monotherapy or in combination with other agents (Aabo *et al*, 1998). The addition of carboplatin to a taxane regimen was expected to result in less emesis and neurotoxicity than cisplatin–taxane therapy, although concerns were expressed that the combined myelotoxicity of carboplatin and a taxane might result in significant myelosuppression, necessitating dose reduction. However, experience with paclitaxel–carboplatin has shown that the two agents can be given safely without reduction in the dosage of either component (Kaye, 2000; du Bois *et al*, 2003). Indeed, it appears that carboplatin-associated thrombocytopenia is reduced by co-administration of paclitaxel — an effect thought to occur at the level of the megakaryocyte rather than by a general pharmacokinetic interaction (Kaye, 2000). Given these promising results, a series of Phase I/II trials have been conducted to assess docetaxel–carboplatin regimens in this setting, and Phase III trials are underway.

Phase I/II experience

In a recent Phase I trial of docetaxel and carboplatin as first-line therapy, 22 patients with ovarian cancer were given docetaxel as a 1-h infusion immediately followed by a 1-h infusion of carboplatin (Hatae *et al*, 2002). Dose-limiting toxicities of febrile neutropenia and grade IV diarrhoea were seen at the dose level of docetaxel 75 mg m^{-2} and carboplatin AUC 6. Pharmacokinetic data for docetaxel were similar to those reported for docetaxel adminis-

tered as a single agent, and no pharmacokinetic drug-drug interactions were seen. The recommended doses were determined as docetaxel 75 mg m^{-2} plus carboplatin AUC 5 or docetaxel 70 mg m^{-2} plus carboplatin AUC 6.

The efficacy and safety of docetaxel-carboplatin regimens as first-line therapy for epithelial ovarian cancer were first reported by the SGCTG group (Vasey *et al*, 2001). Their feasibility study included 139 eligible patients (median age 56 years; 79% FIGO stage III/IV at presentation) treated at one of five docetaxel-cisplatin dosage levels, with docetaxel doses ranging between 60 and 85 mg m^{-2}, and carboplatin doses ranging between an area under the concentration-time curve (AUC) of 5 and 7 mg ml^{-1}. Treatment was administered every 3 weeks for six planned cycles, with a 3-day prophylactic dexamethasone regimen. The overall clinical/radiological response rate was 66, and 75% of patients had a CA125 response. Median progression-free survival was 16.6 months at a median follow-up of 19 months. Response to therapy at each of the five dosage levels is shown in Figure 1. The incidence of neurotoxicity was extremely low and no patients were removed from the study as a direct result of this side effect. Indeed, grade II/III sensory neurotoxicity was reported by fewer than 6% of patients and there were no cases of motor neuropathy of severity greater than grade I; these rates of neuropathy are substantially lower than those reported with paclitaxel-carboplatin regimens. A summary of the neuropathic toxicities reported at the various dosage levels is provided in Figure 2. As anticipated, neutropenia was the major dose-limiting toxicity. CTC grade IV neutropenia occurred in 75% of patients; however, in only 4% of patients was this effect associated with sepsis, and prophylactic antibiotics or growth factors were not routinely required. Grade IV thrombocytopenia was seen in only 4.2% of patients and there were no cases of thrombocytopenic haemorrhage, which suggests that the platelet-sparing effect of paclitaxel when given with carboplatin also extends to docetaxel and is therefore most probably a class effect of the taxoids. On the basis of these results, the dosage regimens recommended by the SGCTG for further trials were docetaxel 75 mg m^{-2} plus carboplatin AUC 5 or 6.

The activity and safety of docetaxel 70–75 mg m^{-2} plus carboplatin to AUC 5–6 every 3 weeks in women with stage III–IV ovarian cancer have been confirmed in three other Phase II studies involving a total of 66 women, 50 of whom were chemonaïve and 16 of whom had received prior platinum-based therapy (Table 2) (Meyer *et al*, 1999; Kolevska *et al*, 2001; Vorobiof *et al*, 2001). In these studies, 27–52% of patients achieved a complete response and 29–53% a partial response following docetaxel-carboplatin therapy, with overall response rates ranging from 81 to 87% (Table 2) (Meyer *et al*, 1999; Kolevska *et al*, 2001; Vorobiof *et al*, 2001). These response rates suggest that this docetaxel-carboplatin regimen is at least as effective as docetaxel-cisplatin regimens.

In all of the studies, neutropenia was the major toxicity. Neurotoxicity was reported in two of the three studies, but the incidence was very low: Kolevska *et al* (2001) reported grade I neuropathy in seven out of 19 patients, whereas Meyer *et al* (1999) reported grade II neuropathy in two out of 26 patients and grade I neuropathy in 15 out of 26 patients (no cases of grade III or above). Survival and quality of life data have been reported for one of the three studies — Kolevska and colleagues found that first-line therapy with docetaxel 70 mg m^{-2} plus carboplatin to AUC 6 every 21 days was associated with a median progression-free survival of 13.1 months in women with cancer of the ovaries, fallopian tube or peritoneum (at the time of the report, median overall survival had not been reached: 9.2+ months) (Kolevska *et al*, 2001). Over the course of the study, 50% of patients experienced a 10-point improvement in the Functional Living Index: Cancer (FLIC) quality of life questionnaire, with 25% experiencing no change and 25% experiencing a 10-point deterioration in FLIC score (Kolevska *et al*, 2001).

Markman *et al* (2001) have reported similarly high response rates in a Phase II study employing a lower 60 mg m^{-2} dose of docetaxel (Table 2). A total of 50 women with cancer of the ovary and fallopian tube and primary cancer of the peritoneum were treated with docetaxel 60 mg m^{-2} plus carboplatin AUC 6 every 3 weeks for six cycles. The vast majority of patients were chemonaïve (94%) and had stage III–IV disease (88%). Of the 42 patients evaluable for efficacy, 34 (81%) demonstrated objective evidence of a response, with similar response rates being noted in patients with ovarian cancer and those with primary peritoneal cancer. At the time of publication, median progression-free survival had not been reached, but was greater than 16 months. Grade IV neutropenia was the most common toxicity (occurring in 64% of patients) and neuropathy was reported by only three patients (grade I = 1; grade II = 2). Hypersensitivity reactions were relatively common (34%) but did not result in the discontinuation of therapy.

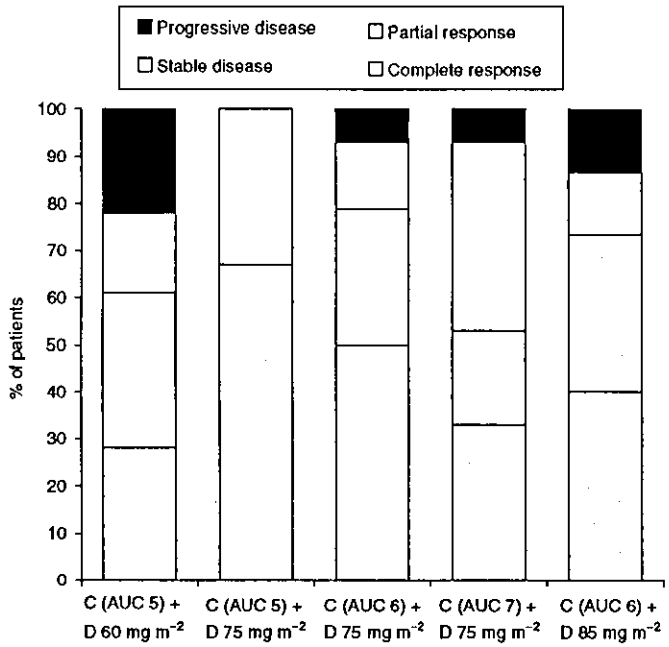

Figure 1 Response rates to first-line docetaxel (D)–carboplatin (C) therapy in a dose-finding study of D 60–85 mg m^{-2} and C AUC 5–7 in women with ovarian cancer (73 evaluable for response) (Vasey *et al*, 2001).

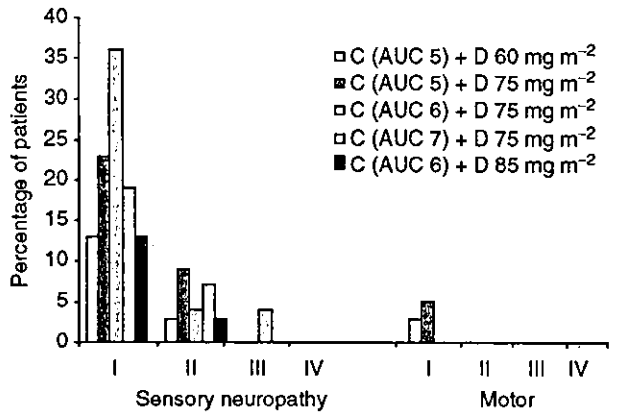

Figure 2 Incidence of neuropathic toxicities reported during first-line docetaxel (D)–carboplatin (C) therapy in a dose-finding study of D 60–85 mg m^{-2} and C AUC 5–7 in women with ovarian cancer (139 evaluable for safety) (Vasey *et al*, 2001).

Table 2 Efficacy and safety of docetaxel (D) 60–75 mg m^{-2} plus carboplatin (C) AUC 5–6 every 3 weeks in women with recurrent or progressive ovarian cancer (OC): results from four Phase II studies (Meyer *et al*, 1999; Kolevska *et al*, 2001; Markman *et al*, 2001; Vorobiof *et al*, 2001)

Reference	Regimen	No. of patients evaluable for		Patient characteristics at presentation	Response rate (% of evaluable patients)			Length of follow-up, median range]	Progression-free survival, median range]	Toxicity (no. of patients)
		Safety	Efficacy		CR	PR	Overall			
Markman *et al* (2001)	D 60 mg m^{-2}+C AUC 6 every 21 days for 6 cycles	50	42	Chemotherapy-naïve (94%) and platinum-pretreated (6%) patients with OC (12% stage I–II; 88% stage III–IV)	NS	NS	81	21+ months 12+ to 41+]	>16 months	Grade IV neutropenia (32); neutropenic fever (8); grade III thrombocytopenia (2); hypersensitivity (17); peripheral neuropathy (3)
Kolevska *et al* (2001)	D 70 mg m^{-2}+C AUC 6 every 21 days for 6 cycles	19	15	Chemotherapy-naïve patients with suboptimally debulked stage IIIc (63%) or IV (37%) OC	27	53	87[a]	8.9 months 0.6–26.4]	13.1 months	Grade III/IV toxicities:[b] neutropenia (15); febrile neutropenia (2); nausea (2); vomiting (1); anaemia (2); thrombocytopenia (3) oedema (1); weight loss (1); dehydration (1); DVT (3); diarrhoea (2)
Meyer *et al* (1999)	D 75 mg m^{-2}+C AUC 5every 21 days for 6 cycles	27	27	Chemotherapy-naïve (41%) and platinum-pretreated (59%) patients with stage III–IV OC	52	29	81	NS	NS	Neutropenia (grade II/III, 24); thrombocytopenia (grade II/III, 7); neuropathy (grade II, 2)
Vorobiof *et al* (2001)	D 75 mg m^{-2}+C AUC 6every 21 days for 6 cycles	20	11[c]	Chemotherapy-naïve patients with stage III–IV OC	46	36	82	NS	NS	Grade III–IV toxicities included anaemia, leucopenia, neutropenia, thrombocytopenia, nausea and vomiting

[a]Includes one minor response. [b]Data presented as number of episodes. [c]Includes patients with measurable disease and excludes those only evaluable for CA125 response.

Phase III trial *vs* paclitaxel

The efficacy and toxicity profile of docetaxel–carboplatin has been directly compared with that of paclitaxel–carboplatin as first-line therapy for stage Ic–IV epithelial ovarian cancer in an international Phase III randomised trial conducted by the SGCTG. The trial, named SCOTROC (Scottish Randomised Trial in Ovarian Cancer), enrolled 1077 chemonaïve patients between October 1998 and May 2000 from 83 centres in 10 countries. Patients were treated with carboplatin to AUC 5 plus either docetaxel 75 mg m^{-2} infused over 1 h or paclitaxel 175 mg m^{-2} infused over 3 h. Survival and longer-term toxicity results were presented at ASCO 2002 (Vasey on behalf of the Scottish Gynaecological Cancer Trials Group, 2002). These results demonstrate that while the paclitaxel and docetaxel regimens are of similar efficacy, there are significant toxicity differences between the two therapies. The median reported follow-up in surviving patients was 21 months, with 94% followed up for more than 1 year. Docetaxel–carboplatin achieved similar median progression-free survival to paclitaxel–carboplatin (15.1 *vs* 15.4 months) and clinical response rates (66 *vs* 62%), but the duration of follow-up is currently insufficient to allow survival comparisons. Nevertheless, paclitaxel–carboplatin was associated with a significantly higher rate of grade II/III sensory neuropathy than docetaxel–carboplatin (30 *vs* 11%; $P<0.01$), while docetaxel–carboplatin resulted in a significantly higher incidence of grade III/IV neutropenia (94 *vs* 82%; $P<0.001$) and febrile neutropenia (10 *vs* 2%; $P<0.001$), although these events were predictable and easily managed (Vasey on behalf of the Scottish Gynaecological Cancer Trials Group, 2002). Global quality of life parameters based on the EORTC QLQ-C30 instrument were comparable in both arms. However, using the ovarian-specific module OV-028 (Cull *et al*, 2001), patients reported significantly less severe symptoms of neurotoxicity (using a score based on tingling in hands or feet and numbness in fingers or toes) with docetaxel–carboplatin than with paclitaxel–carboplatin during treatment and also 6 months after randomisation (both $P<0.001$).

SUMMARY

Over the last few years, the combination of a platinum compound such as cisplatin or carboplatin with paclitaxel has emerged as standard chemotherapy for advanced ovarian cancer (Kaye, 2000). Notwithstanding the clinical and survival benefits afforded by these new regimens compared with previous therapies, mortality from advanced ovarian cancer is high. Thus, research into new agents and new combinations continues apace with the objective of improving overall survival and reducing treatment-related toxicity. Docetaxel offers an alternative taxoid treatment to paclitaxel for use in this setting. Indeed, there is preclinical evidence that docetaxel has greater antitumour potency and a better therapeutic index than paclitaxel (Bissery *et al*, 1995), and its short 1-h infusion also offers a substantial clinical advantage over the 3- or 24-h infusion times required for paclitaxel. In clinical studies, docetaxel monotherapy has demonstrated good response rates and an acceptable toxicity profile in both paclitaxel- and platinum-refractory ovarian cancer patients (Kavanagh *et al*, 1996; Kaye *et al*, 1997; Verschraegen *et al*, 2000). Of particular note, neurotoxicity (a dominant side effect with both paclitaxel and cisplatin) is infrequent and mild with docetaxel, which implies that this drug is a promising new taxane for use in combination with cisplatin and other platinum compounds.

The incorporation of docetaxel into first-line platinum-containing regimens for advanced ovarian cancer has produced successful results. In Phase II studies, overall response rates of 69–74% were achieved with docetaxel 75 mg m^{-2} plus cisplatin 75 mg m^{-2}; corresponding rates with docetaxel 75 mg m^{-2} and carboplatin to AUC 5–6 were 81–87%. The docetaxel–carboplatin combination proved to be better tolerated than the docetaxel–cisplatin combination (Vasey *et al*, 1999, 2001). A Phase III trial comparing docetaxel–carboplatin with paclitaxel–carboplatin suggests that the two taxane regimens are equally efficacious, but demonstrate clear toxicity differences (Vasey on behalf of the Scottish Gynaecological Cancer Trials Group, 2002). In particular, paclitaxel–carboplatin produced significantly more neurotoxicity, leading to early treatment discontinuation compared with docetaxel–carboplatin. While paclitaxel–carboplatin is currently the standard chemotherapy in the clinical setting, docetaxel–carboplatin is an impressive alternative. It appears that certain patient groups – for example, patients at high risk of developing treatment-related neurotoxicity – may benefit from receiving docetaxel as an alternative to paclitaxel in platinum-based regimens (Markman *et al*, 2001; Vasey on behalf of the Scottish Gynaecological Cancer Trials Group, 2002).

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Standardization of the Body Surface Area (BSA) Formula to Calculate the Dose of Anticancer Agents in Japan

Tsutomu Kouno, Noriyuki Katsumata, Hirofumi Mukai, Masashi Ando and Toru Watanabe

Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

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Background: The importance of deciding the appropriate dose of anticancer agents cannot be overemphasized. Body surface area (BSA) has been used to calculate the dose in anticancer therapy since the 1950s. Japanese oncologists, often use their own Japanese BSA formula instead of western BSA formulae. However, it is not widely known that some discrepancies exist between the BSA products of the Japanese and western styles. On the other hand, recently dose-calculations according to BSA were criticized from the standpoint of pharmacokinetics (PK). Lately, we have had many opportunities for international collaborations, which make it necessary to review these BSA formulae, and the BSA-based dosing method. A unified BSA formula in cancer therapy is needed in Japan.

Methods: We searched and compiled frequently used BSA formulae across the world using the MEDLINE search, oncology text, a web search on cancer clinical trial groups, and personally communicated with medical oncologists from western countries. Using these formulae, we calculated BSA for a typical Japanese individual, and compared their products. We calculated BSA using these formulae for individuals of widely varying physique, from 140 to 185 cm in height, and from 30 to 96 kg in weight, and estimated the amount of discrepancies among them.

Results: Among the various BSA formulae used in western countries, the DuBois formula is the standard. In Japan, the Fujimoto formula has been used frequently. The Fujimoto formula was based on a study of 201 Japanese subjects in 1949. For the average Japanese individual, the BSA calculated using the Fujimoto formula was about 3% lower than that which was calculated by western formulae. The BSA calculated for all heights and body weights using the Fujimoto formula, ranged between 0.7 and 4.8% less than those calculated by using the DuBois formula. The other western formulae showed larger discrepancies than the Fujimoto and DuBois formulae.

Conclusion: BSA-based dosing has failed to standardize the variation in PK for most anticancer agents, and individual dosing techniques are currently being investigated. However, until their clinical utilities are confirmed, it is necessary to depend on the BSA-based calculation for determining the dose of most anticancer agents. The DuBois formula, which is the western standard formula, is validated to a greater extent and its accuracy has been confirmed more than others, including the Fujimoto formula. We recommend the use of the DuBois formula instead of the Fujimoto formula in cancer chemotherapy and propose the standardization of this formula in Japan.

Key words: body surface area – dose – calculation – pharmacokinetics – anticancer agents

INTRODUCTION

It is very important to determine the appropriate dose of anticancer agents. Individuals have varying abilities to metabolize and eliminate drugs, and therefore the same dose of anticancer agents will have different pharmacokinetics (PK) and pharmacodynamics (PD). In addition, there is a presumed narrow therapeutic index for most anticancer agents. Reducing the dose of these agents not only reduces toxicity but also the effects on the tumor. This has been shown in breast cancer (1,2), testicular cancer (3), lymphoma (4), and other cancers. It is necessary to balance the ability of the normal tissue to withstand insult and the intrinsic sensitivity of the tumor. Selecting doses of anticancer agents to treat cancer patients can be a challenging decision for medical oncologists.

For all reprints and correspondence: Tsutomu Kouno, National Cancer Center Hospital, 5–1–1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Fax: +81-(0)3-3542-3815.

Table 1. Search results on the BSA formulae

Author	Year of publication	No. of Patients	Formula
DuBois and DuBois (7)	1916	9	$BSA = 0.007184 \times H^{0.725} \times W^{0.425}$
Boyd	1935	411	$BSA = 0.017827 \times H^{0.5} \times W^{0.4838}$
Gehan and George (9)	1970	401	$BSA = 0.0235 \times H^{0.42246} \times W^{0.51456}$
Haycock et al. (10)	1978	81	$BSA = 0.02465 \times H^{0.39646} \times W^{0.5378}$
Mosteller (11)	1987	*	$BSA = \sqrt{H} \times W/3600$
Takahira (5)	1925	Unknown	$BSA = 0.007241 \times H^{0.725} \times W^{0.425}$
Fujimoto (5)	1968	201	$BSA = 0.008883 \times H^{0.663} \times W^{0.444}$

*Conducted by modifying the Gehan and George formula.

In cancer chemotherapy, the doses of chemotherapeutic agents are generally calculated using the body surface area (BSA). Various studies have estimated BSA, and currently several BSA formulae are being used across the world. In Japan, the Fujimoto BSA formula (5), is often used to calculate the dose of anticancer agents in practice or in clinical trials. The Fujimoto formula was first reported approximately forty years ago, and has been subject to the criticism that it may not be suitable for modern Japanese people. Recently, we have had several opportunities for international collaborations and thus we need to standardize the BSA formula. Therefore, we reviewed the BSA formulae and BSA-based anticancer agent dosing, and examined the validity of the Japanese BSA formula.

METHODS

We searched and compiled the frequently used BSA formulae across the world using the MEDLINE search, oncology text, a web search on cancer clinical trial groups, and personally communicated with medical oncologists from western countries. Using these formulae we calculated BSA for a typical Japanese individual, and compared their products. We performed calculations using these formulae for individuals of widely varying physique ranging from 140 to 185 cm in height, and from 30 to 96 kg in weight, and estimated the amount of discrepancies among them.

RESULTS

There were two method groups calculating BSA. The first group utilized both body height and weight. These had the same functional form, that is, $BSA = a0 \times H^{a1} \times W^{a2}$, with different coefficient values. The BSA calculations of the second group did not utilize the preceding formula, and chiefly utilized only body weight. The latter formulae have not been utilized in calculating the dose of anticancer agents because of their inaccuracy (6). Our search results showed seven representative BSA formulae of the former type (Table 1). Among them, the DuBois and DuBois (7), Boyd (8), Gehan and George (GG) (9), Haycock, Schwarta and Wistosky (10) and Mosteller (11) formulae were from western countries, while the Takahira and Fujimoto formulae (5) were from Japan. Among the clinical trial groups, for example, the Southwest Oncology Group (SWOG), described in its policy that the BSA can be determined from weight and height using a nomogram found in standard references (12). The DuBois formula has been used as the standard formula in western countries (13). The Cancer Therapy Evaluation Program (CTEP) in the United States of America has decided not to recommend any particular formula to be used for BSA-based dose calculation in NCI-sponsored treatment trials (12). The Gynecology Oncology Group's (GOG) statistical and data center has adopted western formulae such as the DuBois, Mosteller, Gehan, and Haycock formulae (14), whereas the Japan Clinical Oncology Group (JCOG) has adopted the Japanese Fujimoto formula (15).

For example, in the case of a patient whose height was 170 cm and body mass index was 22 kg/m^2, the BSA calculations using the western formulae and the Takahira formula resulted in similar products, that is, ranging between 1.73–1.75 m^2 (the DuBois formula was at 1.74 m^2). However, for the same example, the BSA calculated using the Fujimoto formula was 1.69 m^2, which was about 3% lower than the others.

Figure 1 graphically displays the discrepancies between the respective formulae and the Fujimoto formula, which is frequently utilized in Japan. Compared to the Fujimoto formula, the Boyd, GG, Haycock and Mosteller formulae have a tendency to overestimate the BSA of short and obese patients and to underestimate it for tall and thin patients. Among these examples, the maximal overestimation was 0.2 m^2 by the GG formula and the maximal underestimation was 0.096 m^2 by the Haycock formula. The discrepancies between the DuBois and Fujimoto formulae ranged between 0.013 m^2 (0.9%) in the shortest and most obese patient (140 cm, 96 kg) and 0.061 m^2 (4.7%) in the tallest and thinnest patient (185 cm, 30 kg). This discrepancy between the DuBois and Fujimoto formulae was smaller than the discrepancies between other western formulae and the Fujimoto formula.

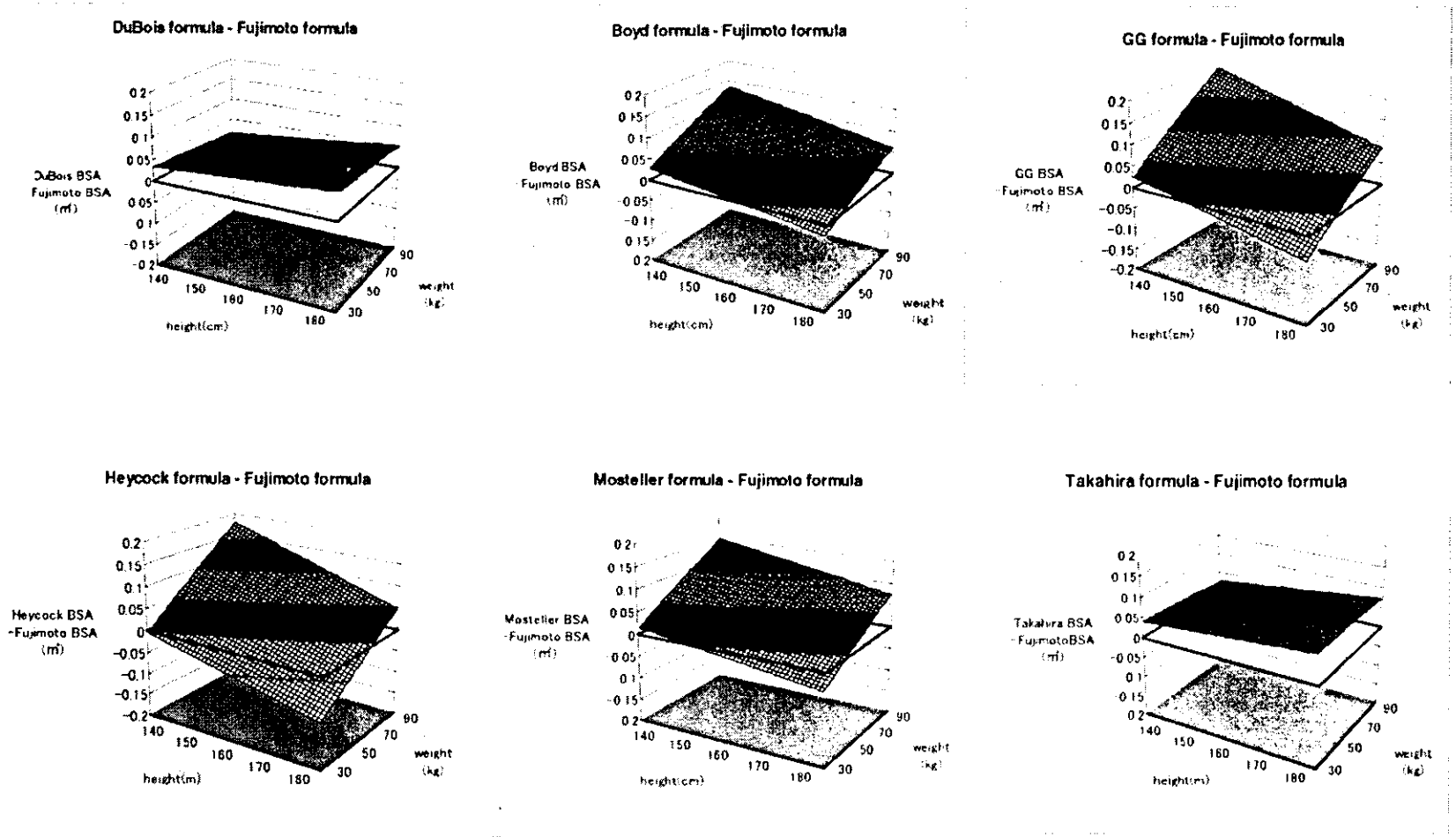

Figure 1. The discrepancies among respective formulae and the Fujimoto formula. The Boyd, GG, Heycock and Mosteller formulae tend to overestimate the BSA of short and obese patients and to underestimate the BSA of tall and thin patients compared to the Fujimoto formula. The discrepancies between the DuBois and Fujimoto formulae range between 0.013 m^2 (0.9%) in the shortest and most obese patient (140 cm, 96 kg) and 0.61 m^2 (4.7%) in the tallest and thinnest patient (185 cm, 30 kg). These discrepancies are smaller than the discrepancies among the other western formulae and the Fujimoto formula.

DISCUSSION

In 1916, DuBois and DuBois reported the BSA formula with direct measurements of nine subjects including a 36-year-old cretin, with an underdeveloped physique, a 12-year-old boy, a tall, thin adult male, and a short, obese adult female (7). In 1935, Boyd reported a formula as a result of investigating 411 subjects (8). In 1970, Gehan and George reported another formula based on the study of 401 subjects (9), and in 1978, Haycock, Schwarta and Wistosky reported another formula based on the measurements of 81 Caucasian, African American and Hispanic subjects (10). In 1984, Martin et al. determined the BSA from 20 aged cadaver subjects by planimetry on paper tracings of dissected skin and compared the measured surface area with the BSA predicted by the DuBois formula. They concluded that the predicted BSA did not differ significantly from the measured surface area and recommended continued use of the DuBois formula (16). In 1987, Mosteller modified the GG formula and simplified it to enable calculation using a pocket calculator (11). This formula has become popular because it is easy to use. In 1992, Wang et al. attempted to determine the accuracy of the BSA formulae proposed in these studies and examined their applicability to patient populations such as neonates and parturients (6). They directly measured the surface area with 60 pregnant women (34 to 40 week gestation) and 148 neonates. Regardless of these highly varying statures, the DuBois formula and other western formulae adequately predicted the measured surface area and they finally recommended the DuBois formula as a standard formula. However, their study did not include the Japanese formulae described below.

In Japan, Takahira et al. (in Fujimoto et al., Ref. 5) considered the DuBois formula inappropriate for Japanese individuals and constructed a new formula based on predetermined conditions, in 1925. In 1968, Fujimoto et al. (5) reported their formula with the direct measurement of 201 subjects, dividing them into three major age groups, namely, infants, children and adults. The Fujimoto formula for adults is one of the most commonly used formulae to calculate the dose of anticancer agents in Japan.

For a typical case where the height was 170 cm and the body mass index was 22 kg/m^2, the five western formulae and the Takahira formula calculations resulted in similar BSA products. However, compared with the other formulae, only the Fujimoto formula underestimated BSA by about 3%. Therefore, it was suggested that the anticancer agents might be underdosed in Japanese patients when using the Fujimoto formula.

BSA was calculated for individuals of widely varying physique from 140 to 185 cm in height, and from 30 to 96 kg in weight. The amount of discrepancies among these formulae was estimated. Since Japanese oncologists frequently use the Fujimoto formula, we evaluated the discrepancies between the Fujimoto formula and the six other formulae. Compared to the Fujimoto formula, the Boyd, GG, Haycock and Mosteller formulae have a tendency to overestimate the BSA of short and obese patients and to underestimate it for tall and thin patients. The discrepancy between the Fujimoto and DuBois formulae was relatively smaller than the discrepancies between the Fujimoto formula and other western formulae.

At present, dose calculations of most anticancer agents are made using BSA. BSA-based cancer chemotherapy began about a half century ago. In 1958, Pinkel (17,18) examined previous studies and determined the conventional pediatric and adult doses for five cytotoxic agents (Mercaptopurine, Methotrexate, Mechlorethamine, Triethylenethiophosphomide, and Actinomycin). For the same drugs, the appropriate therapeutic dose, for experimental animals was also determined from literature. These doses, per unit BSA, were calculated using a representative BSA, estimated using the DuBois formula for humans (7), and for the Meeh's formula for animals (5), which were then compared. It was found that similar values for the doses per unit surface area were obtained for each agent. Then, the use of BSA was recommended for performing dose calculations in chemotherapy. Since the publication of this report, the use of BSA for dose calculations of cytotoxic chemotherapy has become a standard practice.

However, this BSA-based dose calculation was recently criticized (19–22) because it failed to standardize the interpatient variation in PK. PK was analyzed in etoposide (23), calboplatin (24), epirubicin (25), paclitaxel (20), cisplatin (26), CMF (cyclophosmamide, methoterexate, and 5-fluorouracil) (27) and the other anticancer agents or combinations thereof and showed significant interpatient variability regardless of BSA-based dose calculations. With regards to cisplatin, Felix reported a mean plasma clearance of unbounded cisplatin with an interpatient variability of 25.6% (in Moore et al., Ref. 26) and showed that BSA-based dosing did not decrease the variability of unbounded cisplatin clearance. However, Bruno et al. (in Calvert et al., Ref. 28) showed that the variation of docetaxel clearance correlated with BSA. On the whole, most investigators reported that BSA did not correlate with the PK of most anticancer agents.

Besides the BSA-based calculations, several other individual dosing techniques have also been investigated. Calvert et al. (28) showed that the glomerular filtration rate (GFR) alone can predict area under the curve (AUC) for calboplatin, independent of BSA. The dose-calculation formula using patients' GFR was devised to predict AUC for calboplatin. Yamamoto et al. (29) reported that docetaxel clearance did not correlate to BSA and showed that it could be predicted by measuring 6-β-hydroxycortisol after cortisol administration. The possibility of a decrease in the variability of PK and PD by individual dosing of docetaxel is currently being investigated in a prospective trial. However, the complexity of metabolism and elimination of most other cytotoxic drugs makes the deviation of simple formulae difficult, and definitive evidence is awaited.

Therapeutic drug monitoring (TDM) and pharmacological adaptive control has been investigated for some anticancer agents. Methotrexate was one such example. Evans et al. (30) showed, in a prospective trial, that adjusting the dose of methotrexate with TDM to account for the patient's ability to clear

the drug could decrease the variability of PK and moreover, it could improve continuous complete remission in children with B-lineage acute lymphoblastic leukemia. However, TDM can be utilized in the second or later course of chemotherapy because the PK data of the previous course is necessary. Therefore, this technique cannot be used to determine the initial dose, unless a test dose is administered. Further, the introduction of TDM into clinical practice would be difficult because of its cost and inconvenience. Until these problems are overcome or individual dosing techniques are developed, we have to depend on the BSA-based dose calculations for most anticancer agents.

To summarize, the Fujimoto formula is frequently used in Japan. Though this formula was proposed over forty years ago, with the study of 206 Japanese patients, no recent studies have supported the validity of this formula, especially with regard to the modern Japanese physique which has become similar to that of people in western countries. The Takahira formula is not popular and has not been validated. As mentioned above, the results of the Boyd, GG and Haycock formulae showed larger discrepancies as compared with the Fujimoto and DuBois formulae. The DuBois formula has been a standard formula in western countries. Several studies have validated the accuracy of this formula (6,16,19). There was a relatively small discrepancy between the Fujimoto and DuBois formulae. However, the possibility of anticancer agents being underdosed is higher in the Fujimoto formula compared to the DuBois formula. In this age of international collaboration there is a need for a universal cancer treatment. It is therefore necessary to standardize the BSA formula to avoid the complexity of using multiple formulae. We recommend the DuBois formula as the standard BSA formula to calculate the dose of anticancer agents in Japan.

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