

The effect of Gemcitabine/Paclitaxel chemotherapy on the survival of metastatic urothelial cancers

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Word count 244 (abstract) + 2985 (manuscript)

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Abstract

Background

To evaluate the survival benefit of gemcitabine and paclitaxel (GT) chemotherapy for patients with metastatic urothelial cancer (UC), retrospective analysis was performed to compare overall survival in two periods, before (Group I) and after (Group II) the introduction of GT chemotherapy.

Patients and methods

Eighty-five patients with metastatic UC were treated with MEC/MVAC (methotrexate, epirubicin and cisplatin/ methotrexate, vinblastine, doxorubicin and cisplatin) or GT between 1995 and 2007. The response rate, maintenance rate, maintenance duration of each regimen, and the survival time of responding patients in each group were evaluated retrospectively.

Results

The median survival of patients in Group II (20 months) was significantly longer than Group I (13 months) ($p = 0.03$). Especially in patients with a favorable response (CR/PR) to induction chemotherapy, the median survival period was significantly different between Group I and Group II (median 15 months and 28 months, respectively; $p = 0.02$). The rate of the shift to maintenance chemotherapy when using GT chemotherapy was significantly higher than with MEC/MVAC chemotherapy alone ($p < 0.05$), and the cessation rate due to adverse effects was significantly lower when using GT chemotherapy (26.1%) than MEC/MVAC in Group I (42.1%).

Conclusion

Our results demonstrated that the administration of GT chemotherapy may be useful to improve the survival of patients with metastatic UC. This effect was significant, especially among those who were sensitive to the induction course of first-line chemotherapy. The excellent tolerability of GT regimens may be suitable for maintenance chemotherapy.

Mini-abstract

The combination chemotherapy of gemcitabine and paclitaxel showing excellent tolerability and comparable efficacy to MVAC may be beneficial to improve the survival of patients with metastatic urothelial carcinoma.

Key words

gemcitabine / paclitaxel / maintenance chemotherapy / urothelial cancer / second-line chemotherapy

Introduction

Metastatic urothelial cancer (UC) is rarely curable and the prognosis is still poor. It has been two decades since Sternberg et al. investigated the MVAC (methotrexate, vincristine, doxorubicin, cisplatin) regimen and demonstrated a markedly objective response to combination chemotherapy in 1985¹; however, MVAC only achieved short a response duration and low progression-free survival rate in long-term follow-up trials^{2,3}. Moreover, the MVAC regimen causes considerable adverse effects, including myelosuppression, nephrotoxicity, mucositis and neuropathy, and even treatment-related death^{2,4,5}. These toxicities make it difficult to apply MVAC as long-term maintenance chemotherapy or for patients with renal insufficiency or other coexistent clinical disorders. Several new regimens have been developed by modifying MVAC, such as MEC (methotrexate, epirubicin and cisplatin) or MVEC (methotrexate, vincristine, epirubicin and cisplatin), which have been demonstrated to have similar efficacy to MVAC⁶; however, these regimens have similar drawbacks to MVAC chemotherapy. Therefore, it has been an urgent issue to develop novel substitute regimens for metastatic UC to overcome the limitations of MVAC.

In recent years, new representative chemotherapeutic agents, such as gemcitabine and taxanes, have been developed^{7,8}. Especially in the 2000s, the combination of gemcitabine and paclitaxel (GT) was further developed as second-line chemotherapy, which had comparable efficacy to MVAC and fewer adverse effects^{9,10}. Further, the GT regimen also has the advantage of being suitable even for CDDP-unfit patients,

such as those with renal insufficiency or a poor performance status. Several clinical trials have demonstrated that the GT regimen offers an encouraging alternative and promising second-line treatment option for patients with prior cisplatin-based chemotherapy with high response rates and low toxicity⁸⁻¹³; however, it has not been fully elucidated whether administration of the GT regimen can extend the overall survival of patients with metastatic UC.

Our institute adopted the MEC/MVAC regimen as first-line chemotherapy for metastatic UC in the 1990s and then started to use the GT regimen as second-line chemotherapy or chemotherapy for CDDP-unfit patients in 2001. In the present study, we retrospectively analyzed overall survival in the two periods of 1995-2000 and 2001-2007 to evaluate whether the induction of GT chemotherapy was beneficial to improve the survival of patients with metastatic UC.

Patients and methods

Patient characteristics

Eighty-five patients with pathologically confirmed metastatic UC, who were treated by MEC/MVAC or GT between 1995 and 2007 at Kyoto University Hospital, were enrolled in this study (Table 1). These patients were divided into two groups: Group I: 1995-2000 and Group II: 2001-2007 because we started GT chemotherapy as second-line chemotherapy or chemotherapy for CDDP-unfit patients in 2001. No chemotherapy was given within 4 weeks before the study was initiated. Patients were required to have an adequate bone marrow reserve (platelet count $>100,000/\mu\text{l}$, white blood cell (WBC) count $>3000/\mu\text{l}$, hemoglobin level $>10\text{ g/dl}$) and normal hepatic function (serum bilirubin $<1.5\text{ mg/dl}$). Additional requirements for the MEC/MVAC regimen included normal renal function (pretreatment creatinine clearance $>50\text{ ml/min}$). On the other hand, the GT regimen could be adapted regardless of renal impairment, although the dose was reduced to 50-80% for a serum creatinine level $>2\text{ mg/ml}$ or ECOG performance status >2 . During these periods, GC (gemcitabine + cisplatin) chemotherapy was not administered in our institute. All patients who were enrolled in this study signed a written informed consent form. All of the procedures followed were in accordance with the ethical standards of the Institutional Review Board at the Kyoto University Graduate School of Medicine and the Declaration of Helsinki.

Treatment strategy

For the MVAC regimen, methotrexate 30 mg/m² on days 1, 15, and 22, vinblastine 3 mg/m² on days 2, 15, and 22, doxorubicin 30 mg/m² on day 2, and cisplatin 70 mg/m² on day 2 were administered intravenously every 4 weeks. For the MEC regimen, methotrexate 30 mg/m² on day 1, epirubicin 50 mg/m² on day 1, and cisplatin 50 mg/m² on days 2 and 3 were given intravenously every 4 weeks. For the GT regimen, gemcitabine 2500 mg/m² and paclitaxel 150 mg/m² on day 1 were infused intravenously every 2 weeks. From 1995 to 2000, MEC/MVAC was adopted as the standard chemotherapy regimen for patients with metastatic UC. Since 2001, MEC/MVAC has been used as the first-line chemotherapy, and GT as second-line chemotherapy or for CDDP-unfit cases. After the initial one to two cycles of first-line chemotherapy, defined as induction chemotherapy in this study, the response was assessed by CT scan. If progressive disease (PD) was seen, defined as an increase >25% in the size of measurable lesions or the development of any new lesions, the chemotherapy was ceased, followed by the best supportive care (BSC) or other chemotherapy regimens. If the response was stable disease (SD) or favorable (partial response (PR) or complete response (CR)), the same regimens were continued until disease progression or severe toxicity was observed, or patients asked to cease the treatment. Maintenance chemotherapy was defined as 3 or more cycles of administration of the same regimen. When disease progression or severe toxicity was observed in maintenance chemotherapy, the chemotherapy was ceased, followed by the best supportive care or other chemotherapy regimens, as well as in the case of

induction chemotherapy. For some responding cases, dosage and intervals were changed appropriately, so as to use the optimal dosage and intervals of drug administration.

The response rate, maintenance rate, maintenance duration of each regimen, and the survival time of responding patients in each group were evaluated retrospectively. Kaplan-Meier survival curve showed the data within 60 months because of the difference of observation periods between two groups.

Response criteria

Tumor size and new lesions were measured on CT scan at baseline and after each two cycles of chemotherapy or as clinically indicated. Responses were evaluated by the New Response Evaluation Criteria in Solid Tumors: Revised RECIST guideline (version 1.1)¹⁴. The non-parametric Mann-Whitney U-test was used to compare groups. The duration of survival was calculated from the initiation of first-line chemotherapy to the date of death or to the last follow-up. Survival rates curves were constructed using the Kaplan–Meier method. The log-rank test was performed to test associations between chemotherapy and survival. A *p* value <0.05 was considered significant. Toxicity grade was defined according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), Version 4.0.

Results

1. Response

The patient characteristics are shown in Table 1. From 1995 to 2007, 85 patients with metastatic UC were enrolled in this study; 37 and 48 patients were enrolled in Group I (1995-2000) and Group II (2001-2007), respectively. There was no significant difference in patients' background, such as age, status of primary focus, perioperative chemotherapy and metastatic sites between Group I and Group II. The 37 patients in Group I were treated with MEC/MVAC as first-line chemotherapy, although 14 patients received several kinds of perioperative chemotherapy, consisting of MEC, MVAC, CISCA, transarterial infusion of CDDP and doxorubicin for 6, 3, 4 and 1 patient, respectively. On the other hand, 30 patients in Group II were treated with MEC/MVAC as first-line chemotherapy and 18 were treated with GT as first-line chemotherapy because of a CDDP-unfit status (n=5) or a history of perioperative MEC/MVAC chemotherapy (n=13). As second-line chemotherapy, 16 patients received GT chemotherapy after MEC/MVAC chemotherapy.

Response rate of chemotherapy is shown in Table2. Favorable response rates (CR or PR) with the MEC/MVAC regimen were 51.4 % in Group I and 63.3% in Group II, respectively. In Group II, first-line GT chemotherapy showed a 61.1% favorable response rate. Among these patients, 7 (53.8%) of 13 patients with perioperative chemotherapy and 4 (80.0%) of 5 CDDP-unfit patients achieved CR or PR. Overall, there was no difference in the response rate to first-line chemotherapy

between Group I and Group II (51.4% vs. 62.5%, respectively: $p = 0.9409$). Clinical courses in Group II are described in Figure 2. There was a second-line GT chemotherapy for patients treated with MEC/MVAC in Group II, but no standard regimen for second-line treatment in Group I existed. Although most patients with progressive disease after MEC/MVAC shifted to BSC, 5 continued 1 to 3 cycles of other regimens despite poor response. Among them, two patients received TIP (paclitaxel, ifosfamide and CDDP), other two received transarterial infusion of CDDP (and doxorubicin) for liver metastasis, and another received CISCA.

The response rate with second-line GT in Group II was 18.8% overall. When the chemotherapy regimen was changed because of a poor response to first-line MEC/MVAC (MEC/MVAC refractory case), no favorable response was achieved, whereas 3 of 5 (60%) patients who ceased first-line MEC/MVAC because of severe adverse effects (MEC/MVAC-sensitive cases) showed a favorable response to GT ($p < 0.05$).

2. Survival time

Overall survival was examined in Group I and II (Fig. 1a). The median survival period of patients in Group II (20 months, 95% confidence interval [CI] 14-29 months) was significantly longer than in Group I (13 months, 95% confidence interval [CI] 10-16 months) ($p = 0.03$).

The median survival period of SD/PD patients in Group I was 9 (95% [CI] 6–11) months, which did not significantly differ from that of SD/PD patients in Group II

(median 10, 95% [CI] 8–19 months; $p = 0.8$), indicating that the administration of GT chemotherapy did not contribute to the improvement of survival of patients with a poor response (SD/PD) to induction chemotherapy. On the other hand, among patients with a favorable response (CR/PR) to induction chemotherapy, the median survival period was significantly different between Group I and Group II (median 15 (95% [CI] 12–17) months and 28 (95% [CI] 19–48) months, respectively; $p = 0.02$). These results indicate that the administration of GT chemotherapy might contribute to the improved survival of chemotherapy-sensitive patients (Fig. 1b, c).

3. How to continue chemotherapy for PR/CR cases

Based on the above results that the survival of patients with a favorable response (CR/PR) to induction chemotherapy was improved in Group II, the differences in overall treatment for those patients in the two groups were examined (Table 3).

Among 19 CR/PR cases in Group I, although 15 patients (78.9%) could shift to maintenance MEC/MVAC, 8 patients (42.1%) had to cease chemotherapy because of severe adverse effects. The average of the total cycles of chemotherapy was 4.5 cycles (2-14 cycles). In Group II, 19 patients showed CR/PR with induction MEC/MVAC chemotherapy. Twelve received second-line GT chemotherapy, 11 of whom (91.7%) could shift to maintenance chemotherapy. The average of the total cycles of chemotherapy for those patients was 7.2 cycles (2-14 cycles). Moreover, 11 of 18 patients who received first-line GT chemotherapy achieved CR/PR and 10 (90.9%) could shift to maintenance chemotherapy, resulting in 5.5 cycles of chemotherapy

(1-9 cycles). These results indicate that the rate of the shift to maintenance chemotherapy when using GT chemotherapy was significantly higher than with MEC/MVAC chemotherapy alone ($p < 0.05$). Further, the cessation rate due to adverse effects was significantly lower when using GT chemotherapy (26.1%) than MEC/MVAC in Group I (42.1%). This less toxic aspect of GT chemotherapy may contribute to the high maintenance rate and longer survival period in favorable responders. Finally, frequencies of adverse events are shown in Table 4. Neutropenia was the most common serious toxicity observed in 21 patients (61%) but grade 4 neutropenia was observed only in one patient (3%). Bleeding episodes or anemia was not observed. Among non-hematological toxicity, neuralgia and myalgia were the most common toxicities observed in 12 patients (35%), respectively. All were Grade 1 or 2 and controlled by NSAIDs or Chinese herb, but long-lasting symptoms caused treatment cessation in some patients. Three patients had interstitial pneumonitis (IP) possibly attributed to gemcitabine in the initial experience, but later no IP was observed in this study.

Discussion

Our institute adopted the MEC/MVAC regimen as first-line chemotherapy for metastatic UC in the 1990s and then started to use GT regimen as second-line chemotherapy or chemotherapy for CDDP-unfit patients in 2001. This retrospective outcome study demonstrated that the GT regimen was as effective as MEC/MVAC, except for MEC/MVAC refractory cases. Furthermore, comparison of the overall survival suggested that introduction of the GT regimen may contribute to the improved survival of patients with metastatic UC, especially patients with a favorable response to induction chemotherapy in first-line chemotherapy, while MEC/MVAC chemotherapy is still an appropriate regimen for those who can tolerate such intensive chemotherapy.

First-line MEC/MVAC chemotherapy showed an initial response rate of 50–70%, but only achieved a short response duration and low progression-free survival rate in long-term follow-up trials^{2,3}. Moreover, the MVAC regimen caused multiple adverse effects, including myelosuppression, nephrotoxicity, mucositis and neuropathy, and even treatment-related death, and the overall survival of patients with metastatic urothelial cancer is still approximately 10% after 2 years. Patients with renal insufficiency or a poor performance status are not suitable for these cisplatin-containing regimens and, further, an effective and safe regimen against cisplatin refractory cancer is required as second-line chemotherapy. Several reports have demonstrated the effectiveness of carboplatin instead of cisplatin for these patients, but the efficacy of carboplatin is still controversial when compared with

cisplatin^{15,16}. As other candidates, combination regimens of new agents without cisplatin have been investigated, such as gemcitabine and epirubicin, or gemcitabine and docetaxel, but the response rate of these regimens was not superior to that of GT chemotherapy¹⁷⁻¹⁹. Previous trials assessing GT chemotherapy have demonstrated a variable response rate of 38–69%⁸⁻¹³. Our results demonstrating an overall response rate to GT chemotherapy of 41% (14 of 34 patients) are compatible with previous results. In detail, first-line GT chemotherapy was effective for 61% of patients, a similar response rate to previous MEC/MVAC chemotherapy. In particular, the high response rate (80%) of CDDP-unfit patients may indicate that the GT regimen is a promising regimen for these patients. As second-line chemotherapy, the favorable response rate was 0% and 60% in MEC/MVAC refractory patients and sensitive patients, respectively, although 45% of MEC/MVAC refractory patients achieved stable disease with GT. As recent reports suggested that there may be some correlation between the response to first-line MEC/MVAC and the response to second-line GT^{12,13}, we think that chemoresistant characteristics both against GT and MEC/MVAC may originate from a genetic or epigenetic background in bladder cancer, and that novel molecular target therapies based on DNA microarray or proteomics are necessary to overcome this problem.

Because most previous reports regarding GT chemotherapy showed an overall response rate to GT chemotherapy but did not describe the survival benefit of this regimen⁸⁻¹³, we think that the important finding of our study is that the introduction of combination chemotherapy of gemcitabine and paclitaxel may be beneficial to extend

the survival of patients with a favorable response to induction chemotherapy in first-line chemotherapy. Our results showed that the median survival of chemosensitive patients was significantly improved after introduction of the GT regimen. One of the most important reasons may be the less toxic aspect of the GT regimen, because GT could be adopted for 5 CDDP-unfit patients, 4 of whom achieved a favorable response and, further, because the cessation rate due to adverse effects was significantly lower when using GT chemotherapy (26.1%) in Group II than MEC/MVAC in Group I (42.1%). We reported the initial experience of GT chemotherapy in our institute previously, showing no grade 3 gastrointestinal or neuronal side effects, although 26% of patients had grade 3 myelosuppression and 4% had grade 3 interstitial pneumonitis²⁰. After the first report, we eventually did not see any more discontinuance of GT chemotherapy because of severe toxicity. We think that patient selection is important to prevent severe interstitial pneumonia, but the GT regimen is advantageous to continue maintenance chemotherapy because of its excellent tolerability as first-line chemotherapy for CDDP-unfit patients and as second-line chemotherapy for CDDP-treated patients.

The limitation of this study is that data were collected retrospectively from different periods and includes only a small number of patients. The dosage and intervals were changed appropriately to use the optimal settings. From the results that response rate with PR/CR of MEC/MVAC therapy in group II (63.3%) is higher than that in group I (51.4%), improvement of survival may be influenced by other factors including development of supportive care such as bisphosphonate or appropriate

radiation therapy. Further, 12 patients treated with MEC/MVAC in group II could not receive second-line GT chemotherapy because of acute disease progression, severe adverse effect after multiple cycles of MEC/MVAC, although 7 of 12 patients showed the good initial response to MEC/MVAC. We think that it is important in the future prospective study to clarify the criteria to shift from first-line to second-line chemotherapy to show the benefit of second-line GT chemotherapy, because less-toxic maintenance GT regimen possibly show its benefit especially to MEC/MVAC sensitive patients. Metastatic sites may have an influence on the response and survival rate after chemotherapy, although our previous report showed that there was no significant difference in response rate to GT chemotherapy²⁰. To clarify the effect of GT chemotherapy, a multi-institutional prospective and randomized trial is warranted. Recently, GC chemotherapy has become the standard first-line chemotherapy instead of MEC/MVAC chemotherapy after reports of randomized trials^{21,22}. GC chemotherapy is also recommended as first-line chemotherapy in the Japanese guideline for invasive bladder cancer²³, and we changed our first-line chemotherapy from MEC/MVAC to GC in 2008. GC chemotherapy is less toxic and can be continued for more cycles than MEC/MVAC (commonly continued for 6 cycles as induction chemotherapy); however, because the efficacy of GC chemotherapy is not superior to MEC/MVAC, and its adoption for CDDP-unfit patients is still difficult, we think that it may be important and meaningful to elucidate the significance of second-line GT chemotherapy in the age of GC chemotherapy.

Conclusions

Our results demonstrated that the administration of GT chemotherapy may be useful to improve the survival of patients with advanced or metastatic urothelial cancer. This effect was significant, especially among those who were sensitive to induction courses of first-line chemotherapy. The excellent tolerability of the GT regimen may be advantageous as maintenance chemotherapy. Prospective exploration of the optimal dosage or intervals of GT administration, which can maximally prolong the survival time, are warranted.

The authors have no conflicts of interest to declare.

Figure legends.

Figure 1. Overall survival rate of all patients in Group I (red line) and Group II (blue line)(1a). Overall survival rate of poor responders (SD/PD) to induction chemotherapy (1b) and favorable responders (CR/PR) (1c).

Figure 2. The treatment course in group II.

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Table 1. Patients' characteristics in Group I and Group II

	Group I (1995-2000)	Group II (2001-2007)	p value
No. of patients	37	48	
Gender (male ; female)	27;10	35;13	>0.9999
Age	63 (46-84)	66 (37-79)	0.1055
Primary focus			
Location (bladder ;renal pelvis and ureter)	16;24	29;26	0.2983
Depth of invasion (pTa;1;2;3;4;X)	4;7;5;11;7;6	2;9;10;21;11;2	0.2703
Operation before chemotherapy (total cystectomy; nephroureterectomy)	15;17	20;26	0.8195
Perioperative chemotherapy	14	18	>0.9999
Metastasis			
lymph nodes;lung	20;16	25;21	0.7797
bone;liver;others	8;4;5	14;11;7	

Table 2. Response rate of MEC/MVAC or GT chemotherapy

		n	PR/CR	SD	PD
Group I (1995-2000)	MEC/MVAC	37	19 (51.4%)	12	6
	MEC/MVAC	30	19 (63.3%)	4	7
Group II (2001-2007)	first-line GT	18	11 (61.1%)	2	5
	" perioperative MEC/MVAC "	13	7 (53.8%)	2	4
	" CDDP-unfit "	5	4 (80.0%)	0	1
	second-line GT	16	3 (18.8%)	6	7
	" MEC/MVAC refractory "	11	0	5	6
	" MEC/MVAC sensitive "	5	3 (60.0%)	1	1

* The response was assessed by CT scan after the 2 initial courses of chemotherapy

Table 3. Prognosis of the patients with CR/PR by the induction chemotherapy

	regimen	n	mean cycle	maintenance rate	Reasons for cessation			chemotherapy continued
					PD	adverse effect	CR	
Group I (1995-2000)	MEC/MVAC	19	4.5 (2-14)	15 (78.9%)	9	8	1	1 (with salvage operation)
	MEC/MVAC	7	3.4 (2-6)	4 (57.1%)	2	3 (2 with salvage operation)	0	2
Group II (2001-2007)	MEC/MVAC → GT	12	3.4 (1-5) → 4.0 (1-13)	11 (91.7%)	5	4	0	3
	GT	11	5.5 (1-9)	10 (90.9%)	8	2	1 (with salvage operation)	0

Table 4. Adverse effect of GT regimen (NCI-CTC grade)

Toxicity	Grade 1-2 (%)	Grade 3-4(%)
Neutropenia	29	32
Nausea, vomiting	18	0
Neuralgia	35	0
Myalgia	35	0
Diarrhea	12	0
Interstitial pneumonia	9	3
		(% of patients)

Figure 1.

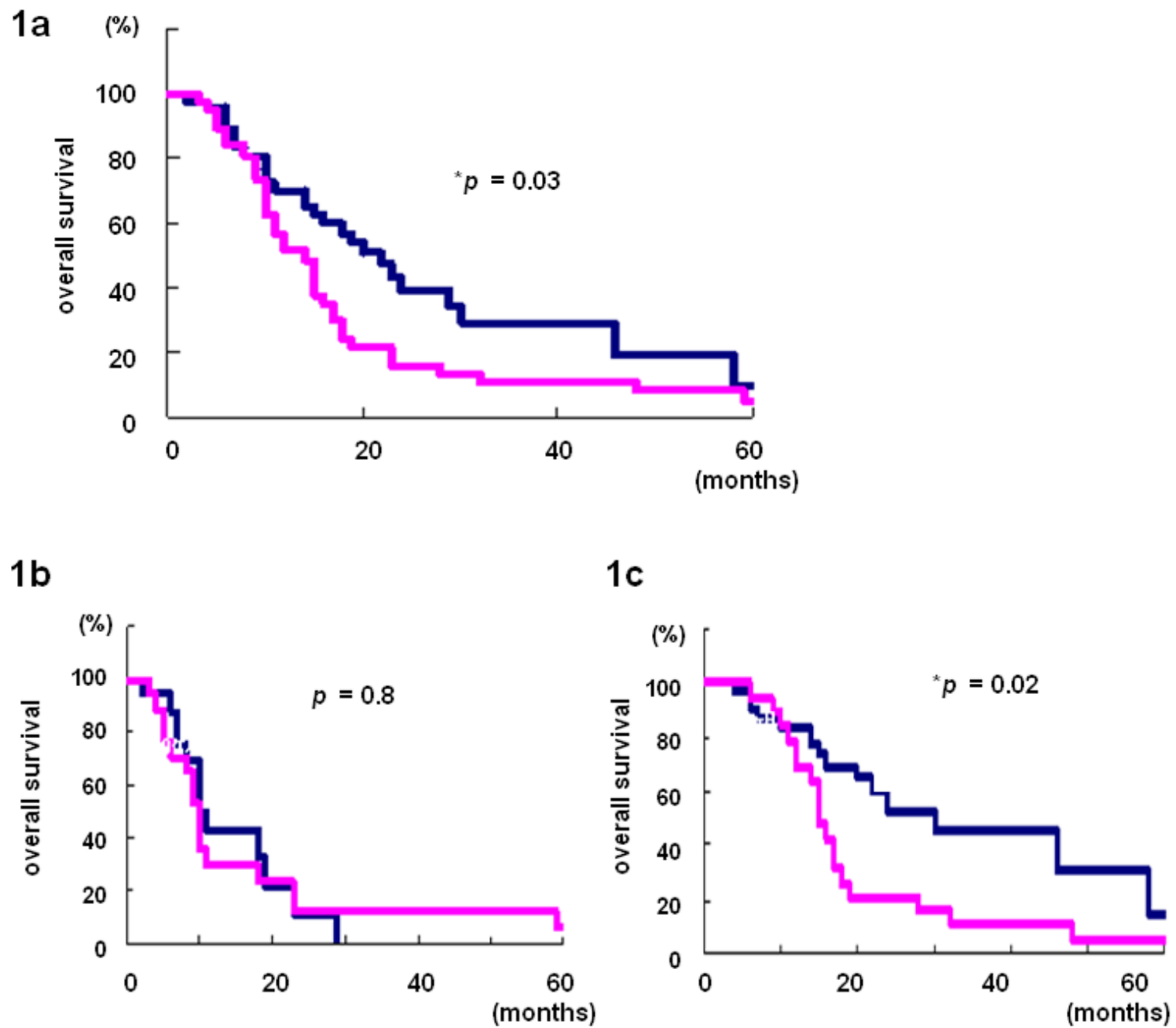
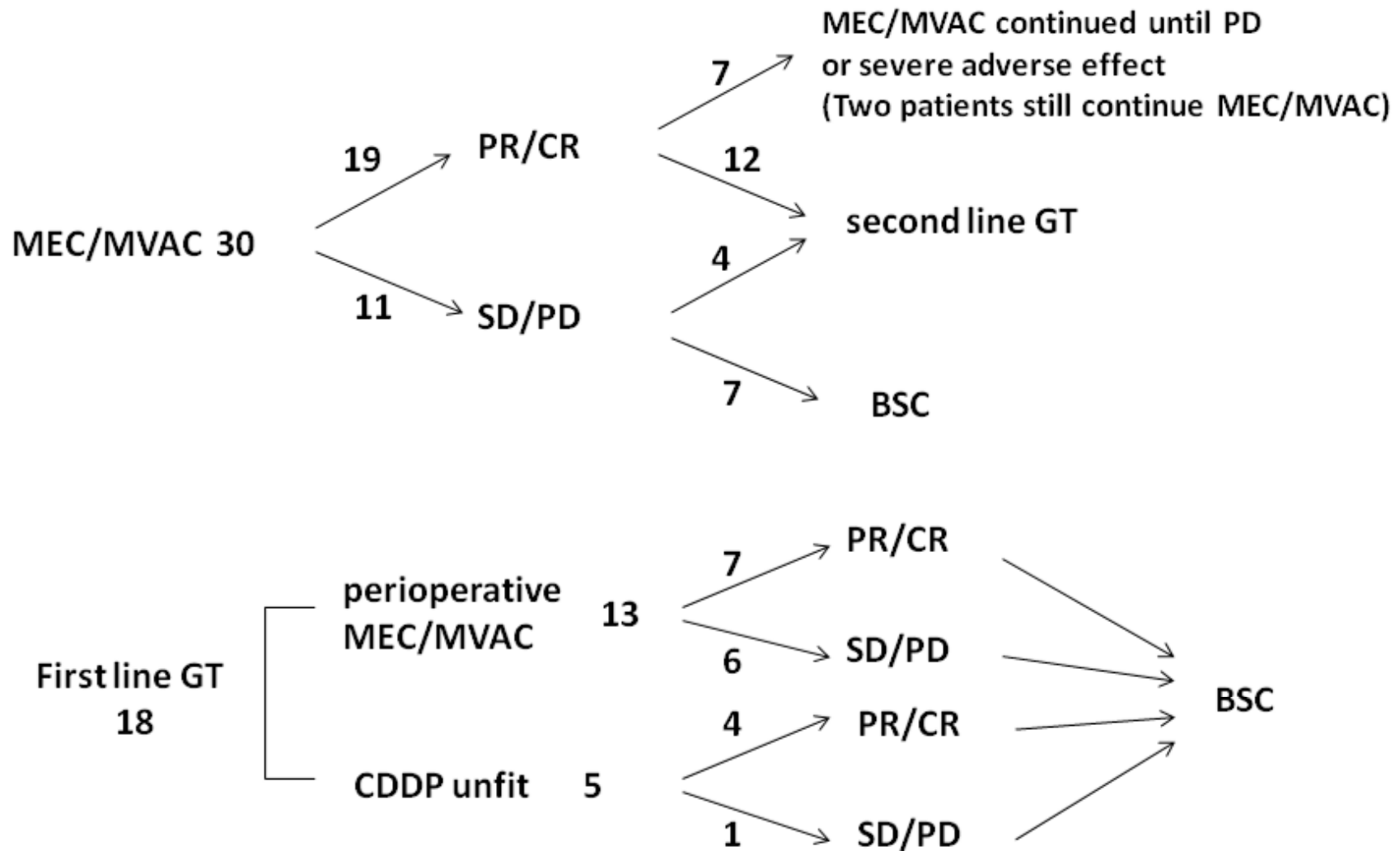


Figure 2.



(CR/PR/SD/PD : response to 2 initial courses of chemotherapy)