permitted.

② Intraperitoneal examination: Immediately after laparotomy, intraperitoneal visual examination and palpation will be performed to determine the presence or absence of hepatic and peritoneal metastasis, and intraoperative lavage cytology from the pouch of Douglas will be performed.

③ Lymph node dissection:

a) In the event of paraaortic lymph node (No.16a2/b1) metastasis: D2+No.16 lymph node dissection will be performed.
b) In the event of bulky lymph node metastasis: D2+No.16 lymph node dissection will be performed.
c) Regional lymph node metastasis of 15 mm or more in size (minor axis): D2 lymph node dissection will be performed.

＜D2 dissection＞

In total gastrectomy lymph nodes No.1 to 7, 8a, 9, 10, 11, and 12a will be dissected. However in the event of esophageal invasion, lymph nodes No.19, 20, 110, and 111 will be additionally dissected.

In distal gastrectomy, lymph nodes No.1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, and 12a will be dissected.

＜No.16 dissection＞

Paraaortic lymph nodes No.16a2/b1 will be dissected.

④ Gastrectomy: Total gastrectomy or distal gastrectomy will be performed.

⑤ Combined resection of surrounding organs: In the event that the tumor extends to the greater curvature of the upper stomach, and macroscopic type 4 tumors, total gastrectomy combined with splenectomy will be performed. If the tumor does not extend to the greater curvature of the upper stomach or is not macroscopic type 4, the spleen will be preserved. In the event of direct invasion into adjacent organs, if combined resection is possible, then the portion of the organ with the invasion, or total resection will be performed. If it is determined that pancreaticoduodenectomy will enable R0 resection, then pancreaticoduodenectomy should be performed. If R0 resection is achieved then the protocol treatment will continue. In the event that performing pancreaticoduodenectomy will only result in R1 and R2 resection, then pancreaticoduodenectomy will not be performed.

⑥ Reconstruction: Reconstruction will be performed in accordance with the guidelines of each institution.

⑦ Bursectomy: The performance of bursectomy is not prescribed in this protocol and shall be performed as per the policy of each institution.

In the event that factors indicating M1 (excluding No.16a2/b1) including P1, H1, and CY1 are found (Japanese classification of Gastric Carcinoma. 14th ed.), the decision to perform surgery will be examined in accordance with the following criteria 'determination of additional surgery ① and ②'.

＜Determination of additional surgery＞

① In the event that R0 resection is deemed possible with additional resection within reason

→ Surgery with additional resection will be performed as part of the protocol treatment

② In the event that R0 resection is deemed impossible → termination of the protocol treatment

'Additional resection' noted above is defined as the resection of lymph nodes exceeding the stipulated

dissection range, combination resection of adjacent organs, and additional resection for peritoneal metastasis surrounding the stomach. Gastrectomy with esophagectomy by thoracotomy, upper left abdominal exenteration, and surgery using Appleby's method will not be permitted.

6.1.3. Postoperative adjuvant chemotherapy (S-1 monotherapy)

If the patient is diagnosed by postoperative pathological findings as R0 according to the 14th edition of the Japanese Classification of Gastric Carcinoma, he or she will start on oral treatment with S-1 within six weeks from the gastrectomy (by 42 days from day 0, the day of the procedure). If he or she could not start on oral treatment with S-1 within 12 weeks frot the gastrectomy (by 84 dayse from day 0, the day of the procedure), the protocol treatment will be terminated. One course shall consist of 28 days of consecutive treatment with S-1 and a 14 day washout period, with S-1 administered for one year postoperatively (8 courses: 48 weeks). The S-1 treatment period shall last until one year after the procedure, with the patient not starting on any new courses until one year has passed from the day of the procedure (until the same date one year after the day of the procedure).

The terms "course" and "term" are defined as follows in this trial.

Course: One course shall consist of 28 days of consecutive treatment with S-1 and a 14 day washout period.

Term: One term shall consist of 14 days of consecutive treatment with S-1 and a 7 day washout period. Two terms shall count as one course.

In accordance with the criteria for skipping in 6.3.2, one course may consist of two terms of two-week treatment and a one week washout period (totaling 42 days) if there is a schedule change. In the event of two weeks of treatment with a one-week washout period, the patient shall not start a new term until the same date one year after the day of the procedure.

If the patient is found intraoperatively to be CY1 and thus diagnosed as R1, protocol-based treatment is discontinued after the procedure, and the patient is free to pursue other forms of treatment.

However, when continued use of flucytosine (antifungal agent: Ancotil®, Domerajin®, Chokol®) is necessary, S-1 will not be administered since flucytosine is contraindicated for coadministration with S-1. If flucytosine administration can be discontinued, the patient should be started on S-1 after flucytosine is discontinued.

If the patient is under continuous administration of phenytoin or warfarin potassium when starting postoperative adjuvant chemotherapy, it should be noted that caution is required when administering those two drugs in combination with S-1. Thus whether phenytoin/warfarin potassium can be discontinued should be carefully investigated when starting S-1. If discontinuing these drugs is not possible, the patient should be fully monitored for signs of phenytoin poisoning and changes in coagulability, with reduction in dosage of phenytoin/warfarin potassium or reduction in dosage or discontinuation of S-1 conducted as necessary.

If the S-1 therapy cannot be started within 42 days after surgey due to reasons including delay in histopathology of the resected specimen and surgical complications, S-1 dosage may be started as protocol-based treatment if that period is within 12 weeks after the procedure (including on the same date, twelve weeks after the day of the procedure). If the S-1 therapy cannot be started within 12 weeks after the procedure, protocol-based treatment will be discontinued. Subsequently, if S-1 therapy has been administered on the patient's request or the discretion of the attending physician, this will be deemed, "continuance of protocol-based treatment with deviation from the criteria for cessation [of treatment].

1) Agent used:

S-1* : Tegafur, gimeracil, and oteracil potassium compound capsule, combination granules, combination OD tablets (Taiho pharmaceuticals: TS-1 combination capsules/ TS-1 combination granules/ TS-1 combination OD tablets) 20, 25 mg

*The use of generic drugs is not permitted

2) Drug dosage/ route of administration :

Drug	Dosage	Route of administration	Days administered	Washout period
S-1	50-120 mg/body	Oral administration twice a day	day 1-28	day 29-42

3) Criteria for initial S-1 dosage

The patient's weight prior to starting postoperative adjuvant chemotherapy shall be used to calculate body surface area and body weight used in Ccr calculation. The initial dosage is calculated using estimated values when the estimated value of Ccr is over 40 mL/min (regardless of the measured value). Actual values are measured when the estimated value of Ccr is under 40 mL/min, with the initial dosage calculated (using measured values) based on the following criteria when the measured value is over 40 mL/min.

Body surface area		Reference variable
Under 1.25 m^2	→	80 mg/day (20 mg x 4 cap)
Over 1.25 m^2, under 1.50 m^2	→	100 mg/day (25 mg x 4 cap)
Over 1.50 m^2	→	120 mg/day (20 mg x 6 cap)

Creatinine clearance		Initial S-1 dosage
Over 60 mL/min	→	Reference variable
Over 40 mL/min, under 60 mL/min	→	1-stage reduction*
Under 40 mL/min	→	Administration inadvisable

* 100 mg/day if the reference variable is 120 mg/day, 80 mg/day if the reference variable is 100 mg/day, and 50 mg/day if the reference variable is 80 mg/day.

Ccr calculation formula : Cockcroft-Gault equation

For males : Ccr= { (140−age) ×weight (kg) } / {72×serum creatinine level (mg/dL) }

For females : Ccr=0.85× { (140−age) ×weight (kg) } / {72×serum creatinine level (mg/dL) }

i) Dosage is not to be changed (recalculated) in response to weight fluctuations after the start of postoperative adjuvant chemotherapy.

ii) Body surface area and agent dosage is to be calculated by the facility, and at the time of enrollment the body surface area and agent dosage provided by the Data Center should be double checked by the attending physician. The facility should calculate and verify body surface area and agent dose. If the body surface calculation formula used by the hospital data system differs from the calculation formula used by the JCOG (Dubois formula: body surface area (m^2) = body weight (kg) $^{0.425}$ x height (cm) $^{0.725}$ x 71.84 ÷ 10,000), it result in a difference in dosage according to the hospital system or the calculation formula used by the JCOG, in which case the research supervisor will choose which dosage will be used.

6.2. Criteria for completion and termination of protocol-based treatment

6.2.1. Definition of completion of protocol-based treatment

The protocol-based treatment will be completed when all of the following in 1), 2), and 3) are satisfied.

In the event that preoperative chemotherapy is terminated, if the patient satisfies the eligibility for surgery (see 6.3.4) then the treatment will proceed to surgery and the protocol-based treatment will not be terminated.

1) Definition of completion of preoperative chemotherapy

Group A: Preoperative chemotherapy will be completed upon completion of 3 cycles of CDDP therapy. Preoperative chemotherapy will be considered completed following 3 cycles of CDDP even if S-1 therapy is discontinued after day 2 due to adverse events.

Group B: Preoperative chemotherapy will be completed upon completion of 3 cycles of CDDP therapy and 3 doses or more of trastuzumab. Preoperative chemotherapy will be considered completed following 3 doses of trastuzumab and 3 cycles of CDDP even if S-1 therapy is discontinued after day 2 due to adverse events.

2) Definition of completion of surgery

Surgery will be considered completed if R0 resection is achieved. The day that surgery is completed will be defined as the day of surgery.

3) Definition of completion of postoperative adjuvant chemotherapy

S-1 therapy administered for one year calculated starting from the day of surgery will be considered complete. When calculating the actual 'treatment completion rate up to postoperative adjuvant chemotherapy, completion of postoperative adjuvant chemotherapy will be determined if the final day of administration is after day 340, with the day of surgery counted as day 0. ('11.3.5. Treatment completion rate up to postoperative adjuvant chemotherapy').

6.2.2. Criteria for the termination of preoperative chemotherapy

Preoperative chemotherapy will be terminated in the event of any of the following.

If preoperative chemotherapy is terminated but the patient satisfies the eligibility for surgery (see 6.3.4) then the protocol-based treatment will not be terminated.

1) If preoperative chemotherapy is deemed ineffective* based on clear exacerbation of the cancer during preoperative chemotherapy.

   * In the event that preoperative chemotherapy is deemed ineffective, the decision to continue preoperative chemotherapy or proceed to surgery will be determined on the basis of image evaluations performed for each cycle as well as clinical findings.

2) If preoperative chemotherapy cannot be continued due to adverse events.

   ① Observation of non-hematological toxicities* of Grade 4 (however the following adverse events are exempt)

   • ALP, γ-GTP, hyperglycemia, hypercalcemia, hypocalcemia, hypernatremia, hyponatremia, hyperkalemia, and hypokalemia.

   *Non-hematological toxicities: adverse events other than anemia, hypocellular marrow, lymphopenia, neutropenia, leukocytopenia, thrombopenia, bone marrow failure, and CD4 lymphopenia in the CTCAE v4.0-JCOG

   ② Upon observation of Grade 3 pneumonitis, peripheral sensory neuropathy, hearing impairment, and tinnitus.

   ③ If the patient falls under any of the provisions for the termination of preoperative chemotherapy in the criteria for the change of treatment (6.3)

   ④ Aside from the criteria for the change of treatment, if the attending physician determines that preoperative chemotherapy should be terminated due to adverse events.

3) Upon request by the patient to discontinue preoperative chemotherapy due to reasons undeniably related to adverse events

   • This classification is used when there is an undeniable connection with adverse events.

4) Upon request by the patient to discontinue preoperative chemotherapy due to reasons not associated with adverse events.

   • Patient refusal prior to initiation of preoperative chemotherapy after enrollment.

   • When there is no association with adverse events such as the patient or their family moving to a new address during preoperative chemotherapy.

5) Death during preoperative chemotherapy (this falls under 6.2.3. Termination of protocol-based treatment)

• Death due to other reasons prior to determination of preoperative chemotherapy termination.

6) Other, exacerbation between enrollment and the start of treatment (preoperative chemotherapy cannot be initiated due to sudden exacerbation), violation of protocol is found, treatment is changed when the patient is found to be ineligible due to a change in pathological diagnosis following enrollment (depending on the reason 6.2.3 Termination of protocol-based treatment may apply).

6.2.3. Criteria for the termination of protocol-based treatment (all treatments)

Protocol-based treatment (all treatments) will be terminated in the event of any of the following.

1) If protocol-based treatment is deemed ineffective due to any of the following reasons.

① When surgery cannot be performed because '6.3.4. Eligibility for surgery ①' is not satisfied

② When, for any reason below, it is intraoperatively deemed not possible to achieve R0 resection. However, if R0 resection is deemed possible through additional resection within reason (6.1.2. <Determination of additional surgery>), the protocol-based treatment will not be terminated.

i) When factors indicating M1 (excluding No.16a2/b1) including P1, H1, and CY1 are found (Japanese classification of Gastric Carcinoma. 14th ed.),

ii) When surgery cannot be continued for any reason.

iii) When the achievement of complete resection cannot be determined based on intraoperative findings (when clear residual tumor is observed for reasons other than those listed above)

③ When residual tumor of R1 and R2 is histologically diagnosed by histopathological examination of the resected specimen.

④ When clear exacerbation is identified by image evaluation after each cycle of preoperative chemotherapy, and when the histological outcome is determined to be grade 0.

⑤ When recurrence is observed during postoperative adjuvant chemotherapy.

2) When protocol-based treatment cannot be continued due to adverse events.

① If surgery cannot be performed because '6.3.4. Eligibility for surgery ②' is not fulfilled.

② If it is difficult to continue surgery in accordance with the protocol due to intraoperative complications.

③ If postoperative adjuvant chemotherapy cannot be initiated by day 84 (12 weeks following surgery), given that the day of surgery is day 0.

⑤ If non-hematological toxicities* of Grade 4 are observed during postoperative adjuvant chemotherapy (however the following adverse events are exempt)

- ALP, γ-GTP, hyperglycemia, hypercalcemia, hypocalcemia, hypernatremia, hyponatremia, hyperkalemia, and hypokalemia.

*Non-hematological toxicities: adverse events other than anemia, hypocellular marrow, lymphopenia, neutropenia, leukocytopenia, thrombopenia, bone marrow failure, and CD4 lymphopenia in the CTCAE v4.0-JCOG

④ If any of the provisions for the termination of protocol-based treatment in the criteria for the change of treatment (6.3) apply during postoperative adjuvant chemotherapy.

⑤ Aside from the criteria for the change of treatment, if the attending physician determines that protocol-based treatment should be terminated due to adverse events during postoperative adjuvant chemotherapy.

(e.g. If adverse events develop, despite reducing the S-1 dosage and changing the administration schedule ofS-1, and as a result the attending physician determines that it is difficult to re-administer S-1)

3) Upon request by the patient to discontinue the protocol-based treatment due to reasons undeniably related to adverse events.

- This classification is used when there is an undeniable connection with adverse events

4) Upon request by the patient to discontinue protocol-based treatment due to reasons not associated with adverse events

- Patient refusal prior to initiation of protocol-based treatment after enrollment.
- When there is no association with adverse events such as the patient or their family moving to a new address during protocol-based treatment.

5) Death during protocol-based treatment (death during preoperative chemotherapy, perioperative death, and death during postoperative adjuvant chemotherapy)
   • Death due to other reasons prior to determination of protocol-based treatment termination
6) Exacerbation between enrollment and the start of treatment (protocol-based treatment cannot be initiated due to sudden exacerbation), violation of protocol is found, treatment is changed when the patient is found to be ineligible due to a change in pathological diagnosis following enrollment, and any other reasons.

The day of termination of the protocol-based treatment will be the day of surgery in the event of 1) ②, ③, and ④, day of death in the event of 5), or the day when the attending physician decided to terminate the protocol-based treatment in other events.

6.3. Criteria for change of treatment

The following terms shall be used in the criteria for the change of treatment.

・Delay : Prolongation of the administration interval. When the treatment is administered later than the stipulated date.

・Terminate : The permanent discontinuation of all treatment, or specific agents and modalities. Treatment will not be recommenced.

・Hold/suspend : The temporary discontinuation, or rest period, if conditions are not fulfilled, and treatment can be recommenced.

・Skip : Proceeding to the next administration schedule, without administration of the subsequent therapeutic agent.

In the CTCAE v.4.0-JCOG, an infusion-related reaction is defined as an 'adverse reaction to the infusion of a drug or biological preparation', and an allergic reaction is defined as 'a systemic or localized adverse reaction developing upon exposure to an antigenic substance'.

In the present study, infusion-related reaction and allergic reactions are defined as follows.

・Infusion-related reaction: a localized or systemic adverse reaction caused by trastuzumab.

・Allergic reaction: a localized or systemic adverse reaction developing upon exposure to antigenic substance other than trastuzumab.

Consult the study secretariat if localized or systemic adverse reactions develop, for which it is difficult to determine whether S-1, cisplatin, or trastuzumab is the cause.

6.3.1. Dosage level for preoperative chemotherapy

Group A

Agent	Dosage level	Dosage/ route				
S-1	Level 0	120	100	80	mg/body/day p.o.	day 1-14
		↓	↓	↓		
	Level -1	100	80	65	mg/body/day p.o.	day 1-14
		↓	↓	↓		
	Level -2	80	65	50	mg/body/day p.o.	day 1-14
CDDP	Level 0	60 mg/m^2 div				day 1
		↓				
	Level -1	50 mg/m^2 div				day 1
		↓				
	Level -2	40 mg/m^2 div				day 1

Group B

Agent	Dosage level	Dosage/ route				
S-1	Level 0	120	100	80	mg/body/day p.o.	day 1-14
		↓	↓	↓		
	Level -1	100	80	65	mg/body/day p.o.	day 1-14
		↓	↓	↓		
	Level -2	80	65	50	mg/body/day p.o.	day 1-14
CDDP	Level 0	60 mg/m^2 div				day 1
		↓				
	Level -1	50 mg/m^2 div				day 1
		↓				
	Level -2	40 mg/m^2 div				day 1
Trastuzumab		8 mg/kg*				day 1
		*2nd and subsequent cycle: 6 mg/kg However, if exceeding 30 days (including day 30) since the previous dosage				

day, counted as day 1, then 8 mg/kg

6.3.2. Criteria for change of S-1+CDDP therapy

1) Criteria to begin S-1+CDDP cycle

- The 2nd and 3rd cycles shall start after confirming that all of the criteria listed below are satisfied on the day of or prior to the start of the 2nd and 3rd cycles,
- The cycle will start on day 22, given that the start of the previous cycle is counted as day 1.
- If any criteria from ① to ⑨ is not satisfied, the start of the cycle will be delayed until it is confirmed that all criteria to start the cycle are fulfilled.

① Fever Grade 0 (body temperature＜38°C, using axillary temperature)

② Neutrophil count≧1,200/mm^3

③ Anemia Grade 0-2 (≧8 g/dL)

④ Platelet count Grade 0-1 (≧7.5×10^4/mm^3)

⑤ AST ≦100 IU/L

⑥ ALT ≦100 IU/L

⑦ Total bilirubin ≦2.0 mg/dl

⑧ Creatinine ≦1.5 mg/dL

⑨ Adverse events listed below are grade 1 or less.
Fatigue, loss of appetite, diarrhea, oral mucositis, nausea, vomiting, dermal toxicity (maculopapular rash, and palmar-plantar erythrodysesthesia syndrome), and heart failure.

- If, due to adverse events, a cycle cannot be started by day 29 (including day 29), counting the start day of the previous cycle as day 1, then the subsequent cycle will be started with the dosage for both S-1 and CDDP reduced 1 level. However, if the cycle cannot be started by day 29 due to a public holiday then the dosage will not be reduced. If the previous cycle was administered with the dosage reduced to level-2 and cannot be administered by day 29 (except for in the event of public holidays), then the preoperative chemotherapy will be terminated (this is also the case on administration of the 4th cycle).
- If a cycle cannot be started by day 43 (including day 43) counting the start day of the previous cycle as day 1, then preoperative chemotherapy will be terminated (this is also the case on administration of the 4th cycle).
- If the criteria to start the 3rd cycle is not fulfilled before day 71 (including day 71), counting the start of the 1st cycle as day 1, and the 3rd cycle cannot be administered, then preoperative chemotherapy will be terminated.
- If R0 resection is deemed possible at the point in time when preoperative chemotherapy is terminated, then after confirming that '6.3.4. Eligibility for surgery' is fulfilled, surgery will be performed as protocol-based treatment in accordance with '6.1.2. Surgery'.

2) Criteria for suspension, recommencement, skips, and dosage reduction in S-1+CDDP therapy

- S-1 will be administered only during the 14 day period (28 doses) from the morning of day 1 to the evening on day 14. If S-1 is started from the evening of day 1, then it shall be administered until the morning of day 15.

- If adverse events are observed that fall under any of the following 'suspension criteria' during each cycle, S-1 will be suspended.
- If all of the 'recommencement criteria' are fulfilled after suspension, then S-1 therapy will be recommenced. The suspended dose (included forgotten doses) will not be administered after the morning of day 15 (or the evening of day 15 if the cycle is started from the evening of day 1).
- If the treatment cannot be recommenced by the evening of day 14/ morning of day 15, then the remaining S-1 in that cycle will be skipped.
- If S-1 is taken orally just once (e.g. morning dose only) it will be counted as one treatment day. Furthermore, days for which the treatment is suspended due to self-judgment or forgetfulness of the patient, irrespective of the 'criteria for suspension' will be counted as treatment days.
- When S-1 is forgotten, it will not be given until the next dosage. At the time of the subsequent S-1 dosage, the 2 doses will not be given together.
- When the suspension period lasts 7 days, the subsequent S-1 doses of the cycle concerned will be skipped.
- If adverse events are observed that fall under any of the following 'skipping criteria' during each cycle, S-1 will be skipped.
- When treatment is suspended or skipped, the start day for the next cycle will be 22, given that the start day of the previous cycle is counted as day 1.
- If any of the following 'criteria for dosage reduction' apply, then the dosage of S-1 and CDDP in the subsequent cycle will be reduced 1 level.
- If after reducing the dosage to level-2, the patient falls under the criteria for dosage reduction or suspension, then preoperative chemotherapy will be terminated.

Table 6.3.2. Criteria for S-1+CDDP therapy suspension, recommencement, skips, and dosage reductions

Adverse event	Suspension criteria	Recommencement criteria	Skip criteria	Dosage reduction criteria
Neutrophil count	Grade 4 ($<500/mm^3$)	$\geqq 1,200\ /mm^3$	-	Grade 4 ($<500/mm^3$)
Platelet count	Grade 3-4 ($<5\times10^4\ /mm^3$)	Grade 2> ($\geqq 7.5\times10^4\ /mm^3$)	-	Grade 3-4 ($<5\times10^4\ /mm^3$)
Total bilirubin	Grade 2-3 (2.25-15 mg/dL)	≦2.0 mg/dL	-	Grade 2-3 (2.25-15 mg/dL)
Creatinine	>1.5 mg/dL	≦1.5 mg/dL	>2.0 mg/dL	>1.5 mg/dL
Febrile neutropenia	-	-	Grade 3	Grade 3-4
Infection※1	-	-	Grade 3	Grade 3
Diarrhea/ oral mucositis	Grade 2	Grade 1>	Grade 3	Grade 2-3
Nausea/ fatigue	Grade 3	Grade 1>	-	Grade 3
Vomiting/ loss of appetite	Grade 3	Grade 1>	-	Grade 3
rash※2, allergic reaction	Grade 2	Grade 1>	Grade 3	Grade 2-3
Peripheral motor neuropathy	Grade 2	Grade 1>	Grade 3	Grade 2-3
Peripheral sensory neuropathy, hearing impairment, tinnitus	Grade 2	Grade 1>	-	Grade 2-3
Heart failure	Grade 2-3	Grade 1>	-	-
ALP, γGTP, hyperglycemia, hypercalcemia, hypocalcemia, hypernatremia, hyponatremia, hyperkalemia, and hypokalemia	Grade 3	Grade 1>	Grade 4	Grade 3
Non-hematological toxicities※3, other than those listed above that have a causal relationship with the protocol-based treatment, (possible 、 probable 、 definite)	Grade 3	Grade 1>	-	Grade 3
Subsequent cycle start day				After Day 30

Infection※1: Pulmonary infection, upper respiratory tract infection, urinary tract infection,

Rash※2: maculopapular rash, and palmar-plantar erythrodysesthesia syndrome

Causal relationship with the protocol-based treatment※3 : Non-hematological toxicities of grade 3 or above that require suspension of treatment at the discretion of the attending physician, should be recorded in detail on the CRF.

6.3.3. Criteria for change of trastuzumab therapy (group B only)

1) Eligibility for trastuzumab therapy

- The 2nd and subsequent doses of trastuzumab shall be administered after confirming that cardiac failure is less than grade 1 on the day of, or, prior to the day of administration. In the event of heart failure of grade 2 or above, the treatment will be delayed, and will only be started until after it is confirmed that heart failure has be reduced to below grade 1 and that LVEF on echocardiography has been restored to above 50%.
- Although there is no need to measure LVEF for each dosage, if heart failure of grade 2 or above is

suspected then echocardiography shall be performed to take measurements (echocardiography is required prior to enrollment, then 7 and 14 days after the final day of the 3rd cycle of S-1 therapy (given that the final day of treatment is counted as day 0))

- In the event of infusion-related reactions of grade 1-2 at the time of the previous dose, the agent administered prior to trastuzumab will be permitted (see 6.4.3).

2) Criteria for termination of trastuzumab

① The appearance of an infusion-related reaction of grade 3 or above.

② If the treatment cannot be started by day 43 (including day 43) after the previous dosage, given that the trastuzumab treatment day is counted as day 1. However, if treatment cannot be administered by day 43 due to public holidays, then the treatment will not be terminated.

6.3.4. Eligibility criteria for surgery

After confirming that all the criteria in ① to ② are satisfied, surgery will be performed less than 56 days (less than 28 days recommended) after the final day of S-1 treatment (the final day of treatment is counted as day 0) of the last cycle. However, test ① will be performed on days 7-14 after the last day of S-1 treatment (the final day of treatment is counted as day 0), and the latest test values will be used for ②, which will be performed less than 14 days prior to surgery. When performing laparoscopy prior to surgery, laparoscopy will be conducted 14-28 days after the last day of S-1 therapy, or, on the day of laparotomy.

If the criteria listed in ① below is not fulfilled, or if ② is not fulfilled within 56 days of the final day of S-1 therapy of the last cycle (the final day of treatment is counted as day 0), then the protocol-based treatment will be terminated.

① R0 resection deemed possible (irrespective of tumor exacerbation or reduction) on image evaluation to assess the efficacy of the final cycle (see 8.2.2.). There is no need for confirmation by laparoscopy.

② The latest values should meet all of the criteria listed below. However, if the eligibility for surgery is not fulfilled after day 21 (including day 21) of the last day of S-1 therapy (the final day of therapy is counted as day 0), and if it is determined that bone marrow activity is improving, then the values in parenthesis will be used.

i) White cell count ≧3,000 mm^3 (≧2,000 mm^3)

ii) Platelets ≧10.0×10^4 / mm^3 (≧5.0×10^4 / mm^3)

iii) AST ≦100 IU/L

iv) ALT ≦100 IU/L

v) Total bilirubin ≦2.0 mg/dL

vi) Creatinine ≦1.5 mg/dL

vii) Fatigue Grade 0-1

viii) Diarrhea Grade 0-1

ix) Pneumonitis Grade 0-1

6.3.5. Criteria for starting postoperative adjuvant chemotherapy

If the patient is diagnosed by postoperative pathological findings as R0 according to the 14th edition of the Japanese Classification of Gastric Carcinoma, he or she will start on oral treatment with S-1 within six weeks from the gastrectomy (by 42 days from day 0, the day of the procedure). If he or she could not start on oral treatment with S-1 within 12 weeks frot the gastrectomy (by 84 dayse from day 0, the day of the procedure), the protocol treatment will be terminated.

1) Criteria for starting postoperative adjuvant chemotherapy

Postoperative adjuvant chemotherapy should be started after confirming that the patient meets all of the following criteria on the day the patient starts the first course or by seven days prior to that day.

The patient must fullfil all of the following:

1) Unsufficient Ingestion: Grade 0-1
2) PS (ECOG) 0-2
3) Fever Grade 0 (less than 38°C or higher, use axillary temperature)
4) Neutrophils ≧1,200 /mm^3 (or white blood cells ≧2,500 /mm^3 if neutrophils have not been measured)
5) Hemoglobin Grade 0-2 (Hemoglobin≧8.0 g/ld)
6) Platelets Grade 0-1 (≧7.5×10^4 /mm^3)
7) AST ≦100 IU/L
8) ALT ≦100 IU/L
9) Total bilirubin ≦2.0 mg/ld.
10) Ccr ≧40 mL/min

Protocol-based treatment will be discontinued if all of the criteria for starting postoperative adjuvant chemotherapy are not satisfied by 12 weeks after surgery.

2) Criteria for starting a course of postoperative adjuvant chemotherapy

From the second course and on, the next course should be started after confirming that the patient meets all of the following criteria on the day the patient starts the course or by seven days prior to that day. The start of the course will be postponed if the patient does not meet one of (1)-(9). Protocol-based treatment will be discontinued when treatment cannot be started within 28 days (after day 29) from the scheduled date for the start of the next course (with day 1 being the scheduled date for the start [of the course]).

Furthermore, the next term should be started after confirming that the patient meets all of the following criteria on day 22 when the patient's treatment schedule has been changed to consist of two weeks of treatment and one week washout period. The start of the term will be postponed if the patient does not meet one of (1)-(9). Protocol-based treatment will be discontinued when the criteria for starting treatment is not be met within 28 days from the scheduled date for the start of the next term.

Criteria for starting a course: the patient must fulfill all of the following conditions

1) Must not have a fever of 38°C or higher (use axillary temperature)
2) Neutrophils ≧1,200 /mm^3 (or white blood cells ≧2,500 /mm^3 if neutrophils have not been measured)
3) Hemoglobin Grade 0-2 (Hemoglobin≧8.0 g/dL)

4) Platelets Grade 0-1 (≧7.5×10^4 /mm^3)

5) AST ≦100 IU/L

6) ALT ≦100 IU/L

7) Total bilirubin ≦2.0 mg/dL

8) Creatinine ≦1.5 mg/dL

All of the following side effects observed in the previous course are Grade 1 or less: Grade 2 Diarrhea, nausea, vomiting, loss of appetite, or oral mucositis; and Grade 3 (or higher) non-hematotoxicities (when a causal relationship with S-1 is at least possible)

6.3.6. Skips, dosage reduction and changesin treatment scheduled for postoperative adjuvant chemotherapy

When the following criteria for skipping apply during S-1 therapy, the remaining S-1 therapy in that course may be skipped. When the patient's treatment schedule has been changed to consist of two weeks of treatment with one week washout period, the remaining S-1 therapy in that term may be skipped.

- When the criteria for skipping apply, 1-step reduction in S-1 dosage (see Table 6.3.6) or change in treatment schedule (from four weeks of treatment with two week washout period to two weeks of treatment with one week washout period; see Fig. 6.3.6.a and Fig. 6.3.6.b) will be undertaken starting with the next course. We do not specify whether change in treatment schedule or reduction in dosage should be prioritized from the next course. However, reduction in dosage should be prioritized when the timing at onset of the worst grade of adverse reaction requiring discontinuation is within 14 days from the start of the [orally administered] S-1 course. Change in treatment schedule should be prioritized when the timing is 15 days or more from the start of the course. Although a differing order of precedence for reduction in dosage and change in treatment schedule will not be considered deviation from protocol-based treatment, both measures (reduction in dosage and change in treatment schedule) may not be conducted simultaneously. Figures 6.3.6.c-e show patterns for reduction in dosage.

-Table 6.3.6 shows dosage levels. Dosage should not be decreased below those levels. Treatment schedule will be changed when dosage is reduced to allowable dosage levels.

-Stipulations on the start date for the next course

---If the treatment schedule has not been changed

Treatment can be srarted earlier than the scheduled start date for the next course (day 43 of the previous course) if the washout period in the course is longer than 14 days

--- If the treatment schedule has been changed (see below and Fig. 6.3.6.b for cases of two week treatment with one week washout period)

The next administration of S-1 can be started earlier than the scheduled start date for S-1 therapy (day 22 or day 43 of the course in question) if the washout period from the previous administration of S-1 is longer than seven days.

-Protocol-based treatment will be discontinued if criteria for skipping apply once again despite reduction in dosage to allowable levels and change in treatment schedule before the start of therapy.

-Washout period may not be shortened for any of the treatment schedules.

-If S-1 is taken orally just once (example: if just the morning dose is taken), that will count as one treatment day, and days without the drug being taken due to self-judgment of the patient or forgetfulness will be counted as treatment days. One course consists of two terms of two weeks of treatment with one week washout period (totaling 42 days; see Fig. 6.3.6.b), when treatment schedule is for two weeks of

treatment with one week washout period.

-Dosage may not be further increased or the schedule further changed once dosage has been reduced and schedule changed.

•

Criteria for skipping: one of the following must apply

① Neutrophils Grade 3-4 (<1,000 /mm^3) (white blood cells <2,000/mm^3 if neutrophils have not been measured)

② PLatelets Grade 3-4 (<5.0×10^4 /mm^3)

③ AST >100 IU/L

④ ALT >100 IU/L

⑤ Total bilirubin >2.0 mg/dL

⑥ Creatinine >1.5 mg/dL

⑦ Grade 2 or grade 3 diarrhea, nausea, vomiting, loss of appetite. Oral mucositis or fever

⑧ Grade 3 non-hematotoxicity aside from the above

Table 6.3.6. Dosage level for S-1

Drug	Dosage level	Dosage (mg/body/day)		
S-1	Level 0	120	100	80
		↓	↓	↓
	Level-1	100	80	50
		↓	↓	↓
	Level-2	80	—	—

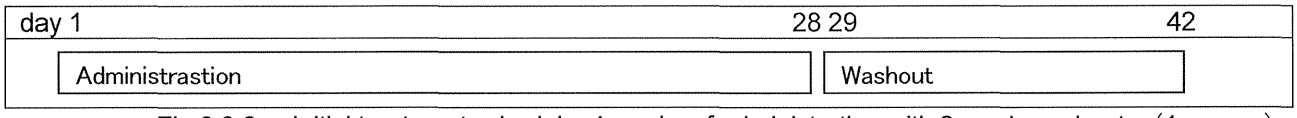

Fig 6.3.6.a. Initial treatment schedule: 4 weeks of administration with 2 week washout (1 course)

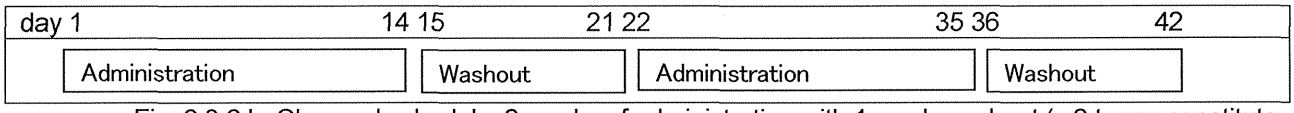

Fig. 6.3.6.b. Changed schedule: 2 weeks of administration with 1 week washout (x 2 terms constitutes 1 course)

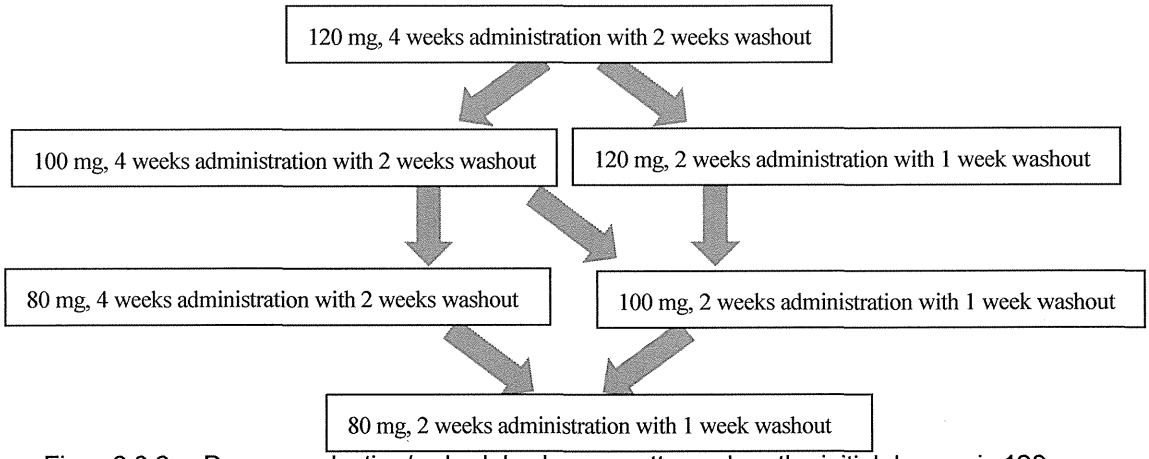

Fig. 6.3.6.c. Dosage reduction/ schedule change pattern when the initial dosage is 120 mg

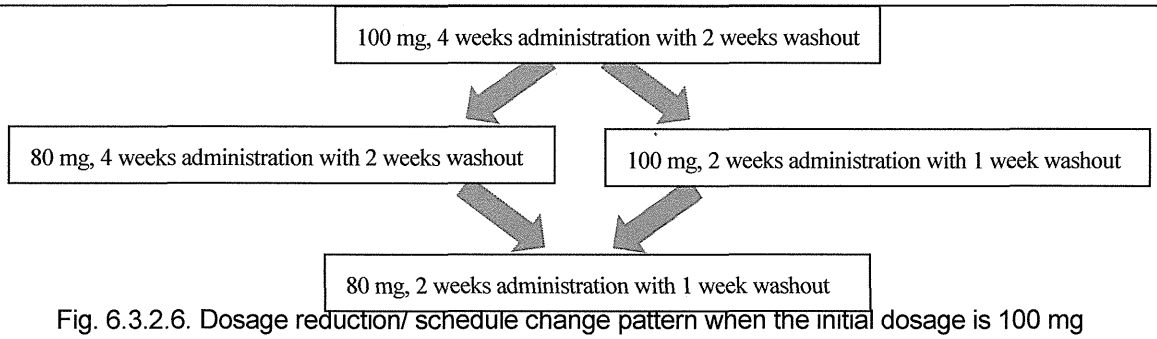

Fig. 6.3.2.6. Dosage reduction/ schedule change pattern when the initial dosage is 100 mg

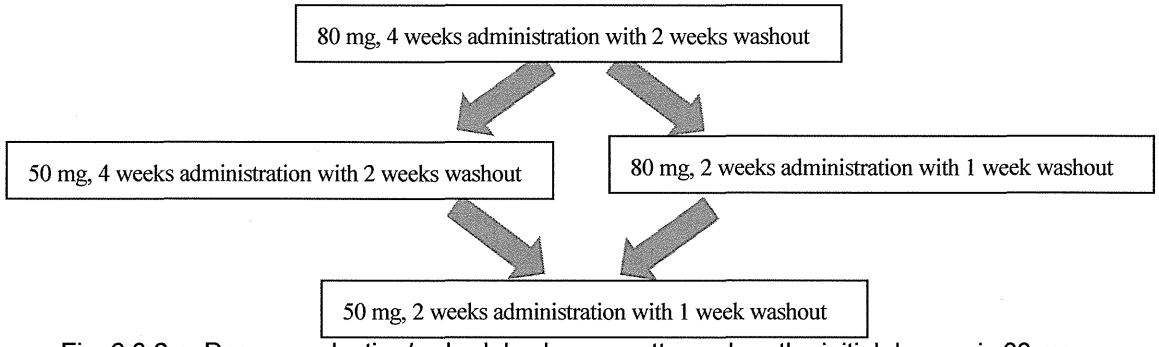

Fig. 6.3.6.e. Dosage reduction/ schedule change pattern when the initial dosage is 80 mg

6.3.7. Consultation regarding change in treatment

For queries regarding treatment changes, contact the '16.6 research secretariat'.

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6.4. Combination therapy and supportive therapy

6.4.1. Specified combination and supportive therapies

1) Tests and supportive therapy for HBs antigen-negative, HBc antibodies-positive and/or HBs antibody-positive patients

i) When pre-chemotherapy HBV-DNA ≥ 2.1 log copies/mL

In the event of patients negative for HBs antigens but positive for HBc and/or HBs antibodies, it has been found that while at low levels, HBV-DNA replication continues in the liver and peripheral bleed mononuclear cells. Thus in patients with a history of infection, it has been reported that the use of strong immunosuppressors causes the re-activation of HBV, and can lead to the onset of severe hepatitis.

In the event that HBV-DNA is 2.1 log copies/ ML or above, there is a high risk of HBV re-activation as in HBs antigen-positive patients, and thus preventive treatment with nucleic acid analogues (Entecavir or Tenofovir) will be administered. Pre-chemotherapy tests, administration route/dosage and monitoring of supportive therapy will be performed in accordance with 'the Japanese guidelines for the management of hepatitis B, 2nd ed. (the Japanese Society of Hepatology)'.

However, patients positive for HBs antibody only, and who have received the HBV vaccine will be excluded.

① Testing prior to the start of chemotherapy

Prior to the start of chemotherapy, 'HBV-DNA quantification' must be performed at least once. HBV-DNA quantification is performed using the PCR method, or the real time PCR method.

② Administration route and dosage of supportive therapies (preventive treatment with nucleic acid analogues)

- **Agents used:**
  - **Entecavir (Bristol-Myers: Baraclude tablets 0.5 mg)**
  - **Tenofovir (Glaxo Smith Kline: Tenozet tablets 300 mg)**

In accordance with the drug dosage and administration route below, treatment with nucleic acid analogues will be initiated more than 1 week (as early as possible) before the start of chemotherapy, and will be continued for more than 12 months after completion of chemotherapy. When conditions *1 and 2 are fulfilled for terminating treatment with nucleic acid analogue 12 months or more after completion of chemotherapy, the nucleic acid analogue treatment may be terminated. However a hepatologists must be consulted when terminating treatment with nucleic acid analogues, and treatment will only be terminated after the hepatologists deems that it is appropriate. Keep in mind that reactivation can occur after completion of treatment with nucleic acid analogues, and HBV-DNA quantification should continue at intervals stipulated in '③ monitoring'. Moreover, if HBV-DNA > 2.1 log copies/mL after completion of treatment with nucleic acid analogues, recommence treatment with nuceic acid analogues immediately.

※1 Requirements for the termination of nucleic acid analogues: all of the following must be fulfilled.

1. Two years or more have passed since the start of nucleic acid analogue treatment.
2. HBV-DNA levels are below detection sensitivity.
3. HBe antigen negative.

※2 Patient attribute requirements: all of the following must be fulfilled.

1. The attending physician and patient must fully understand that there is a high incidence of hepatitis reactivation after completion of nucleic acid analogues with the risk of aggravation.
2. Able to undergo follow up observation after termination, and able to receive suitable treatment upon reactivation.
3. Mild hepatic fibrosis with good hepatic spare ability, and in the event of reactivation the disease is deemed unlikely to deteriorate.

(modified and reprinted according to the Japanese guidelines for the management of hepatitis B, 2nd ed. (Japanese Society of Hepatology)

Entecavir

- **Administration route:** Oral administration on an empty stomach (more than 2 hours after and prior to meals).
- **Dosage:**

Creatinine clearance (mL/min)	Dosage
≥ 50	0.5 mg once a day
≥ 30, < 50	0.5 mg once in 2 days
≥ 10, < 30	0.5 mg once in 3 days
> 10	0.5 mg once in 7 days

- **Side effects (incidence of all grades):** Patients not treated with nucleoside analogues before Side effects include: diarrhea (6.0%), nausea (4.5%), constipation (3.7%), upper abdominal pain (3.0%), fatigue (1.5%), nasopharyngitis (3.0%), muscle stiffness (2.2%), headache (14.2%), dizziness

(3.0%), rash (incidence unknown), hair loss (incidence unknown), laboratory testing: elevated AST (GOT) (3.7%), elevated ALT (GPT) (3.7%), increased serum bilirubin (6.0%), increased serum amylase (10.4%), elevated lipase (10.4%), increased blood glucose (6.0%), increased serum lactic acid (23.1%), elevated BUN (6.7%), urinary occult blood positive (4.5%), urinary leukocyte positive (3.0%), leukopenia (8.2%), increased neutrophils (0.7%), **【severe side effects (incidence unknown)】** exacerbation of hepatitis after completion of therapy, anaphylactic-like reaction, lactic acidosis, and severe hepatomegaly due to fatty deposition (fatty liver).

Tenofovir

- **Administration route:** Oral administration of a dose of 300 mg given once a day.
- **Dosage:**

Creatinine clearance (mL/min)	Dosage
≥ 50	300 mg once a day
≥ 30, < 50	300 mg once in 2 days
≥ 10, < 30	300 mg once in 3-4 days
Hemodialysis	300 mg once in 7 days note) Or, 300 mg after completion of a total of 12 hours of dialysis Note) given after hemodialysis. Pharmacokinetics not examined in patients with a creatinine clearance > 10 mL/min and who do not undergo dialysis.

- **Treatment precautions:**

In long-term treatment with tenofovir, care should be paid to renal dysfunction, hypophosphatemia (including Fanconi's syndrome), and loss of bone density. During tenofovir treatment it is recommended to routinely assess renal function and measure serum phosphorus levels.

- **Side effects (incidence of all grades):**

Abnormal values in hepatic function test (elevated AST, ALT, and γ-GTP) in 7 patients (4.9%), increased creatinine in 4 patients (2.8%), increased amylase, increased lipase, and nausea in 3 patients respectively (2.1%), and abdominal pain in 2 patients (1.4%), **【severe side effects (incidence unknown)】** renal dysfunction, renal failure, acute renal failure, proximal renal tubular dysfunction, Fanconi's syndrome, acute tubular necrosis, severe renal dysfunction including nephrogenic diabetes insipidus and nephritis, severe hepatomegaly (fatty liver) due to lactic acidosis and fatty deposition, and pancreatitis

③ Monitoring: HBV-DNA quantification (during and upon completion of treatment with nucleic acid analogues)

During treatment with nucleic acid analogues (Entecavir or tenofovir):

Every 4 weeks monitoring will be performed by HBV-DNA quantification and liver function (AST, ALT). However, during treatment with nucleic acid analogues, if HBV-DNA< 2.1 log copies/ mL, then testing every 4-12 weeks is permitted.

After completion of nucleic acid analogue treatment:

Keep in mind that reactivation can occur after completion of treatment with nucleic acid analogues, and on consultation with a hepatologist, follow-up will be performed for one year after completion of nucleic acid analogue treatment with HBV-DNA quantification and examination of liver function (AST, ALT) performed every 4 weeks. If HBV-DNA > 2.1 log copies/mL after completion of treatment with nucleic acid analogues, recommence treatment with nuceic acid analogues immediately.

ii) When pre-chemotherapy HBV-DNA < 2.1 log copies/mL

Monitoring of HBV-DNA levels and liver function (AST, ALT) is performed, and nucleic acid analogue treatment (Entecavir or tenofovir) will be initiated when HBV-DNA ≥ 2.1log copies/mL.

The 'Japanese guidelines for the management of hepatitis B, 2nd ed.' by the Japanese Society of

Hepatology, recommends monitoring of HBV-DNA levels during and after chemotherapy to manage the risk of reactivation.

① Monitoring: HBV-DNA quantification

HBV-DNA quantification will be performed every 4-12 weeks from the start of chemotherapy until at least 12 months after completion of chemotherapy.
If HBV-DNA quantification reveals levels of 2.1 log copies/mL or greater, nucleic acid analogue treatment will initiated immediately in accordance with 'the Japanese guidelines for the management of hepatitis B, 2nd ed.' (the Japanese Society of Hepatology). A hepatologist should be consulted prior to the start of nucleic acid analogue treatment.

② Supportive treatment in the event of reactivation

Nucleic acid analogues will be administered in accordance with supportive therapy in '6.4.1.2. i) When prechemotherapy HBV-DNA ≥ 2.1 log copies/mL. Once nucleic acid analogue treatment has started, a hepatologist must be consulted when terminating nucleic acid analogue treatment, and the treatment will be terminated only after the hepatologist deems appropriate.

6.4.2. Recommended/non-recommended combination and supportive therapies

The following combination/supportive chemotherapies are recommended. In the event that these therapies are not performed it will not be considered a protocol deviation.

1) G-CSF

G-CSF is administered according to the approved administration route and doses listed below. Preventive treatment will not be administered.

Start time	・When fever (in principal over 38 °C) with a neutrophil count of < 1,000 /mm^3 is observed. ・When a neutrophil count of < 500 /mm^3 is observed. ・During the previous course, if fever (in principal over 38 °C) is observed with a neutrophil count of < 1,000 /mm^3 is observed, or if a neutrophil count of < 500 /mm^3 is observed, then after completing the same chemotherapy, a neutrophil count of <1,000 /mm^3 is observed.
Dosage/ administration route	・Filgrastim: hypodermic injection of 50 μg/m^2 per day, or, intravenous injection of 100μg/m^2 per day ・Nartograstim: hypodermic injection of 1 μg/kg per day, or, intravenous injection of 2μg/kg per day ・Lenograstim: hypodermic injection of 2 μg/kg per day, or, intravenous injection of 5μg/kg per day
Termination	・Administration of the agent should be discontinued if the neutrophil count exceeds 5,000 /mm^3 after reaching its lowest level. ・Discontinuation or dose reduction will be considered when the neutrophil count returns to above 2,000 /mm^3, when there are no symptoms suggestive of infection, and when patient safety can be ensured because of reactivity to the agent.

2) Countermeasures for fever during neutropenia

① In the event of neutrophil count ≤ 500/ mm^3, or ≦ 1,000 /mm^3 expected to decrease to ≦500 /mm^3 within 48 hours, and axillary temperature ≥ 37.5°C (oral temperature ≥ 38°C), risks should be assessed immediately and antibiotics started to manage the risks.

② Risk assessment will be performed using the scoring system from the Multinational Association for Supportive Care in Cancer (MASCC) ※1.

③ The initial assessment will be determined according to testing of complete blood count including differential white blood count and platelet count, renal function (BUN, and creatinine), electrolytes, liver function (transaminase, total bilirubin, and alkaline phosphatase), examination of 2 or more

venous blood culture sets prior to the start of antibiotics, and in the event of an indwelling central venous catheter, examination will be performed of one culture set from the catheter and one set from the peripheral vein, as well as a culture test from the site of suspected infection, and in the event of respiratory signs or symptoms, chest X-ray will be performed.

④ In high risk patients, beta-lactam antibiotic with anti-Pseudomonas aeruginosa activity will be transvenously administered as a single agent. However for patients in an unstable condition, or with complications, and in the event of drug-resistance bacteria strongly suspected, in addition to the single agent in the initial regimen, other antibiotics (aminoglycoside derivatives, fluoroquinolone and/or vancomycin) should be administered. In low risk patients, antibiotics will be administered orally or by intravenous injection, and treatment can be administered to in-patients, or on an out-patient basis if it is deemed suitable after thorough assessment.

⑤ On reassessment 3-4 days after the start of antibiotics, the continuation or change of antibiotics will be examined, and as a general rule, antibiotics will be continued until the neutrophil count is restored to 500 /mm^3 or above.

⑥ In high risk patients who do not respond to broad spectrum antibiotics in 4-7 days, experimental treatment with antifungal agents is recommended.

⑦ In high risk patients for whom it is expected that a neutrophil count of less than 100 /mm^3 will continue for more than 7 days, preventive treatment with fluoroquinolone is recommended.

⑧ Preventive treatment with G-CSF is recommended for patients in whom the risk of febrile neutropenia onset is 20% or above, and when the risk of onset is 10-20%, as well as i) elderly individuals aged 65 years or older, ii) patients with advanced stage or equivalent disease, iii) patients who are not given preventive antibiotics, and iv) patients with a history of febrile neutropenia. In patients with a risk of onset of less than 10%, G-CSF is only recommended if sever progress is predicted.

⑨ In the event that febrile neutropenia (FN) develops in patients with an indwelling central venous catheter, blood cultures will be performed from the catheter and peripheral blood, and when the difference in time to positivity from the two cultures is 120 min or more, it will be considered a catheter-related infection. If there is no improvement despite 72 hours of suitable antibiotic treatment, the catheter will be removed. Furthermore the catheter will be removed in the event of infection from *Staphylococcus* aureus, *Pseudomonas* aeruginosa, bacillus, fungus, or acid-fast bacterium, and appropriate antibiotic treatment will be given on the basis of the results of the cultures.

⑩ Infection prevention strategies will be implemented through hand hygiene, standard infection prevention measures of health care providers, and precautions to isolate the pathogen from the patient.

※1 Multinational Association for Supportive Care in Cancer (MASCC) scoring system

(cited with partial revision from the revised guidelines for the treatment of febrile neutropenia (FN) [published by the Japanese Society of Medical Oncology]※2)

Item	Score
Clinical symptom (choose one of the following indicated by *) *No symptoms *Mild symptoms *Moderate symptoms	 5 5 3
No decrease in blood pressure	5
Chronic obstructive pulmonary disease absent	4
Solid cancer, or hematopoietic tumor, with no history of fungal infection	4
No dehydration	3
Patient developed fever during treatment as out-patient	3