Adjuvant Chemotherapy With Etoposide Plus Cisplatin for Patients With Pathologic Stage II Nonseminomatous Germ Cell Tumors

Deaglan J. McHugh, MD1,2; Samuel A. Funt, MD1,2; Deborah Silber, BA1; Andrea Knezevic, MS3; Sujata Patil, PhD3; Devon O'Donnell, BS1; Stephanie Tsai, BA1; Victor E. Reuter, MD4; Joel Sheinfeld, MD5; Brett S. Carver, MD5; Robert J. Motzer, MD1,2; Dean F. Bajorin, MD1,2; George J. Bosl, MD1,2; and Darren R. Feldman, MD1,2

PURPOSE
The relapse rate after primary retroperitoneal lymph node dissection (RPLND) for patients with pathologic stage (PS) IIA nonseminomatous germ cell tumors (NSGCTs) is 10%-20% but increases to ≈ 50% for PS IIB disease. We report our experience with 2 cycles of adjuvant etoposide plus cisplatin (EP×2) after therapeutic primary RPLND.

PATIENTS AND METHODS
All patients with PS II NSGCT seen at Memorial Sloan Kettering Cancer Center from March 1989 to April 2016 and who were planned to receive EP×2 were included. Each cycle consisted of cisplatin 20 mg/m² and etoposide 100 mg/m² on days 1 through 5 at 21-day intervals. Demographic characteristics, histopathologic features, therapeutic and survival outcomes were recorded.

RESULTS
Of 156 patients, 30 (19%) had pathologic N1, 122 (78%) had pathologic N2 (pN2), and 4 (3%) had pathologic N3 (pN3) disease. The median number of involved lymph nodes was 3 (range, 1-37 nodes), and the median size of the largest involved node was 2.0 cm (range, 0.4-7.0 cm); extranodal extension was present in 69 patients (45%). Embryonal carcinoma was the most frequent RPLND histology, present in 143 patients (92%). One hundred fifty patients (96%) received EP×2, five received EP×1 and one received EP×4. With a median follow-up of 9 years, 2 patients (1.3%; 1 patient each with pN2 and pN3 disease) experienced relapse; both patients remain continuously disease free at more than 5 and 22 years after salvage chemotherapy. Three patients died, all unrelated to NSGCT, yielding 10-year disease-specific, relapse-free, and overall survival rates of 100%, 98%, and 99%, respectively.

CONCLUSION
Adjuvant EP×2 for PS II NSGCT is highly effective, has acceptable toxicity, and incurs less drug cost than 2 cycles of bleomycin, etoposide, and cisplatin. Inclusion of bleomycin in this setting is not necessary.

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INTRODUCTION
Primary retroperitoneal lymph node dissection (RPLND) remains a standard treatment option for patients with marker-negative clinical stage (CS) I and low-volume CS II nonseminomatous germ cell tumors (NSGCTs). For patients with proven regional lymph node metastases at RPLND (pathologic stage [PS] II NSGCT), the following 2 management options exist: adjuvant chemotherapy and active surveillance. Provided patient compliance is optimal, patients with pathologic N1 (pN1) disease (defined as ≤ 5 nodes positive, all nodes ≤ 2 cm, and no extranodal extension) have a relapse rate of 10%-20%, and surveillance is usually favored. Conversely, because up to 50% or more of patients with pathologic N2 (pN2) disease (defined as > 5 nodes involved, any node ≥ 2 cm but ≤ 5 cm, or extranodal extension) will experience relapse on observation alone, management with 2 cycles of adjuvant chemotherapy is often preferred. Patients with pN1 disease who are unlikely or unable to adhere to a surveillance protocol should also receive adjuvant chemotherapy. Currently, the accepted adjuvant chemotherapy regimens consist of 2 cycles of either bleomycin, etoposide, and cisplatin (BEP×2) or etoposide plus cisplatin (EP×2). In reported series, with median follow-up times of 7 and 8 years, respectively, the disease-specific survival was 100%. Although 2 cycles of adjuvant cisplatin-based chemotherapy reduce the risk of relapse to approximately 1%, questions regarding patient selection and the necessity of bleomycin remain unanswered. Considering the excellent disease-specific survival regardless of adjuvant strategy, minimization of toxicity while maintaining optimal efficacy is critical. We report our experience with the efficacy and tolerability of adjuvant EP×2.

PATIENTS AND METHODS
From March 1989 to April 2016, 156 patients with NSGCT were treated with adjuvant etoposide and cisplatin (EP) at Memorial Sloan Kettering Cancer
were updated.7 Relapse-free survival was determined, and the salvage regimen and time to relapse were calculated using the Kaplan-Meier method;11 the survival outcomes for the 87 previously reported patients were updated.7 Relapse-free survival was defined as the time from the start of chemotherapy to the date of relapse. Patients who were alive and continuously disease free were censored at the date of their last follow-up. The site and time of relapse were determined, and the salvage regimen and response to salvage therapy were recorded. Regimen drug cost was estimated using Centers for Medicare and Medicaid Services Average Sales Price (ASP) Drug Pricing.12 The institutional review board approved this retrospective analysis.

RESULTS

Patient Characteristics and Treatment

The median age was 28 years (Table 1). Before chemotherapy, minimal baseline elevations in α-fetoprotein (AFP; > 15 ng/mL) and human chorionic gonadotropin (hCG; > 2.2 mIU/mL) were seen in 2 patients (1%) and 6 patients (4%), respectively. One of these patients was treated with EP×4 for an increase in AFP during his first cycle (see later discussion in Adjuvant Chemotherapy). One patient with elevated baseline hCG (3.5 mIU/mL) before chemotherapy experienced relapse after a complete response to EP×2 (see later discussion in Relapse-Free and Overall Survival).

Marker values of the remaining 4 patients remained stable throughout follow-up (3+, 10+, 15+, and 21+ years) and were deemed clinically insignificant. Seventy-two percent and 20% of patients had pathologic T2 and pathologic T1 disease at orchiectomy, respectively. In the orchiectomy specimen, embryonal carcinoma was the most common histologic component, observed in 94% of patients, followed by teratoma (41%). Information about intratubular germ cell neoplasia in the orchiectomy specimen was available for 152 patients, and was present in 128 (84%). The median time between orchiectomy and primary RPLND was 39 days. While awaiting RPLND, disease was upstaged from stage I to stage II based on postorchietomy imaging in 19 patients (12%). Before RPLND, the majority of patients had either CS IB (40%) or CS IIA (41%) disease (Table 1).

RPLND

Most patients underwent either a full (67%) or modified (14%) bilateral RPLND (Table 2). Almost 95% of patients had their RPLND performed at MSKCC. All patients who underwent ipsilateral RPLND at MSKCC did so before 1999; bilateral RPLND was performed exclusively thereafter. Among 124 patients with total nodal yield available from the histopathology report, the median number of lymph nodes resected was 44 (range, 6-129 nodes). The median number of positive lymph nodes present was 3 (range, 1-37 nodes), and the median size of the largest positive node was 2.0 cm (range, 0.4-7.0 cm). Embryonal carcinoma was the most frequent histology (n = 143, 92%) observed in the RPLND specimens and was also the predominant histologic component in 115 (90%) of the 128 patients for whom this information was available. The most common pathologic lymph node stage was pN2, present in 122 patients (78%).

Adjuvant Chemotherapy

The median time from RPLND to chemotherapy was 26 days (range, 1-73 days). Six patients (4%) did not receive EP×2. Five patients (3%) received 1 cycle of EP as a result of small bowel obstruction, Clostridium difficile infection, and poor wound healing after adhesiolysis (n = 1); acute renal failure (n = 1); ascites (n = 2); and patient refusal (n = 1). One patient who had mildly elevated hCG and AFP before chemotherapy received EP×4 as a result of an increasing AFP after his first cycle, which was felt to be consistent with marker surge in the setting of good-risk micrometastatic disease. This patient is free of disease at more than 19 years from the start of chemotherapy.

Relapse-Free and Overall Survival

The median follow-up time for survivors was 9 years (range, 2 months to 26 years), with distribution illustrated in Appendix Figure A1 (online only); among the original 87 patients, the median follow-up time was 15 years. There were 3 deaths among the 156 patients, all of which were unrelated to NSGCT or treatment, yielding 10-year disease-specific, relapse-free, and overall survival rates of 100%, 99%, and 98%, respectively (Figs 1 and 2). One patient...
TABLE 1. Patient Characteristics

| Characteristic | No. (%) of Patients (N = 156) |
|----------------|--------------------------------|
| Median age at chemotherapy, years (range) | 28 (15-52) |
| AJCC stage before RPLNDa |  |
| I b | 2 (1.3) |
| IA | 7 (4.5) |
| IB | 62 (40.0) |
| IS | 1 (0.7) |
| II b | 2 (1.3) |
| IIA | 64 (41.3) |
| IIB | 17 (10.9) |
| Baseline AFP > 15 ng/mLc | 2 (1.3) |
| Baseline hCG > 2.2 mIU/mLc | 6 (3.9) |
| Baseline LDH elevatedd | 13 (9.0) |

| Orchiectomy pathologic T stage |  |
| pT1 | 31 (19.9) |
| pT2 | 113 (72.5) |
| pT3 | 6 (3.8) |
| pTX | 6 (3.8) |

| Orchiectomy histology |  |  |
| Embryonal carcinoma | 147 (94.2) |  |
| Teratoma | 64 (41.0) |  |
| Yolk sac | 58 (37.2) |  |
| Seminoma | 56 (35.9) |  |
| Syncytiotrophoblast | 28 (18.0) |  |
| Choriocarcinoma | 12 (7.7) |  |

Note: Values are reported as numbers and percentages unless otherwise noted. Abbreviations: AFP, α-fetoprotein; AJCC, American Joint Committee on Cancer; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; RPLND, retroperitoneal lymph node dissection.

aMissing for 1 patient.
bInadequate information to classify as A or B subgroup.
cRemained stable throughout follow-up and deemed clinically insignificant.
dMissing for 11 patients.

and are disease free at more than 5 and 22 years, respectively, from the start of TIP.

Toxicity

Of 150 patients who received EP×2, 140 patients were evaluable for dose delay (Table 3). Dose delays (≥ 7 days) occurred in 54 patients (36%) and were predominantly a result of neutropenia, occurring in 46 patients (31%; Table 3). Of the 46 patients with dose delays as a result of neutropenia, 41 (86%) had WBC nadir values available, with a median WBC nadir of 1,800/µL (range, 700-3,600/µL). Only seven (5%) of 150 patients were hospitalized for neutropenic fever; 5 of these patients had a 7-day delay in the administration of cycle 2.

Drug Cost

Using publicly available drug cost information, the drug costs, based on ASP in July 2019, for a 1.8 m² male are $180.04 for EP×2 and $511.68 for BEP×2 (Appendix Table A1, online only). Bleomycin costs were determined from unit costs for a total of 30 units received weekly for 6 weeks.

DISCUSSION

This series represents the largest group of patients who received adjuvant chemotherapy for PS II NSGCT and reaffirms the efficacy of EP×2. At a median follow-up time of 9 years, disease-specific survival was 100% and 10-year relapse-free survival was 98.7%. The 1.3% relapse rate is the same as, or less than, the relapse rate in other adjuvant trials. Two patients experienced relapse, both within 6 months of completing EP, and both achieved durable relapse-free survival with salvage TIP chemotherapy. One patient with CS IIB disease had pN3 disease before receiving adjuvant chemotherapy. Today, this patient would have received EP×4 or BEP×3 rather than a primary RPLND. The Indiana University experience in 86 patients with adjuvant BEP×2 revealed that 49 patients (57%) had PS II A disease and 37 patients (43%) had PS II B disease (Table 4). These proportions of stage II A and stage II B disease contrast with those in our series, in which 81% of patients had pN2 or pN3 disease. With almost double the number of patients treated and more than triple the number of patients with pN2 or pN3 disease, EP×2 demonstrated survival outcomes that are the same as BEP×2. Because EP×2 and BEP×2 are equally effective, the major contemporary questions are the optimal management of CS II B NSGCT (RPLND v surveillance v adjuvant BEP) and CS IIA NSGCT and the comparative clinical toxicity and financial cost of adjuvant BEP×2 or EP×2 in patients with PS II NSGCT.

The debate regarding surveillance, BEP×1, and RPLND for CS II B NSGCT (T2-4 primary tumor but no other evidence of disease) has been extensively reviewed. At MSKCC, we prefer a nerve-sparing RPLND to maximally limit chemotherapy exposure. The management of marker-negative CS II A disease has not been as heavily debated. Because between 25% and 40% of CS II A patients are found to have PS I...
disease at RPLND and do not need chemotherapy, we prefer RPLND, thereby avoiding chemotherapy in most patients proven to have PS I disease. A primary RPLND should be limited to patients with normal markers or markers that have normalized; patients with CS IS or CS IIA disease and an elevated (marker half-life taken into consideration) or increasing AFP and/or hCG should receive primary chemotherapy.1

One limitation of this study is that all RPLNDs were performed at MSKCC by highly experienced surgeons, potentially decreasing the risk of relapse. Nodal dissections performed at lower volume centers, with less experienced surgeons, could be less complete. Once the primary RPLND is performed, most patients with pN1 disease (relapse rate of approximately 10%-20%) should be observed, unless compliance or other factors suggest that the benefit of adjuvant chemotherapy exceeds the risk of unnecessary

### TABLE 2. RPLND Characteristics

| Characteristic | No. (%) of Patients (N = 156) |
|---------------|--------------------------------|
| Median No. of lymph nodes dissected* | 44 (6-129) |
| Median No. of positive lymph nodes† | 3 (1-37) |
| Largest lymph node size, cm,‡ median (range) | 2.0 (0.4-7.0) |
| RPLND type§ |  |
| Full bilateral | 104 (67.5) |
| Modified bilateral | 22 (14.3) |
| Modified left | 17 (11.0) |
| Modified right | 8 (5.1) |
| Bilateral | 1 (0.7) |
| Full bilateral with suprahilar dissection | 1 (0.7) |
| Left modified with suprahilar dissection | 1 (0.7) |
| Pathologic N stage |  |
| pN1 | 30 (19.2) |
| pN2 | 122 (78.2) |
| pN3 | 4 (2.6) |
| Extranodal extension* | 69 (45.1) |
| RPLND histology |  |
| Embryonal carcinoma | 143 (91.7) |
| Teratoma | 36 (23.1) |
| Yolk sac | 25 (16.0) |
| Seminoma | 13 (8.3) |
| Syncytiotrophoblast | 6 (3.9) |

NOTE. Values are reported as numbers and percentages unless otherwise noted. Abbreviation: RPLND, retroperitoneal lymph node dissection.

*Missing for 22 patients.
†Two patients had 0 positive lymph nodes; data missing for 14 patients.
‡Missing for 58 patients.
§Missing for 2 patients.
¶Missing for 3 patients.

### TABLE 3. Chemotherapy Treatment

| Factor | No. (%) of Patients (N = 156) |
|--------|--------------------------------|
| Median time from RPLND to chemotherapy, days (range) | 26 (1-73) |
| No. of cycles |  |
| 1 | 5 (3.2) |
| 2 | 150 (96.2) |
| 4 | 1 (0.6) |
| Febrile neutropenia* | 7 (5) |
| Chemotherapy dose delay† | 54 (36) |
| Reason for chemotherapy dose delay |  |
| Neutropenia | 46 (31) |
| Febrile neutropenia | 5 (3) |
| Not available | 3 (2) |
| Median WBC nadir, × 10⁹/μL (range) | 1.8 (0.7-3.6) |

NOTE. Values reported as numbers and percentages unless otherwise noted. Abbreviation: RPLND, retroperitoneal lymph node dissection.

*Reported in 150 patients who had 2 cycles; 10 patients were not evaluable for dose delay.
†Reported in 41 of 46 patients with afebrile neutropenia.
chemotherapy. Patients with pN2 disease are usually offered adjuvant chemotherapy because surveillance followed by relapse would require a greater amount of chemotherapy and, therefore, a greater risk of short- and long-term toxicity. Although the presence of extranodal extension did not affect the recurrence risk in one retrospective analysis,18 most studies (and the AJCC staging system) have included this criterion, and we continue to do so at MSKCC.

Toxicity is 1 of 2 major issues in the choice of chemotherapy regimen once pN2 disease is established. Although myelosuppression is observed with both regimens, febrile neutropenia occurred in 5% of patients receiving EP×2 and 12% of patients who received BEP×22 (Table 4). In one small study, BEP×2 was associated with more frequent grade 2-3 leukopenia than EP×2.15 Febrile reactions may occur within 48 hours in up to 50% of patients treated with intravenous bleomycin.20 Bleomycin-induced pulmonary toxicity and Raynaud phenomenon21 are other well-recognized adverse effects of BEP. Although clinical pulmonary and vascular toxicity are rare when treatment is limited to 2 cycles, a recent meta-analysis of 25 trials examined the pulmonary toxicity of regimens containing or not containing bleomycin to treat metastatic disease and showed that bleomycin administration was significantly associated (P = .012) with all-grade pulmonary toxicity when compared with no bleomycin administration.22 The authors noted that an insufficient sample size prevented an assessment of a linear relationship between doses of bleomycin and toxicity. In a United Kingdom–based prospective evaluation of BEP×2 in the setting of high-risk stage I NSGCT, no symptomatic respiratory dysfunction was reported. However, of 16 patients with pretreatment pulmonary function testing (PFT) and repeat PFT at least 9 months after treatment, 15 patients showed a significant mean decrease (15%; range, 2%-36%; P = .002) in transfer factor coefficient (KCO).23 The MRC TE17 trial studied the use of 2 cycles of bleomycin, vincristine, and cisplatin in high-risk NSGCT, with pretreatment and posttreatment PFT at 12 and 24 months. Similarly, although there was no clear evidence of clinically relevant changes, there was a significant mean reduction in KCO (5%; P = .03).24 The risk of pulmonary or vascular sequelae is essentially eliminated with EP×2.

The cost of drug therapy is an increasingly recognized and important consideration. Because the doses of etoposide and cisplatin in BEP and EP are the same, the drug cost difference between the 2 regimens is attributable to bleomycin administration. Using publicly available drug cost information, bleomycin in BEP×2 increases the total drug cost by $331.64 per patient (Appendix Table A1).12 This additional cost of bleomycin does not include the additional facility fee charges and possible professional fees for the weekly bleomycin visit. In addition, the more frequent episodes of febrile neutropenia associated with BEP would also add financial cost to the clinical risk described earlier.

BEP×2 and EP×2 are unlikely to be directly compared in a sufficiently powered study to determine the optimal adjuvant chemotherapy regimen for PS II NSGCT. Because bleomycin administration adds cost and potential toxicity, we believe EP×2 should be considered the preferred treatment regimen in patients with pN2 NSGCT after RPLND.

### TABLE 4. Adjuvant Chemotherapy in Patients With Pathologic Stage II NSGCT

| Study          | No. of Patients | pN2/3 (%) | Adjuvant Chemotherapy | Relapse (%) | Neutropenic Fever (%) | DSS (%) |
|----------------|----------------|-----------|-----------------------|-------------|-----------------------|--------|
| Behnia et al10 | 86             | 43        | BEP×2                 | 1           | 12                    | 100    |
| McHugh et al (present study) | 155  | 81        | EP×2                 | 1           | 5                     | 100    |

Abbreviations: BEP×2, 2 cycles of bleomycin, etoposide, and cisplatin; DSS, disease-specific survival; EP×2, 2 cycles of etoposide and cisplatin; NSGCT, nonseminomatous germ cell tumor.

### AFFILIATIONS

1Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
2Department of Medicine, Weill Medical College of Cornell University, New York, NY
3Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY
4Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY
5Division of Urology, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

### CORRESPONDING AUTHOR

Darren R. Feldman, MD, Genitourinary Oncology Service and Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 300 East 66th St, Box 138, New York, NY 10065; e-mail: feldmand@mskcc.org.

### PRIOR PRESENTATION

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AUTHOR CONTRIBUTIONS
Conception and design: Deaglan J. McHugh, Samuel A. Funt, Sujata Patil, Robert J. Motzer, Darren R. Feldman
Financial support: Darren R. Feldman
Administrative support: George J. Bosl, Darren R. Feldman
Provision of study materials or patients: Victor E. Reuter, Robert J. Motzer, George J. Bosl, Darren R. Feldman
Collection and assembly of data: Deaglan J. McHugh, Samuel A. Funt, Deborah Silber, Devon O’Donnell, Stephanie Tsai, Victor E. Reuter, Brett S. Carver, Robert J. Motzer, Darren R. Feldman
Data analysis and interpretation: Deaglan J. McHugh, Samuel A. Funt, Deborah Silber, Andrea Czecevic, Sujata Patil, Stephanie Tsai, Joel Sheinfeld, Brett S. Carver, Robert J. Motzer, Dean F. Bajorin, George J. Bosl, Darren R. Feldman

MANUSCRIPT WRITING: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Deaglan J. McHugh
Consulting or Advisory Role: Progenics

Samuel A. Funt
Stock and Other Ownership Interests: Kite Pharma, Urogen Pharma (I), Hubble (I), Second Science, Allogene Therapeutics, Neogene Therapeutics (I), Kronos Bio (I), Vida Ventures (I)
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Travel, Accommodations, Expenses: Bristol-Myers Squibb, AstraZeneca/MedImmune

Victor E. Reuter
Consulting or Advisory Role: Cepheid
Uncompensated Relationships: PaigeAI

Robert J. Motzer
Consulting or Advisory Role: Pfizer, Novartis, Eisai, Exelixis, Merck, Genentech, Incyte, Eli Lilly
Research Funding: Pfizer (Inst), Bristol-Myers Squibb (Inst), Eisai (Inst), Novartis (Inst), Genentech (Inst)

Dean F. Bajorin
Honoraria: Merck Sharp & Dohme
Consulting or Advisory Role: Bristol-Myers Squibb, Novartis, Genentech, Merck, Roche, Eli Lilly, Fidia Farmaceutici S.p.A., Urogen Pharma, Pfizer, EMD Serono
Research Funding: Novartis (Inst), Genentech (Inst), Merck (Inst), Bristol-Myers Squibb (Inst), AstraZeneca (Inst), Astellas Pharma (Inst), Seattle Genetics/ Astellas (Inst)
Travel, Accommodations, Expenses: Genentech, Merck, Bristol-Myers Squibb, Eli Lilly, Urogen Pharma

Darren R. Feldman
Research Funding: Novartis, Seattle Genetics, Decibel Therapeutics (Inst), Astellas Pharma
Other Relationship: UpToDate

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FIG A1. Distribution of follow-up time for patients with pathologic stage II nonseminomatous germ cell tumors treated with adjuvant etoposide plus cisplatin.

TABLE A1. Estimated Difference in Cost for BEP×2 and EP×2

| Drug                        | Unit   | Cost per Unit ($) | Cost per Course of EP×2 for Male 1.8 m² ($) | Cost per Course of BEP×2 for Male 1.8 m² ($) |
|-----------------------------|--------|-------------------|---------------------------------------------|---------------------------------------------|
| Etoposide injection        | 10 mg  | 0.622             | 111.96×                                     | 111.96×                                     |
| Cisplatin 10 mg injection  | 10 mg  | 1.891             | 68.08×                                      | 68.080×                                     |
| Bleomycin sulfate injection| 15 units| 27.637           | 0                                           | 331.64×                                     |
| Total cost                 |        | 180.04            | 511.68                                      |                                             |

Abbreviations: BEP×2, 2 cycles of bleomycin, etoposide, and cisplatin; EP×2, 2 cycles of etoposide and cisplatin.

×Total etoposide dose for 2 cycles in a 1.8 m² male is 1800 mg.

*Total cisplatin dose for 2 cycles in a 1.8 m² male is 360 mg.

+Total bleomycin dose for 2 cycles (flat dosing at 30 units/wk for 6 weeks) is 180 units.