Perioperative prophylaxis with granulocyte colony-stimulating factor (G-CSF) in high-risk colorectal cancer patients for an improved recovery: A randomized, controlled trial

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Background. *We aimed to improve the postoperative outcome of high-risk patients (American Society of Anesthesiologists class 3 and 4) recovering from colorectal cancer surgery by using recombinant human G-CSF (filgrastim) as perioperative prophylaxis.*

Methods. *In a double-blinded, placebo-controlled trial, 80 patients undergoing left-sided colorectal resection were randomized to filgrastim or placebo. Filgrastim (5 μg/kg) or placebo was administered in the afternoon on day –1, 0, and +1 relative to the operation. Primary endpoints were in a hierarchic order: quality of life (QoL) over time (determined at discharge, 2 and 6 months after operation with the European Organization for Research and Treatment of Cancer questionnaire) and the McPeek recovery score, which measures death and duration of stays in the intensive care unit and hospital. Predefined secondary endpoints were global QoL, subdomains of QoL, postoperative recovery, duration of stay, 6-month overall survival, complication rates, and cellular and immunologic parameters.*

Results. *There were no significant differences in both primary endpoints between the treatment groups. A significant improvement ($P < .05$) was obtained by filgrastim prophylaxis in the QoL subdomain family life /- social functioning,; thus, more patients recovered to their preoperative state (14 vs 4 with placebo) as determined by structured interviews. Duration of hospital stay (14 vs 12 days) and noninfectious complications were decreased from 8% to 3%.*

Conclusions. *High-risk patients undergoing major operation for colorectal cancer profited from filgrastim prophylaxis with regard to duration of hospital stay, noninfectious complications, social QoL, and subjective recovery from operation. These endpoints, however, were secondary, and the primary endpoints (overall QoL and the McPeek index) did not show comparable benefits. A new confirmatory trial with the successful endpoints of this trial, as well as a cost analysis, will be needed to confirm the results before a general recommendation for the prophylactic use of G-CSF in high-risk cancer patients can be given. (Surgery 2007;141:501-10.)*

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HIGH-RISK SURGICAL PATIENTS often suffer from nonoptimal outcomes after major operations. In addition to increased mortality, these considerations include raised morbidity, which prolongs the duration of hospital stay and impairs quality of life (QoL). Postoperative outcome may be improved by new treatment options and standard operating procedures, as well as clinical pathways guided by evidence-based guidelines.[1] For example, postoperative improvements were obtained by maintaining normothermia,[2] nutritional support,[3] early mobilization, and adequate pain management.[4] Another approach, for which hitherto high evidence is lacking, is the immune stimulation of high-risk patients. To overcome problems associated with previous negative studies of immune modulation, we developed a new trial design including the following key points:

1) Filgrastim (recombinant, human granulocyte-colony stimulating factor [G-SCF]) was selected as study drug because, similar to activated protein-C and hydrocortisone, it is a substance with a broad spectrum of activities. Filgrastim increases the number of leukocytes, improves granulocyte activity against microbes, and reduces the systemic inflammatory response (SIRS) reaction by downregulation of proinflammatory cytokines.[5,6] Furthermore, research has demonstrated that G-CSF has improved QoL in neutropenic patients.[7]

2) We selected a frequent operation in high risk patients—left-sided colectomy for colorectal cancer in patients with American Society of Anesthesiologists (ASA) scores of 3 and 4.[8] High ASA scores may be accompanied by an impaired immune function.[9]

3) Perioperative management, operation, and the management of postoperative complications were standardized.[8,10] In addition, an evidence-based guideline for the management of postoperative anastomotic leakage was developed and implemented in the participating centers.[10]

4) For the definition of trial conditions, clinic modeling randomized trials (CMRTs) were performed in animals beforehand. In particular, the appropriate dosing of G-CSF[11] and its interactions with other medications (antibiotics, heparin, H_1/H_2 histamine antagonists) and operative interventions[12] were tested in a validated sepsis model of peritoneal contamination and infection. In these preclinical trials, filgrastim decreased mortality and improved various other outcome measures (eg, improved sickness behavior and polymorph nuclear cell activity against microbes, reduced inflammation).[11]

Based on the elements described above, a randomized, controlled, double-blinded, multicenter trial with filgrastim was performed. The aim of the trial was to assess the effectiveness of filgrastim prophylaxis to improve outcomes after operation for colorectal cancer in high-risk patients as evaluated by patients (QoL measurements) and determined by clinicians (McPeek recovery score, duration of stay, complication rate) in a mid-sized trial with 80 patients.

METHODS

Patients. After approval by the institutional review board, written, informed consent was obtained from all patients. From June 2000 to July 2002, 371 patients with colorectal cancer were operated in 3 German clinics: University Marburg, Clinic Stade, and Clinic Lichtenfels; 80 of these 371 patients with colorectal cancer and increased perioperative risk (ASA class 3 and 4) were enrolled in the trial. Patients were males and females of any age between 53 and 90 years. They all had histologically proven and clinically resectable adenocarcinoma of the colon or rectum. Only patients with elective, left-sided resections were included. In the case of anterior resections of the rectum, all patients were operated using the total mesorectal excision (TME) technique.[13] Operation techniques were standardized and are described in detail in the study protocol (see Table I).[10]

Design. The study was designed as a randomized, double-blinded, placebo-controlled trial (n = 40 patients/group) to assess the effect of filgrastim prophylaxis according to the a priori published trial protocol.[6,8,10] The sample size was calculated with $\alpha = 0.05$ and $\beta = 0.2$ estimating an improvement from 350 points to 430 points in the primary endpoint QoL over time by filgrastim prophylaxis.[8]

Outcome measurement. For the outcome analysis, an integrated outcome model[14] was used consisting of patient-expressed endpoints (QoL, structured interview), clinician-determined endpoints (McPeek recovery score, duration of hospital stay, complication rates) and immunologic variables.

Patient self-reported QoL was determined using the European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer patients with 30 items (EORTC-QLQ-C30) in combination with an organ-specific module for colorectal cancer (CR38). Measurements were performed at hospital discharge (QoL_1), 2 (QoL_2), and 6 months (QoL_3) after operation. Death before a planned measurement of QoL was taken as zero QoL points. The first primary

Table I. Patient selection and randomization

	All centers	*Center Marburg*	*Center Stade*	*Center Lichtenfels*
Recruitment period (m)		24	12	10
Patients undergoing elective operation	7010	4390	1580	1040
Patients with colorectal cancer	371	229	103	39
Target population: ASA 3 and 4 including a left-sided operation	162	110	36	16
Excluded by further criteria:	82	48	20	14
• Inability to fill out questionnaire	17	13	2	2
• Concomitant acute infection	12	6	5	1
• Failure to give consent	8	5	0	3
• Uncertain diagnosis of cancer	7	5	2	0
• Cortisone pretreatment	7	7	0	0
• Antibiotic treatment	6	5	1	0
• Absence of the study clinician	5	0	1	4
• Excluded by the surgeon	4	3	1	0
• Local resection	4	0	4	0
• Not elective	3	1	0	2
• Not the first patient elected/day	3	2	1	0
• Multidrug adverse reactions	1	0	0	1
• Pregnancy	1	0	0	1
• Included in another trial	1	0	1	0
• Other medical reasons	3	1	2	0
• Randomized – no. (% from target population)	80 (49)	62 (56)	16 (44)	2 (13)

endpoint in the hierarchic order QoL over time was determined by an area under the curve (AUC) measure ($AUC = QoL_1 + 3QoL_2 + 2QoL_3$) as described in detail in the trial protocol.[8] Optimum score points for QoL-AUC are 600 points and, for all other QoL-measures are 100 points. Healthy people do not normally have more than 80% of the optimum.[15] The global QoL, the three domains (physiologic, psychologic, and social) and their subdomains (physical functioning, role functioning, pain, negative affect, cognitive functioning, family life, and social encounters) were also analyzed with the EORTC questionnaire. A value judgment of relevance was performed by the analysis of a structured interview obtained 6 months postoperatively.

For outcome assessment as second primary endpoint in a hierarchic order, the McPeek recovery score was used.[16] Patients were assigned a total McPeek score of 1 to 9 points based on mortality (1 point for mortality in the operating room or 2 points during hospital stay), amount of critical care (4 or 5 points), and duration of hospitalization (7 to 9 points). Hospitalization was defined as short duration (less than 8 days = 9 points), average (8 to 12 days = 8 points, and long (exceeding 12 days = 7 points). After operation, the patients were scheduled to be admitted to the intensive care unit (ICU) for 1 day. ICU treatment for 2 to 3 days was defined as moderate increase in ICU treatment (5 points), and for more than 3 days as great increase (4 points). Further clinician-determined endpoints were mortality rate, complication rates during the half-year follow-up, and duration of hospital stay after primary operation.

PROCEDURES

Randomization and allocation were concealed. The randomization sequence was computer-generated by the study statistician and was delivered in opaque, sealed envelopes to the pharmacist responsible for the study packages containing filgrastim or placebo. Placebo and filgrastim vials and their contents were undistinguishable in size, color, and density. Balanced block randomization with 10 patients was used to allow an equal number of filgrastim and placebo at the 3 centers. Patients were randomized the day before operation, and medication was started the same evening. The code for group assignment was broken after all clinical, QoL, and immunologic data were calculated.

From 7010 elective colorectal cancer operations, 162 high-risk patients (ASA 3 and 4) scheduled for left-sided colon resection were identified. Of these, 80 patients were randomized into the trial (Table I). For exact classification, the ASA score was determined by the study surgeon, the anesthesiologist on duty,

Table II. Baseline demographic data and physiologic characteristics of participants (n = 76)

	Filgrastim (n = 36)	*Placebo (n = 40)*	P *value*
Age – y - median (range)	74 (59-89)	71 (53-90)	.64
Male sex – no. (%)	18 (50)	29 (72)	.044
ASA class 3 – no. (%)	32 (89)	38 (95)	.32
Nutritional status – no. (%)			.66
• Malnourished	1 (3)	0 (0)	
• Thin	3 (8)	3 (7.5)	
• Normal	18 (50)	16 (40)	
• Obese	13 (36)	20 (50)	
• Morbidly obese	1 (3)	1 (2.5)	
Concomitant disease – no. (%)			
• Heart	33 (92)	33 (82.5)	.24
• Vascular system	31 (86)	30 (75)	.22
• Respiratory tract	10 (28)	17 (42.5)	.18
• Kidney, urinary tract	9 (25)	12 (30)	.63
• Liver	9 (25)	10 (25)	1.0
• Metabolic	24 (67)	25 (62.5)	.70
• Central nervous system	6 (17)	5 (12.5)	.61
• Allergy	2 (5.5)	4 (10)	.47
Tumor stage – no. (%)			.70
• pT0	1 (3)	2 (5)	
• pT1	3 (8)	4 (10)	
• pT2	8 (22)	7 (17.5)	
• pT3	22 (61)	22 (55)	
• pT4	2 (6)	5 (12.5)	
First operation – no. (%)	32 (89)	37 (92)	.59
Types of operation – no. (%)			.86
left hemi colectomy	3 (8)	5 (12.5)	
sigmoid Resection	7 (20)	5 (12.5)	
sub-, total colectomy	3 (8)	4 (10)	
anterior resection of rectum	15 (42)	15 (37.5)	
Hartmann procedure	3 (8)	4 (10)	
Abdominoperineal resection	5 (14)	7 (17.5)	
Global quality of life before operation (mean ± standard deviation)	61 ± 28	55 ± 24	.31

and by an experienced study anesthesiologist who had the final decision for classification.

Patients received 5 μg/kg filgrastim or placebo (isotonic NaCl) subcutaneously at about 8:00 PM on day –1, 0, and +1 relative to operation. Cefuroxime/metronidazole 1.5/0.5 g/patient or ofloxacin/metronidazole 0.4/0.5 g/patient were given intravenously (iv) 1 hour before skin incision. All patients received an iv prophylaxis with 0.1 mg/kg dimetindene (H_1 receptor antagonist) and 5 mg/kg cimetidine (H_2 receptor antagonist) at least 15 minutes before anesthesia induction.[17] General anesthesia was induced with thiopentone or etomidate iv and was maintained based on a volatile anesthetic (sevoflurane or isoflurane), supplemented with fentanyl. In patients who chose an epidural catheter for postoperative analgesia, a lumbar catheter was inserted prior to general anesthesia.

The postoperative follow-up included a daily visit of the patient by the study surgeon until discharge. At discharge and at 2 and 6 months postoperatively, the patient self-reported QoL was assessed. All complications and adverse events were registered. In addition, 6 months after operation, a structured interview (15 min) was obtained during an outreach visit to the patient's home by a study physician, undisturbed by relatives.

As surrogate parameters, differential white blood cell counts were determined every day for 6 days after operation. Blood samples for immunomonitoring (cytokine serum levels, capacity to produce cytokines after endotoxin challenge, phagocytosis of granulocytes, HLA-DR expression on monocytes) were drawn on day 0 (before anesthesia), and on days 1, 3, and 6. In vitro whole blood stimulation was performed immediately after blood sampling with 500 pg/ml LPS

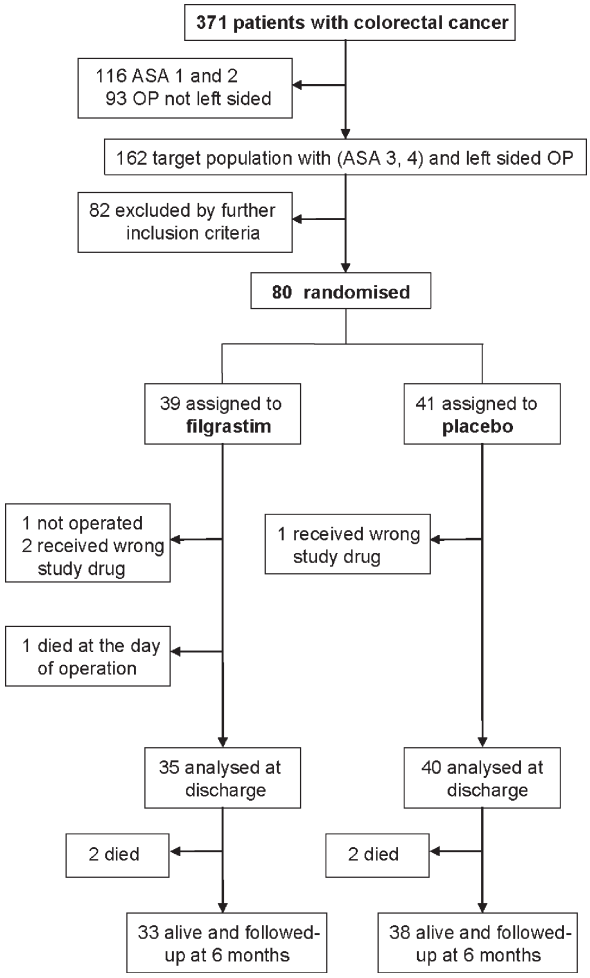

Fig 1. Trial profile. All patients except the 3 patients treated with the wrong study drug and the patient not operated were included into the analysis for all endpoints.

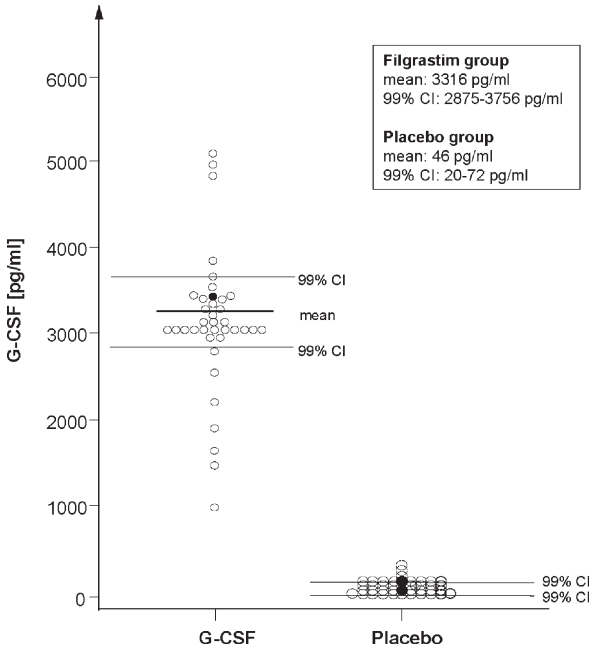

Fig 2. Determination of G-CSF plasma levels. Mean plasma levels on the day of operation and 99% confidence levels are demonstrated. Correctly assigned patients are depicted in *white* and wrongly assigned patients in *black*. Two patients from the filgrastim group received placebo, and one patient from the placebo group got filgrastim.

over 2 hours at 37°C with a standardized assay (DPC Biermann, Bad Homburg, Germany). Supernatants from LPS-stimulated whole blood and EDTA-plasma were used to assess the cytokines IL-6 and TNF-α with the Immulite® system (DPC Biermann). Flow cytometry was used to assess granulocyte phagocytic activity of *E. coli* (PAHAGOTEST®, Orpegen Pharma, Heidelberg, Germany) and quantitative HLA-DR receptor expression on monocytes (QuantiBrite® Anti-HLA-DR, Becton Dickinson, San Jose, Calif).

Statistical analysis. The primary endpoints QoL over time and the McPeek recovery score were assessed by intention to treat analysis and by per protocol analysis. Per protocol analysis was performed for all secondary endpoints.

QoL data and blood cell parameters are given as means ± standard deviation. Group differences of primary endpoints were analyzed with the *t* test (QoL) or the nonparametric Mann-Whitney test (McPeek score); correction for multiple testing followed the principle of closed testing.[18] Secondary endpoints were analyzed in an explanatory manner and, therefore, no corrections for multiple testing were used. The significance of changes in cytokine level over time was determined with a *t* test for dependent variables. Duration of hospital stay was analyzed with the Mann-Whitney test. Mortality rates, complication rates, and recovery after 6 months were analyzed with chi-square tests. *P* values $< .05$ were considered statistically significant.

RESULTS

Performance of the trial. Baseline demographic data, physiologic characteristics, and global QoL of the patients are depicted in Table II. Groups did not differ significantly in terms of age, ASA class, nutritional status, concomitant diseases, tumor stage, type of operation, and global QoL. More male patients were included in the placebo group ($P < .05$).

In accordance to the revised CONSORT statement[19] the trial profile (Fig 1) shows the allocation of patients to treatment groups. Determination of

Table III. Patient-expressed and clinician-determined endpoints

	Filgrastim	*Placebo*	P *value*
Primary endpoints			
Global quality of life (AUC)	366 ± 152	345 ± 120	.281
McPeek score (median, interquartiles)	8 (5; 9)	7.5 (5; 9)	.248
Secondary endpoints			
Global quality of life at discharge	54 ± 24	51 ± 20	.594
Physical functioning at discharge	59 ± 29	48 ± 30	.148
Role functioning at discharge	49 ± 31	40 ± 35	.277
Pain at discharge	64 ± 27	52 ± 31	.277
Negative affect at discharge	71 ± 23	62 ± 27	.099
Cognitive functioning at discharge	75 ± 26	65 ± 31	.108
Family life, social functioning at discharge	80 ± 30	63 ± 23	.040
Recovery to a state as before surgery	no/partial/yes	no/partial/yes	.042
interview at 6 months	4/6/18	14/4/14	
LOS, days (median, interquartiles)	12 (10; 14)	14 (13; 21)	.036
6-month overall survival rate – no. (%)	33 (92)	38 (95)	.558
Complications – no. (%)	12 (33)	17 (42.5)	.289

LOS, length of stay.
Quality of life (QoL) data are means ± standard deviations with an optimum of 600 points for AUC and 100 points for all other QoL measures. Healthy persons do not have normally more than 80% from the optimum. A structured interview of 15 min was obtained 6 months after operation from 60/76 patients at their home. In between, 5 patients died, 5 were mentally unable to answer the questions, and 6 were unwilling to participate in the interview.

plasma levels of G-CSF on the day of operation and the days after operation (not shown) demonstrated that 3 patients (no. 75 to 77) received the wrong study drug by mistake (Fig 2). These 3 patients and the 1 omitted from the operation schedule after allocation were excluded in the per protocol analysis.

Main findings. No adverse reactions to filgrastim were observed. There was no significant difference in the first primary endpoint (QoL over time) and the second primary endpoint (the McPeek score) (Table III) independent of the mode of analysis—intent to treat or per protocol. At hospital discharge, mean scores of QoL were uniformly higher in the filgrastim than in the placebo group, but a significant difference emerged only with regard to family life and social functioning ($P < .05$). In the structured interview, the most relevant question was asked: "Are you now recovered to your health as before surgery?" Only 4 patients in the filgrastim group answered "no" compared with 14 patients in the placebo group ($P < .05$).

Duration of hospital stay was decreased from 14 to 12 days in the filgrastim group ($P < .05$). The 6-month overall survival rate was 93.4%; 2 patients died during hospital stay and 3 died in the 6-month postoperative observation period. There was no difference between the treatment groups. The number of complications of all types, postoperative infections, and noninfectious complications were less in the filgrastim group. A significant difference was achieved for the overall rate of noninfectious complications (7% vs 3%; $P < .05$).

Cellular and immunologic parameters. Blood leukocyte counts were increased in the filgrastim groups from day 0 through day 6 (Fig 3, *A*). The phagocytosis of *E. coli* by PMNs was significantly increased in the filgrastim group after operation (Fig 3, *B*). HLA-DR receptors on monocytes and TNF-α release after LPS stimulation were not altered by the filgrastim prophylaxis (Figs 3, *C* and *D*). G-CSF plasma levels were significantly increased from day 0 to day 3 (Fig 3, *E*). IL-6 plasma levels increased at day 1 after operation in both groups decreased at day 3, and was lower at this time point in the filgrastim group compared to the placebo group (Fig 3, *F*).

DISCUSSION

Mortality is the most commonly used endpoint in clinical trials. This endpoint, however, is frequently insensitive because perioperative mortality rates of less than 5% after major operation preclude statistical power.[20] Therefore, a change in methods for defining and measuring outcomes has been proposed.[21,22] New treatment options with immune-modulators showed frequently no or only little effect on mortality but did offer promising results with regard to morbidity[23] and QoL.[24] In this trial, we used an innovative integrated outcome concept with both patient-expressed and doctor-assessed outcome variables.[14] QoL over time and

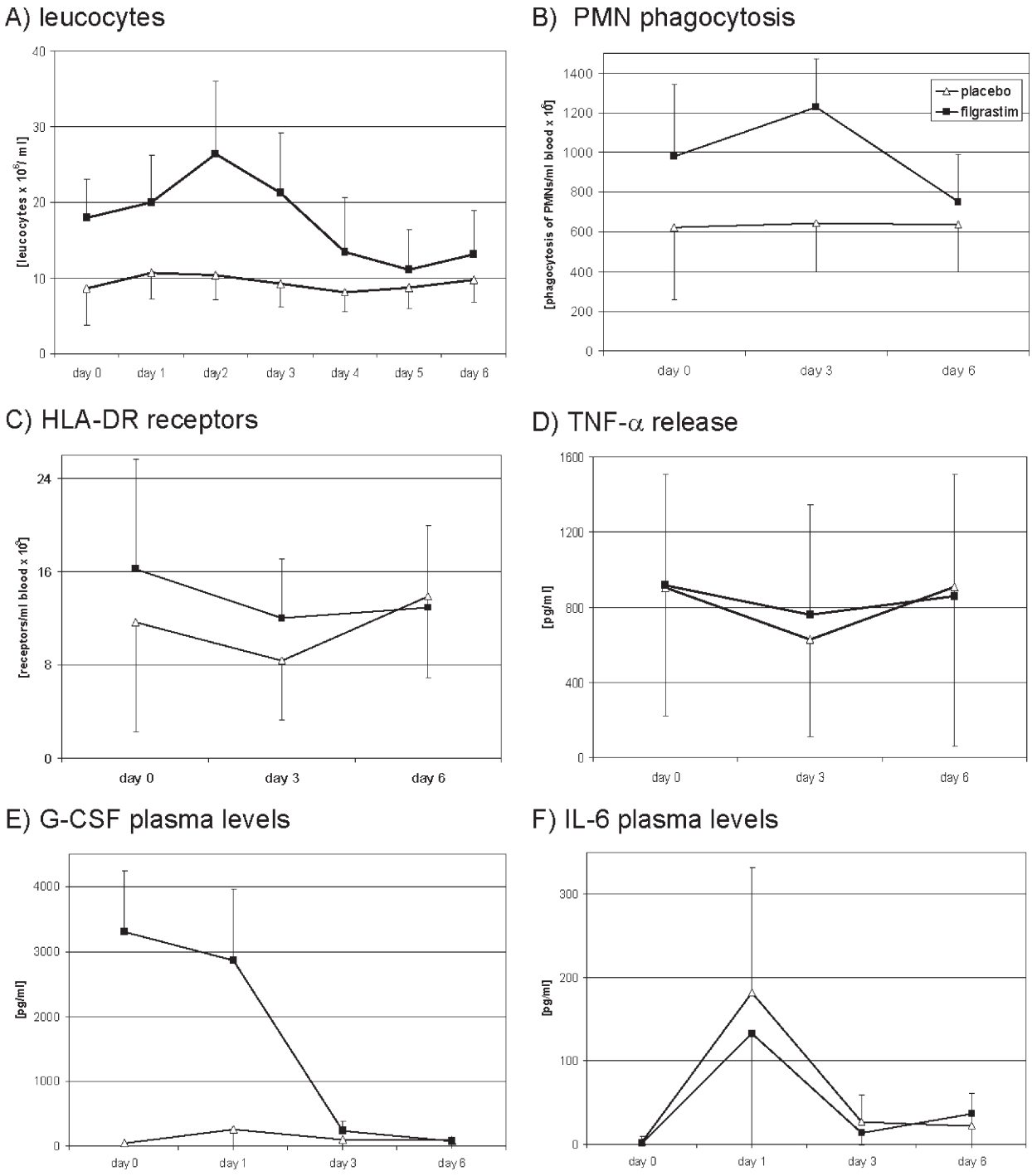

Fig 3. Determination of cellular and immunologic parameters. Data are means ± SD. Statistical analysis was performed with the t test. **A,** Peripheral leukocytes: The leukocyte count was increased from day 0 to day 6 ($P < .001$ to day 4, $P < .05$ afterward). **B,** Phagocytosis of E. coli by PMNs: Groups were different after operation ($P < .005$ at day 3, and $P < .05$ at day 6). **C,** HLA-DR receptors on monocytes: There was no significant difference between the groups in the number of HLA-DR receptors ($P = .10$ at day 3). **D,** TNF-α release after LPS stimulation: There were no significant differences in the TNF-α release. **E,** G-CSF plasma levels: Groups were different in the *t* test ($P < .001$ at day 0 and day 1, $P < .05$ at day 3, but not at day 6). **F,** IL-6 plasma levels: Groups were different at day 3 ($P < .05$).

the McPeek recovery score were used as prospectively defined primary endpoints. The McPeek score is sensitive to treatment changes as demonstrated in the validation of this recovery score in 3 trials.[25] Nevertheless, prophylaxis with filgrastim did not improve these 2 endpoints in high-risk surgical patients in our trial. The analysis of secondary endpoints as defined in the study protocol[8] for duration of hospital stay and noninfectious complications demonstrated a benefit for the prophylaxis with filgrastim. In future trials, these endpoints are good candidates for primary endpoints.

Filgrastim improved QoL in all subdomains; however statistical significance was reached only for family life and social functioning. Recently, the potency of filgrastim to improve QoL and to reduce treatment-related side effects was also reported by others.[26] Furthermore, the structured interview at 6 months after operation showed that a lesser number of patients felt completely recovered after operation with placebo than with filgrastim. Patient preferences and value judgments are often neglected; however, these types of concerns are essential parts of evidence-based medicine.[27]

As shown in a population based cohort study on rectal cancer in the local area of Marburg, most patients cope with their difficult health status after 6 months,[15] resulting in global QoL scores that are close to healthy persons. Therefore, filgrastim effects using a standardized QoL questionnaire were most pronounced at discharge from hospital. This is in agreement with the pharmacologic properties of filgrastim, which did not remain active probably after discharge. In addition, we have also shown in a rat model of sepsis recovery from sepsis and restoration of normal behavior is improved by G-CSF prophylaxis.[28] These behavioral changes, called sickness behavior, are induced partially by cytokine release in the brain,[29] which will be not detectable in plasma.

Beside the increase of the G-CSF levels and leukocyte counts, which can be attributed to the filgrastim applications, serum cytokines differed little between treatment groups. The phagocytic capacity of the PMNs was improved by the filgrastim prophylaxis, but the number of HLA-DR receptors on monocytes was not affected by the filgrastim prophylaxis. In both groups, the number of HLA-DR receptors decreased on day 3 after operation. A decrease in the HLA-DR receptor level represents a shift toward a less immunologically active state of monocytes.[30] A lesser number of HLA-DR receptors was also found by Schneider et al[31] on the third postoperative day and a less pronounced reduction in the filgrastim group. The third postoperative day represents a vulnerable phase in the course of postoperative recovery. A second marker of monocyte activity, the endotoxin-stimulated release of TNF-α was also less decreased on day 3 in the filgrastim group.

Another trial with G-CSF as prophylaxis in patients with esophageal resection did not show any benefits of cytokine prophylaxis.[32] Other clinical trials in infectious diseases or inflammation and filgrastim treatment demonstrated heterogeneous results. Significant benefits in curing diabetic foot infections and a reduced rate of amputations[33] were reported, but no effect was reported in another trial with diabetic foot infections.[34] G-CSF attenuates the rate of opportunistic infections in HIV patients[35] and (as cotreatment) in surgical infections.[36] In a nonrandomized trial, filgrastim demonstrated a reduction of the mortality rate from 73% to 31% in an endemic tropical disease: septic shock due to *Burholderia pseudomalei* infections.[37] In patients with community-acquired pneumonia, filgrastim showed promising results initially, but no effectiveness was evident in subsequent trials.[38] Failure of these trials may be explained by the use of filgrastim for treatment instead of prophylaxis. Also in a trial with 40 radical vulvectomies, G-CSF had no effect on wound healing and QoL.[39]

Due to high drug costs, careful cost-benefit analyses are needed with regard to the use of filgrastim in further indications as has been noted in cancer patients with chemotherapy.[40] G-CSF is ineffective for treatment of malignant lymphoma, because it decreases the number of patients with severe neutropenia and febrile neutropenia; however, it did not reduce the use of antibiotics nor the infection-related mortality or improve the complete tumor response.[41] Saving ICU care and reducing duration of hospitalization may reimburse drug costs, particularly in high-risk patients (high ASA class and age). These patients will have the greatest benefit because they have a decreased immune response.[9]

In summary, the present trial showed that high-risk patients (ASA III and IV) undergoing major resections of left-sided colorectal cancer profited from preoperative filgrastim prophylaxis with regard to duration of their hospital stay, noninfectious complications, social quality of life at discharge from hospital, and subjective recovery from operation after 6 months. These endpoints, however, were secondary, while the primary endpoints (overall QoL over six months and the McPeek index) showed equivalent results; for these reasons, implications of these results have to be interpreted with caution. It may well be that we used the wrong "primary" endpoints. A confirma-

Table IV. Type, number, and rate (%) of complications

	Filgrastim	*Placebo*
All types of complications	12 (33)	17 (42.5)
Postoperative infections	9 (25)	11 (27.5)
Wound infection	5	6
Abscess formation	—	1
Urinary tract infection	—	2
Fever	1	1
Bacteremia	1	—
Peritonitis	2	1
Noninfectious complications*	3 (8)	8 (20)
Hemorrhage	1	3
Myocardial ischemia	—	2
Apoplexy	—	1
Disturbance of micturition	1	1
Gastrointestinal atony	1	1

The actual number of complications is presented; some patients had more than 1 complication.
*Significant differences were observed for noninfectious complications ($P = .048$).

tory prospective trial with the successful parameters of duration of hospital stay, complication rate, social QoL, mid-term subjective recovery, and a financial cost-benefit analysis as primary endpoints should be performed. Only when such a trial can replicate and confirm the present results, a general recommendation can be given for the prophylactic use of G-CSF for high-risk cancer patients undergoing major operations for colorectal cancer.

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