Cancer Immunol Immunother (1997) 44: 301–304

ORIGINAL ARTICLE

S.H. Goey · J. Verweij · R.L.H. Bolhuis · D. de Gooyer
A.M.M. Eggermont · P.I.M. Schmitz · G. Stoter

Tunnelled central venous catheters yield a low incidence of septicaemia in interleukin-2-treated patients

Received: 9. January 1997 / Accepted: 13. March 1997

Abstract A retrospective study on the incidence of catheter-related complications and catheter indwelling time (t_{CI}) during treatment with continuous interleukin-2 (IL-2) infusion in patients with metastatic renal cell cancer, who were equipped with tunnelled central venous catheters (CVC). A group of 72 patients were treated with IL-2-based immunotherapy. Two induction treatment cycles of 35 days each were used. Treatment consisted of IL-2 as a continuous intravenous infusion (c.i.v.) with lymphokine-activated killer cells and interferon α intramuscularly. A tunnelled CVC was inserted at the start of treatment and was kept in place for the duration of the therapy or until the occurrence of complications. Out of 72 CVC, 30 (42%) functioned uneventfully for a median t_{CI} of 64 days. In another 12 clinically uncomplicated cases (16%), catheter tips were positive in routine culture after a median t_{CI} of 33 days. In 18 patients (25%), CVC-related infections were noted, including 8 (11%) local tunnel infections and 10 (14%) septic episodes. These complications occurred at a median t_{CI} of 28 and 20 days respectively. In 15 (83%) of these 18 catheter infections, *Staphylococcus aureus* was isolated, whereas in the remaining 3 (17%) *Staphylococcus epidermidis* was found. Subclavian vein thrombosis was noted in 12 (17%) CVC at a median t_{CI} of 31 days; 5 (36%) of these were diagnosed in the first 14 patients. This prompted us to administer prophylactic heparin 15000 IU c.i.v. daily during IL-2 treatment. Thereafter the incidence of thrombosis dropped to 7 (12%) in the subsequent 58 CVC inserted ($P = 0.03$). In conclusion, in contrast to previous reports on the high incidence of CVC-related septicaemia and thrombosis, we observed a relatively low incidence of these complications, which we ascribe to the use of tunnelled catheters and prophylactic heparin.

Key words Interleukin-2 · Central venous catheters · Catheter-related infections · Immunotherapy · Septicaemia

S. H. Goey (✉) · J. Verweij · D. de Gooyer · G. Stoter
Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands
Fax: +31 10 4851618

A. M. M. Eggermont
Department of Surgical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, Rotterdam, The Netherlands

P. I. M. Schmitz
Department of Biostatistics, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, Rotterdam, The Netherlands

R. L. H. Bolhuis
Department of Medical and Tumor Immunology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, Rotterdam, The Netherlands

Introduction

Interleukin-2 (IL-2) is approved for the treatment of metastatic renal cancer. The drug has various side-effects, which are well characterized [7, 12, 13, 15]. Because of the protracted administration of IL-2 and the drug-induced tendency towards clotting in peripheral veins at the site of infusion, indwelling central venous catheters (CVC) are required. The frequency of CVC-related bacterial infections has been reported to vary between 10%–38% in studies using high-dose IL-2 regimens [2, 14, 16]. In all of these studies non-tunnelled CVC were used. High-dose IL-2 appeared to double the relative risk of bacteraemia as compared to low-dose IL-2 regimens, leading to a related reduction of catheter indwelling time (t_{CI}) by 40% [14]. Skin colonization with *Staphylococcus aureus* and IL-2-induced desquamation of the skin increased the relative risk of *Staphylococcus aureus* bacteraemia up to 14.5-fold [16]. In addition, neutrophil dysfunction during IL-2 treatment may also contribute to the risk of bacteraemia [4, 6, 11]. In our IL-2 study protocols, we have used tunnelled CVC to obtain continuous vascular access for a prolonged period of time. We selected a tunnelled CVC procedure because of our previous experience showing a long t_{CI} in immunocompromised patients [5]. The study reported here presents a

retrospective analysis of the usefulness of these CVC in the areas of catheter infection, catheter-related sepsis, catheter thrombosis, and t_{CI} in IL-2-treated patients.

Materials and methods

Eligibility

Patients with metastatic renal cell carcinoma (RCC) were treated in the framework of a phase II study of IL-2-based adoptive cellular immunotherapy. Inclusion criteria included measurable or evaluable metastatic RCC, age below 70 years, a Karnofsky performance status of at least 80, no evidence of brain metastases and normal organ functions. Patients with relevant clinical metabolic or endocrine disorders, systemic infections, positive HIV or HBsAg serology and patients requiring systemic corticosteroids were excluded. All patients gave informed consent according to institutional rules.

Treatment

IL-2 was given as a continuous intravenous infusion (c.i.v.) at a dose of 18 MIU m^{-2} day^{-1} on days 1–5. Lymphapheresis was performed on days 7–9 and lymphokine activated-killer (LAK) cells were reinfused in 60 min on days 12–15 together with 18 MIU m^{-2} day^{-1} IL-2 c.i.v. and 5 MU m^{-2} day^{-1} interferon α (IFNα) intramuscularly (i.m.) on days 12–16. This cycle was repeated on day 36. After these two induction cycles, tumour evaluation was performed. Patients with objective response or stable disease continued to receive four monthly maintenance cycles with 18 MIU m^{-2} day^{-1} IL-2 c.i.v. and 5 MU m^{-2} day^{-1} IFNα i.m. on days 1–5. After 17 patients, IFNα was also administered on days 1–5 of each induction cycle at a dose of 5 MU m^{-2} day^{-1} i.m.

Ex vivo activation of lymphocytes with IL-2

We have previously reported the details of this procedure [8]. Briefly, all lymph-apheresis procedures were performed using a Travenol CS-3000 blood cell separator (Travenol, Deerfield, Ill.). Buffy coats were placed into culture using a semi-closed bag system: Travenol-Fenwall PL 732 bags, containing 1500 ml activation medium with 3×10^6 cells/6000 IU IL-2/ml. Bags were loaded with cells and medium using a Travenol-Fenwall model SAV EX 2 fluid fill/weight unit. The activation medium consisted of 78% RPMI-1640 medium, 20% AIM-V and 2% autologous human plasma. L-Gutamine (2 mM), 50 µg/ml streptomycin, and 40 µg/ml gentamycin were added to the medium. After incubation for 5 days in 5% carbon dioxide (CO_2) in a humidified, 37 °C incubator, cells were harvested on a Fenwall cell harvester. The harvested cells were washed with 0.9% saline and resuspended in 5% human serum albumin supplemented with 6000 IU IL-2/ml to a volume of 500 ml.

Surveillance for bacterial contamination of harvested cells involved culturing of samples from the culture bags in TCS medium (Gibco Ltd., Buckingham, UK): (a) immediately after lymphapheresis, (b) 24 h prior to cell harvest, and (c) 1 hour before LAK cells were reinfused into the patient.

Catheters

Catheters used were double-lumen Hemed CVAC 5200 (11 Fr) (Gish Biomedical Inc., Santa Ana, Calif., USA) and double-lumen Groshong CVC (9.5 Fr) (Cath-tech, Salt Lake City, Utah, USA). Both catheters were equipped with a Dacron cuff. All catheters were inserted under sterile conditions in the operating room by a closed method under local anaesthesia by staff surgeons. The subclavian vein was the preferred site of insertion and all catheters were tunnelled, the Dacron cuff being placed at the end of a 15 to 20 cm subcutaneous tunnel (2 cm from skin entry). After the procedure, a chest X-ray was performed to confirm the proper position of the CVC and to rule out the existence of a pneumothorax. Mask and sterile gloves were used for all dressing changes, and dressings were changed daily by trained nursing personnel. The skin around the catheter was cleansed first with 0.5% chlorohexidine in 70% alcohol. Fixomull (Beiersdorf, Hamburg, Germany) was placed over sterile gauze on all dressings to cover the insertion site. In between treatment courses, dressings were changed once a week and catheter lumina were flushed with 2 ml 0.9% saline solution containing 150 U/ml heparin. If an infection was suspected or at the end of treatment, catheters were removed in a sterile fashion after the skin surrounding the entry site had been cleansed. The distal 2 cm of the catheter was submitted for culture using a semiquantative culture method as described by Maki et al. [10]. If an infection was suspected, peripheral blood samples were drawn via peripheral venous puncture and cultured in TCS medium (Gibco Ltd., Buckingham, UK). Skin cultures were taken using a premoistened Stuart Culturette (Transwab, MW&E Co. Ltd., Potley, Corsham, Wiltshire, UK). All culture samples were incubated both aerobically and anaerobically at 37 °C for 72 h.

Definitions

Catheter-related septicaemia was defined as the growth of the same micro-organisms from the catheter tip and the peripheral blood without evidence of other sources of infection. A tunnel infection was defined as tenderness and redness of the subcutaneous tunnel with or without evacuation of pus. A positive culture was defined as growth of 15 or more bacterial colonies per plate.

All catheters showing evidence of a tunnel infection were promptly removed; no attempts were made to save the catheter by antibiotic treatment. Catheter-related thrombosis was defined as venous occlusion on angiogram.

Statistical methods

To compare variables between two groups the Fisher exact test or the χ^2-test was used where appropriate. A P value of 0.05 or less was considered statistically significant.

Results

A total of 72 patients were analysed for the usefulness of their initial CVC. The median age of the study population was 54 years. The male:female ratio was 2:1, The median Karnofsky performance status was 100 (range 80–100), and 60% of the patients had at least two metastatic organ sites.

In 30 patients (42%) the CVC functioned uneventfully for a median t_{CI} of 64 days. In other words, these patients received two induction treatment cycles using one CVC. Twelve CVC (16%), which were removed routinely because of treatment cessation (median t_{CI} = 33 days), turned out to have positive tips in routine culture. There were 18 (25%) infectious episodes: 8 (11%) tunnel infections and 10 (14%) septicaemias.

All catheter-related infections were caused by staphylococci. *S. aureus* was the micro-organism isolated in 15 (83%) of 18 catheter infections (see Table 1). In 2 additional patients *S. aureus* septicaemia was due to contaminated LAK cells, the culture results of which became positive on the third day after the start of LAK cell reinfusion. *Staphylococcus epidermidis* was isolated in 3 (17%) of 18 catheter infections.

Table 1 Central-venous-catheter (CVC) and non-CVC-related infections. *LAK* lymphocyte-activated killer cell; percentages relate to all 72 patients

Infection	CVC-related	CVC-unrelated
S. aureus tunnel infections	7 (10%)	
S. aureus sepsis	8 (11%)	2 (infected LAK culture) (3%)
S. epidermidis tunnel infection	1 (1%)	
S. epidermidis sepsis	2 (3%)	
E. coli sepsis		1 (urinary tract infection) (1%)
Routine CVC-tip culture		
S. aureus	4 (5%)	
S. epidermidis	8 (11%)	

In 12 cases of routine removal of clinically uncomplicated CVC after discontinuation of treatment, a routine culture was found to be positive with 4 cultures showing *S. aureus* (5%) and 8 cultures showing *S. epidermidis* (11%).

Thrombosis of the subclavian vein occurred in 12 (17%) of the 72 CVC; 5 (36%) of these occurred in the first 14 inserted. Owing to this high incidence, all subsequent patients received prophylactic heparin at a dose of 15 000 IU c.i.v. per 24 h during IL-2 treatment. With this regimen only 7 (12%) thrombotic events were observed in the subsequent 58 CVC ($P = 0.03$).

Discussion

Prolonged central venous access is frequently necessary in cancer patients treated with continuous IL-2 therapy because of the thrombophlebitis-inducing potential of IL-2. In addition, the i.v. administration of IL-2 is often associated with haemodynamic changes that require volume replacement and i.v. medication, which are usually given via a second lumen of the CVC.

In view of our previous experience with CVC in immunocompromised patients [5], we have chosen the tunnelling procedure for CVC placement in our IL-2-treated patients, since this insertion technique was found to be safe and rapid and resulted in a long t_{CI}. In an attempt to reduce further the hazard of CVC-related sepsis, we used a CVC equipped with a Dacron cuff. Both the Dacron cuff and the tunnel are intended to act as a barrier against invading micro-organisms. Of all CVC inserted initially, 42% (30/72) functioned uneventfully for a median of 64 days. In addition, 16% (12/72) were removed routinely at the end of treatment and had thus served their purpose, although routine bacterial culture of the catheter tip turned out to be positive. Overall, these results indicate that in 58% of patients only one operation for catheter insertion was sufficient, avoiding the risk of pneumothorax related to multiple blind CVC insertions. A less expensive and invasive alternative to central access are single- or dual-lumen, peripherally inserted central catheters. However, because of the smaller calibre of the catheter lumen, such lines are associated with a number of insertion and maintenance problems, including clotting and catheter fracture (51.6%) [9].

The frequency of staphylococcal bacteraemias has been reported to range from 10% to 38% in patients receiving IL-2 [2, 11, 14, 16]. IL-2-related side-effects, such as transient impairment of neutrophil function [4, 6, 11], dose-dependent incidence of staphylococcal bacteraemia [14], colonization with *S. aureus* and skin desquamation [16], are well-documented risk factors for the development of catheter infection and sepsis.

Richards et al. [14] reported a septicaemia incidence of 18% after a mean t_{CI} of 20 days, associated with low-dose (9 MIU m^{-2} day^{-1}) IL-2 treatment. In cases of high-dose bolus IL-2 (1.8 MIU kg^{-1} day^{-1} ≈ 72 MIU m^{-2} day^{-1}) the incidence of septicaemia rose to 38% and the mean t_{CI} decreased to 12 days. An uncuffed non-tunnelled double-lumen CVC was used in their patients. Our patients received intermediate doses (18 MIU m^{-2} day^{-1} c.i.v.) of IL-2. This dose, as a continuous infusion, has been shown to be equitoxic to bolus administration of 72 MIU m^{-2} day^{-1} IL-2 [17]. Hence, the relatively low incidence of septicaemia of 14%, taken together with a long overall median t_{CI} of 43 days in our series, compare favourably. In a prospective randomized study comparing prophylactic oxacillin i.v. with placebo in patients treated with high-dose bolus IL-2 (1.8 MIU $kg\,day^{-1}$), Bock et al. [2] demonstrated that, in the oxacillin arm, no catheter-related septicaemia was seen while, in the placebo arm, 10% of the patients experienced septicaemia ($P = 0.05$). Moreover, catheter colonization was reduced significantly in the oxacillin arm (10%) relative to the placebo arm (44%, $P = 0.0001$). To date, in their study t_{CI} has deliberately been kept short at ± 4 days and therefore their results cannot easily be compared with ours. Moreover, Vlasveld et al. [18] found 34 (63%) catheter-related infections out of a total of 54 CVC that had been inserted in cancer patients treated in a phase I-II study with low-dose IL-2 (0.18–9 MIU m^{-2} day^{-1}) c.i.v. via an implantable Port-a-Cath. In order to prevent infection, subsequent patients received prophylaxis with oxacillin (4×1 g i.v. for 24 h) starting 1 h before CVC insertions followed by oral pefloxacin (1×400 mg daily), given during the entire period of IL-2 treatment. These investigators could not demonstrate a reduction in the risk of infection by prophylactic antibiotics. In contrast, we have found a 14% rate of septicaemia after a median t_{CI} of 20 days, despite the fact that we used a much more intensive regimen of cytokines without antibiotic prophylaxis, since we wanted to avoid the development of bacterial resistance and superinfection related to long-term antibiotic treatment.

The relatively high rate of catheter-related thrombosis observed in the first 14 patients (36%) might well be attributable to the production of secondary cytokines such as tumor necrosis factor α (TNFα) during IL-2 administration [13]. Baars, et al. [1] reported that IL-2 activates the coagulation and fibrinolytic systems in vivo, which changes resemble the perturbations observed after TNFα administration. Following the institution of prophylactic heparin during IL-2 administration, the frequency of CVC-related thrombosis decreased significantly to 12% in the subse-

quent 58 patients (P = 0.03). As an alternative, daily administration of low-dose warfarin may also reduce the risk of thrombosis [3].

In conclusion, 58% of our patients required only one CVC for the duration of their treatment. The infection rate related to the technique of CVC insertion that we used is relatively low, in view of the high doses of IL-2 used and the avoidance of prophylactic antibiotics. This compares favourably to previously reported experience. Therefore, we recommend the use of this technique in long-term IL-2 treatment schedules. Low-dose heparin should be given prophylactically to avoid thrombotic complications.

Acknowledgement The authors wish to thank Miss L. de Smit for preparation of the manuscript.

References

1. Baars JW, Boer JP de, Wagstaff J, Roem D, Eerenberg-Belmer AJM, Nauta J, Pinedo HM, Hack CE (1992) Interleukin-2 induces activation of coagulation and fibrinolysis: resemblance to the changes seen during experimental endotoxaemia. Br J Haematol 82:295
2. Bock SN, Lee RE, Fisher B, Rubin JT, Schwartzentruber DJ, Wei JP, Callender DPE, Yang JC, Lotze MT, Pizzo PA, Rosenberg SA (1990) A prospective randomized trial evaluating prophylactic antibiotics to prevent triple-lumen catheter-related sepsis in patients treated with immunotherapy. J Clin Oncol 8:161
3. Denny DFJ (1993) Placement and management of long-term central venous access catheters and ports. Am J Roentgenol 161:385
4. Jablons D, Bolton E, Mertins S, Rubin M, Pizzo P, Rosenberg SA, Lotze MT (1990) IL-2 based immunotherapy alters circulating neutrophil Fc receptor expression and chemotaxis. J Immunol 144:3630
5. Jansen FM, Wiggers T, van Geel BN, van Putten WLJ (1990) Assessment of insertion techniques and complication rates of dual lumen central venous catheters in patients with hematological malignancies. World J Surg 14:101
6. Klempner MS, Noring R, Mier JW, Atkins MB (1990) An acquired chemotactic defect in neutrophils from patients receiving interleukin-2 immunotherapy. N Engl J Med 322:959
7. Kruit WHJ, Punt CJ, Goey SH, Mulder PHM de, Hoogenhuyze DC v., Henzen-Logmans SC, Stoter G (1994) Cardiotoxicity as a dose-limiting factor in a schedule of high dose bolus therapy with interleukin-2 and alpha-interferon. An unexpectedly frequent complication. Cancer 74:2850
8. Lamers CHJ, Griend RJ van de, Braakman E, Ronteltap CPM, Bénard J, Stoter G, Gratama JW, Bolhuis RLH (1992) Optimization of culture conditions for activation and large-scale expansion of human T lymphocytes for bispecific antibody-directed cellular immunotherapy. Int J Cancer 51:973
9. Longhran SC and Borzatta M (1995) Peripherally inserted central catheters: a report of 2506 catheter days. J Parenter Enteral Nutr 19:133
10. Maki DG, Weise CE, Serafin HW (1977) A semiquantitative method of identifying intravenous catheter-related infection. N Engl J Med 296:1305
11. Murphy PM, Lane HC, Gallin JI, Fauci AS (1988) Marked disparity in incidence of bacterial infections in patients with acquired immuno deficiency syndrome receiving interleukin-2 or interferon-gamma. Ann Intern Med 108:36
12. Pockaj BA, Topalian SL, Steinberg SM, White DE, Rosenberg SA (1993) Infectious complications associated with interleukin-2 administration: a retrospective review of 935 treatment courses. J Clin Oncol 11:136
13. Poll T vd, Buller HR, Cate H ten, Wortel CH, Bauer KA, Sander MD, Deventer JH v., Hack CE, Sauerwein HP, Rosenberg RD, Cate JW ten (1990) Activation of coagulation after administration of tumor necrosis factor to normal subjects. N Engl J Med 322:1622
14. Richards JM, Gilewski TA, Vogelzang NJ (1991) Association of interleukin-2 therapy with staphylococcal bacteremia. Cancer 67:1570
15. Siegel JP, Puri RK (1991) Interleukin-2 toxicity. J Clin Oncol 9:694
16. Snydman DR, Sullivan B, Gill M, Gould JA, Parkinson DR, Atkins MB (1990) Nosocomial sepsis associated with interleukin-2. Ann Intern Med 112:102
17. Thompson JA, Lee DJ, Lindgren CG, Benz LA, Collins C, Shuman WP, Levitt D, Fefer A (1989) Influence of schedule of interleukin 2 administration on therapy with interleukin 2 and lymphokine activated killer cells. Cancer Res 49:235
18. Vlasveld LT, Rodenhuis S, Rutgers EJTh, Dubbelman AC, Hilton AM, Batchelor D, Rankin EM (1994) Catheter-related complications in 52 patients treated with continuous infusion of low dose recombinant interleukin-2 via an implanted central venous catheter. Eur J Surg Oncol 20:122