1316 POSTER

Venous thrombosis complication and totally implantable subcutaneous infusion port among oncological patients

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Purpose: Venous thrombosis is a major complication of malignant disease. Totally implantable subcutaneous infusion port is a well known factor of susceptibility for thrombosis complication. Its prevention is not well definite and must be cleared.

Methods: We present a prospective registration on 9 months from mid-July 2000 to mid-April 2001 on thrombosis complications of 195 central venous catheters (one patient have had two catheters). No catheter heparinisation was performed. The patients were treated in the same oncology unit. Patients were 90 females and 105 males, of whom 41 are head and neck, 39 breast, 20 lung and 19 colorectal cancers. Median age was 62 years (23-81).

Results: Six clinical phlebitis were recorded, confirmed by Doppler echography plus catheter opacification for two. These events occurred at 17, 28, 59, 59, 77 and 79 days post implantation. Four of them presented a very large tumor, 2 head and neck cancers T3N3 and 2 lung cancers with a mediastinal mass larger than 5 cm. Large tumor is a significant risk of thrombosis (p=0.0007) with 4 events out of 11 bulky tumors and 2 events out of 184 non bulky tumors. Seven catheter occlusions occurred without clinical symptom at a median of 43 days (20-103) post implantation. The diagnosis was made in the seven cases because of catheter malfunction and confirmed by catheter opacification; for one patient the Doppler echography showed a venous thrombosis. For three of these seven cases the localization of catheter extremity was over T4 (significant risk p=0.00009).

Conclusion: 1) Position of the catheter tip distal over T4, must be replaced; 2) the high risk of phlebitis, when there is a very large cervical and/or mediastinal tumor mass must consider the question of prophylactic treatment. This study continues to assert the first hypothesis and to correlate them with sepsis.

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Catheter embolism in cancer patients: the pinch-off syndrome is the main cause but can be prevented

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Purpose: Catheter embolism is a serious complication of long-term venous access for administration of chemotherapy, blood products and nutritionnal support in cancer patients. Pinch-off syndrome (POS) is a compression of a subclavian catheter in the costoclavicular space and can lead to catheter fracture and embolism. In this two-parts study the incidence of POS was retrospectively evaluated, then we prospectively evaluated the efficacy of preventive guidelines.

Methods: The medical reports of 56 patients who had between 1989 and september 1996 an embolized fragment or entire catheter removed by an interventional radiologic procedure have been retrospectively analysed. A POS was considered as responsible when a chest X-ray showed a rupture of the catheter in front of the costoclavicular space. In september 1996 preemptive guidelines were proposed (choice of others catheter accesses than subclavian vein when possible, removal of catheters when clinical and/or radiological signs of POS are present) and were prospectively evaluated.

Results: From 1989 to the end of 1996, 56 catheter embolisms by fracture or disconnection have been reported. The rupture by POS was the main cause of embolism (24 patients/56). Its incidence was 8‰ of implanted ports inserted via a subclavian access [95 p.cent confidence interval: 4‰–13‰]. Preliminary clinical or radiological signs of pinching have been found in 50% of POS: resistance during initial insertion, radiological compression aspect, arm or shoulder pain, infusion rate and/or ebb depending on arm position. From september 1996 to the end of 2000, 3849 ports were implanted and two catheter fractures occurred versus 18 POS-related catheter embolisms among 2682 ports implanted between 1992 and august 1996 ($p < 0.001$, Chi-square).

Conclusions: POS is the first cause of catheter embolism in cancer patients and must suggest the use of another access than the subclavian vein. When a catheter is inserted via a subclavian access, clinical and/or radiological signs of POS require its removal.

1318 POSTER

Single i.v. infusion of clodronate 1500 mg is effective in the treatment of hypercalcemia of malignancy

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Purpose: Hypercalcemia is a serious complication of various malignancies, caused either by osteolysis or humoral hypercalcemia. Rapid therapeutic approach is warranted to prevent life-threatening consequences of hypercalcemia. In this report the efficacy and safety of single i.v. infusion of clodronate 1500 mg or 900 mg was compared with a single i.v. infusion of 90 mg pamidronate in the treatment of malignant hypercalcemia.

Methods: The databases of three separate but parallel randomized double-blind multicenter studies, conducted with the patients with hypercalcemia of malignancy (serum corrected calcium, S-Ca,cor more than 2.68 mmol/l), were pooled. The total number of patients was 67, and 51 of them were evaluable for the primary efficacy variable, the proportion of normocalcemic patients at day 5. Out of the evaluable patients 21 were in the clodronate 1500 mg group, 10 in the clodronate 900 mg group and 20 in the pamidronate 90 mg group. After the rehydration the patients were given single i.v. infusion of clodronate 1500 mg, clodronate 900 mg or pamidronate 90 mg. The patients were followed up for five days after the date of drug administration, and S-Cacor was measured daily.

Results: At day 5, a total of 16 patients (76%) in the clodronate 1500 mg group, 6 patients (60%) in the clodronate 900 mg group and 17 patients (85%) in the pamidronate 90 mg group were normocalcemic (S-Ca,cor equal or lower than 2.68 mmol/l). The mean S-Ca,cor at day 5 was 2.44 mmol/l in clodronate 1500 mg group, 2.57 mmol/l in clodronate 900 mg group and 2.52 mmol/l in pamidronate 90 mg group.

Conclusion: A single i.v. infusion of both clodronate 1500 mg and 900 mg were effective in the treatment of hypercalcemia of malignancy. There was no difference between clodronate 1500 mg and pamidronate in the achievement of normocalcemia in this study. Both study drugs were safe and well tolerated.

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Prophylaxis with low moleculair weight heparin reduces the risk for catheter-related venous thrombosis in cancer patients with centrally but not peripherally inserted central venous catheters for administration of chemotherapy

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We evaluated the incidence and risk factors for catheter-related thrombosis from 1994 till 2000 in our Department of Clinical Oncology. Of the 145 patients, 61 (42.1%) received a central (central port) and 84 (57.9%) a peripheral vein catheter (arm port). Patients received various types of combination chemotherapy, including antracyclines (82%), cisplatin (79%) and continuously 5-FU (27%), for bone (n=78), GI-tract (n=32), ovarian (n=14) and other types of cancer (n=23). The diagnosis of thrombosis was confirmed by ultrasound or angiography. Since December 1997, all 81 patients received thrombosis prophylaxis with low molecular weight heparin (Fraxiparin® 7500IE s.c. daily).

Thirty-two (22:1%) of the 145 patients developed catheter-related thrombosis. The risk for thrombosis was increased in patients with arm as compared to central ports (OR=3.3; 95% CI 1.3-8.2). In patients without heparin prophylaxis, the risk to develop thrombosis was similar in patients with arm (33.3%) and central (28.3%) ports. In patients with prophylaxis, 12 (31.6%) in the arm port and only 1 (2.2%) in the central port group developed thrombosis (OR=19.4; 95% CI 2.4-157.9). Sixty-eight patients were evaluated for coagulation risk factors. Three (4.4%) patients had a heterozygous mutation in factor V Leiden (FVL) (n=2) or factor II 20210 GA (PT20210A) (n=1). One developed thrombosis. Twenty-nine patients had elevated fibrinogen levels (>3.8 g/l). Only two (11.8%) patients developed thrombosis as compared to 27 (52.9%) out of 51 patients who did not. Five (7.4%) patients had elevated levels of Factor VIII (> 2.0 IE/ml). Two (11.8%) had developed thrombosis. Of the 24 (35.3%) patients with elevated FIX levels (>150 U/dl), 4 (23.5%) out of 17 patients who developed thrombosis had elevated levels. One (5.9%) out of 17 patients with thrombosis had elevated levels of FXI (> 150 IU/dl). The mean homocysteine plasma concentrations did not differ between the patients with (13.4 umol/l; range 8.3-20.1 umol/l) or without thrombosis (13.9 umol/l; range 6.4-31.8 umol/l).

In conclusion, FVL or PT20210A gene mutations, fibrinogen, homocysteine, factor VIII, IX and XI plasma concentrations were not associated with

the risk to develop catheter-related thrombosis. Heparin prophylaxis protected cancer patients undergoing chemotherapy against the increased risk of catheter-related venous thrombosis in centrally, but not in peripherally inserted ports.

1320 POSTER

Open-label, phase I/II dose escalation study of NESP in patients with chronic anemia of cancer

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Purpose: NESP stimulates erythropoiesis by the same mechanism as recombinant human erythropoietin (rHuEPO), but has a 2- to 3-times longer serum half-life than rHuEPO. A limited number of rHuEPO studies indicate potential benefit in patients with chronic anemia of cancer not on chemotherapy. However, no systematic dose finding studies have been reported.

Method: This study includes anemic patients (Hb ≤ 11.0 g/dL) with non-myeloid malignancies who are not on chemotherapy or planned radiotherapy and not iron deficient. Patients were assigned sequentially to one of the following NESP doses: 0.5, 1.0, 2.25, or 4.5 μg/kg/wk for 12 doses.

Results: 102 patients (mean (SD) age: 70 (12) yrs; 53% men), mainly with breast, prostrate and lymphoid malignancies, received study drug. NESP was well tolerated no dose limiting toxicities were reported. Only 6 subjects were enrolled in the 0.5 μg/kg/wk cohort and therefore data are not presented. Increasing doses of NESP associated with an increase in efficacy. All doses demonstrate significant biological and clinical effect with a ≥66% of subjects achieving a Hb response in all cohorts.

NESP (μg/kg/wk)	1.0	2.25	4.5
Number of subjects	33	33	30
RBC tfs from wks 5–12/n	8	4	2
% (95% CI)[b]	36 (10, 62)	14 (1, 26)	7 (0, 17)
Δ in Hb from baseline to end of treatment, mean (SD) g/dL[a]	1.66 (2.22)	2.07 (2.14)	2.91 (1.99)
Hb Response/n	20	19	25
% (95% CI)[b]	68 (50, 86)	66 (49, 84)	92 (80, 100)
Time to Hb response (median no. wks)	8	6	7
Hb correction[d]/n	20	19	24
% (95% CI)[b]	65 (47, 82)	67 (49, 84)	86 (73, 100)
Time to Hb correction (median no. wks)	8	8	5

[a] Excluding Hb values within 28 d of a RBC tfs. Subjects who withdrew after 1 dose of study drug with no post treatment Hb value had a change score of 0.
[b] Determined from the Kaplan-Meier estimate: 1-S(t) at last non-censored time point;
[c] Hb response: ≥2 g/dL increase from the baseline Hb concentration in the treatment phase in the absence of RBC transfusion during the preceding 28 days.
[d] Hb correction: Hb concentration ≥ 12 g/dL in the treatment phase in the absence of any RBC transfusion on that day or during the preceding 28 days.

1321 POSTER

Is a physical training necessary for women post radical mastectomy?

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Purpose: Physical capacity depends on aerobic and anaerobic potential. Radical treatment of breast cancer can affect these factors and limitation of physical capacity can be a result of these disorders. The aim of the study was evaluation of change of physical capacity under an influence of physical training. It was assumed that limitation of physical capacity in women post radical mastectomy is reversible under an influence of systematic exercises.

Methods: Examination of physical capacity on the treadmill according to Bruce's protocol was performed in 60 women aged from 45 to 60 years (mean 54,5) post radical mastectomy divided into two 30-persons groups before and after 6-week physical training. Exercise test included passing the distance with defined speed and angle of inclination of treadmill together and the change of both of these parameters every 3 minutes. Average time of exercise test, oxygen consumption and metabolic equivalent were recorded. All women performed physical training 3 times a week during 6 weeks. Women from group I performed efficiency exercises including active exercises, increasing range of motion and strength of muscles, which lasted for 45 minutes. Women from group II performed endurance exercises on the bicycle ergometer for 30 minutes until submaximally heart rate (85% of maximally heart rate).

Results: After endurance exercises average time of test increased statistically significant (p=0,001) from 9,4 minutes before training to 12,4 minutes after training, oxygen consumption from 18,5 ml/min/kg to 37,0 ml/min/kg and metabolic equivalent from 5,2 met to 10,5 met. After efficiency exercises examined parameters increased statistically significant too (p=0,001) from 7,2 minutes to 8,5 minutes, from 10,3 ml/min/kg to 15,5 ml/min/kg and from 2,9 met to 4,4 met respectively. Increment of examined parameters was statistically significant (p=0,001) greater in women after endurance training than in women after efficiency exercises.

Conclusion: 6-week physical training caused considerable improvement of physical capacity in women post radical mastectomy, which was greater after endurance exercises than after efficiency exercises.

1322 POSTER

Effectiveness of "Supportive Care" for cancer patients

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Background: The terms 'Best Supportive Care' or 'Supportive Care' (BSC/SC) have been frequently used in randomised controlled trials of cancer treatments. However, BSC is usually not well defined, which questions the validity of these trials.

Aims of the Study: We aim to systematically review the literature of cancer trials which include BSC/SC in order to examine the effectiveness/outcomes and the quality of BSC interventions versus cancer therapies, with a view to propose an agreed definition and components of BSC/SC.

Methods: Of the 95 randomised BSC/SC cancer trials we found as a result of our searches of 15 databases, 44 are in non-small cell lung cancer (NSCLC), and 18 are in gastrointestinal cancer (includes colorectal/colon cancer, but excludes pancreatic cancer). We are currently developing two Cochrane-based systematic reviews:

1. 'Supportive Care' in NSCLC (Awaiting registration with Cochrane) and
2. 'Supportive Care' in Gastrointestinal Cancer (Registered with Cochrane).

We will use previously published criteria on the quality of palliative trials. The proposed definition and components of BSC will be linked to an existing EORTC project funded by the EC.

Main Outcome Measures: We will focus mainly on symptom control, pain relief and quality of life.

Findings: We intend to complete the literature review by the time of the conference, and present preliminary data.

Implications for Palliative Care: This work will help oncologists and researchers in palliative care to design better studies when symptom control, and quality of life issues are being evaluated as endpoints in the treatment of cancer.

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Systemic treatment with granulocyte macrophage colony-stimulating factor (GM-CSF) of severe mucositis induced by 5-fluorouracil (5-FU) based chemotherapy

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Purpose: Mucositis is a common side-effect of the chemotherapy, in particular by 5-FU. Stomatitis causes pain, interferes with oral nutrition and can be a potential source of infection. Diarrhea gives discomfort and can be complicated by severe dehydration. Preliminary data suggest that GM-CSF can reduce dose-limiting side-effects and improve the quality of life.

Methods: We evaluated the effect of GM-CSF in 30 colorectal cancer patients suffering from ≥ grade 2 mucositis after a 5 days administration of 5-FU and leucovorin (LV). At the next cycle GM-CSF 4 μg/kg s.c. from days 6 to 10 was given without chemotherapy dose reductions. The mucositis disappearence or its decrease ≥ one grade were recorded as a success.

Results: Seventy-six GM-CSF cycles have been administered (median per patient, 2). We reported a success in 20 (66%) patients. In 6 (20%) cases there was not evidence of efficacy, while 4 (13%) patients stopped the treatment because of an allergic reaction. The efficacy was assesable in 13 patients affected by grade 2–3 stomatitis and in 7 cases suffering from grade 2–3 diarrhea. The responsive patients continued to have benefit from GM-CSF in the subsequent cycles of chemotherapy.

Conclusions: GM-CSF seems to reduce significantly the severity of 5-FU-based chemotherapy-induced mucositis. These data are preliminary because we have completed only 2 of the 3 planned steps of our study.