Frozen socks use in the prevention of docetaxel induced nail and skin reaction: results of a case - control study

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ABSTRACT

Background. Nails and skin disorder of the hand occurs in about 50 % of patients (pts) treated with docetaxel [D]. No data exists on specific nail and skin toxicity (NST) of the foot after D. We investigated the efficacy and safety of an Elasto-Gel™ (Akromed. France) flexible frozen sock (FS) for the prevention of D - induced NST.

Methods. Cancer pts receiving D at 75 to 100 mg/m^2 (1 hour infusion q 3 w) alone or in combination chemotherapy were eligible for this matched case - control study. Each patient wore a FS for a total of 90 minutes (min) on the right foot (15 min before to 15 min after D - infusion). Left foot, acted as control. was not protected by FS. NST were assessed at each cycle by NCI - CTC v 3 criteria and documented by photography. Comfort in socks wearing was assessed by ad hoc scale. Wilcoxon matched - pairs ranks test was used to determine the magnitude of difference between two matched groups.

Results. 49 pts were evaluated. Median age: 64 years; M / F: 37/12; performance status 0/1/2 (%): 46/39/15: cancer type (%). prostate: 53. breast: 20. lung: 18. others: 8 . Nail toxicity was significantly lower in the FS - protected foot compared with the control foot (p = 0.002. Wilcoxon test). Grade (G) of nail toxicity were (FS vs control %). GO: 100 vs 79, G1-3:0 vs 21. Skin toxicity was not significantly different (p = 0.18) with a low rate of disorder (%) GO: 98 vs 94, G1: 2 vs 4, G2: 0 vs 2 (missing data 2 pts). Median time until nail toxicity was not significantly different and occurred at 105 days with FS vs 87 days in control foot. Skin toxicity occurred in the two sides at 101 days. FS comfort satisfied 77 % of patients.

Conclusions. Frozen Sock significant reduces nail toxicity of the foot associated with docetaxel.

BACKGROUND

- Nail changes were more often described with docetaxel than with paclitaxel. with an overall incidence of approximately 30% [1].
- Cutaneous toxicity reported with docetaxel treatment manifested as erythema and desquamation of the skin of the extremities (hand and foot syndrome) and nail changes [2].
- In a previous study. we reported that the use of an Elasto-Gel™ frozen glove (-25° to -30° C) significantly reduced the incidence of nail and skin toxicity of the hands induced by docetaxel 75 mg/m administered every three weeks. either alone or in combination [3].
- These abnormalities are in most cases not serious, but hemorrhagic onycholysis and subungual abscesses can occur producing important morbidity.

Frozen glove study results (ASCO 2004)

Nail toxicity (p = 0.0001)

	CONTROL (n = 45)	PROTECTED HAND (n = 45)
Grade 0	49 %	89 %
Grade 1	29 %	11 %
Grade 2	22 %	0 %

Skin toxicity (p = 0.0001)

	CONTROL (n = 45)	PROTECTED HAND (n = 45)
Grade 0	38 %	67 %
Grade 1	44 %	22 %
Grade 2	9 %	2 %
Lost	9 % (4 pts)	9 % (4 pts)

STUDY DESIGN

- The present matched, case - control, phase 11 study was designed to assess the efficacy and safety of cold therapy in the prevention of docetaxel - induced onycholysis and skin toxicity of the foot.
- Patients enrolled in this prospective study were undergoing treatment for a variety of tumor types with docetaxel. between 70 - 100 mg/m^2 as an one - hour intravenous infusion every 3 weeks, either alone or in combination with other cytotoxic agents.
- No prior treatment with taxanes.
- The absence of skin and nail disorders at the start of chemotherapy.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2.
- Patients were excluded if they had Raynaud's syndrome, distal bone or cutaneous metastases. ungual pathology, arteriopathy, cold intolerance, and peripheral neuropathy (grade≤ 2). All patients provided written informed consent before inclusion.
- Nail disorders categories:
  - Grade 1: discoloration. ridging (koilonychia). or pitting.
  - Grade 2: partial loss of nail(s) (onycholysis) or pain in nail beds not interfering with function.
  - Grade 3: partial loss of nail(s) (onycholysis) or pain in nail beds interfering with function. or complete loss of nail(s).
- Patients' comfort was assessed using a four - point rating scale: 0 = dissatisfied: 1 = not satisfied; 2 = satisfied; 3 = very satisfied.

STATISTICAL DESIGN

- Analyses of toxicities were carried out on the per - protocol population defined as the totality of included patients. which use the FS at least on time at the first cycle.
- Two - sample Wilcoxon matched - pairs rank test adjusted for tied was used as the main method to determine the statistical significance of difference between the incidence of nail and skin toxicities between FS - protected and unprotected feet.
- Kaplan-Meier method was used to estimate differences in time to toxicity occurrence (patients were censored if no toxicity occurred at the end of chemotherapy or during follow-up).
- The impact on the time to nail toxicity occurrence of some confounders as the ECOG PS. sex. number of cycles and dose of docetaxel was studied using multivariate Cox regression analysis (forward stepwise selection).
- No adjustment for multiplicity of tests was performed.

RESULTS

Patient characteristics (per-protocol population, n=48)

CHARACTERISTICS		Nb OF Pts & (%)	[95 % CI]
Sex	Male	36 (75)	[60 - 86]
	Female	12 (25)	[14 - 40]
Age (years), median [range]		62 [36 - 80]	-
ECOG performance status	0	22 (46)	[31 - 61]
	1	20 (42)	[28 - 57]
	2	6 (12)	[5 - 25]
Type of tumor	Prostate	25 (52)	[37 - 68]
	Lung (non - small cell)	10 (21)	[11 - 35]
	Breast	9 (19)	[9 - 33]
	Other	4 (8)	[2 - 20]
Docetaxel treatment, median [range]	Single agent	20 (42)	[28 - 57]
	Combination therapy	28 (58)	[43 - 72]
	Number of cycles	5 [1 - 9]	-
	Cumulative dose (mg)	720 [150 - 1260]	-
Docetaxel schedule (mg / m^2)	70	18 (38)	[24 - 53]
	75	14 (29)	[17 - 44]
	85	3 (6)	[1.3 - 17]
	100	13 (27)	[15 - 42]
Prior chemotherapy	Yes	15 (31)	[19 - 46]
	No	33 (69)	[54 - 81]

CI = Confidence Interval ; ECOG = Eastern Cooperative Oncology Group ; n = number of patients

- The application of a FS significantly reduced the incidence of nail toxicity with grade 1 - 2 toxicity occurring in none of the FS - protected feet compared to 21% in the unprotected feet (p = 0.002).
- Skin toxicity was registered in 2% of the FS - protected feet versus 6% of the unprotected feet (p = 0.18).
- No differences were observed in term of time to occurrence of nail and skin toxicity between protected and unprotected feet: 105 versus 87 and 101 versus 101 days. respectively.
- The time until nail toxicity occurrence for unprotected foot was associated with:
  - The total number of cycles of docetaxel: HR=0.36 (95% CI [0.17 - 0.77]). p = 0.008.
  - A borderline relationship was found for ECOG PS: HR = 0.31 (95% CI [0.09 - 1.10]). p = 0.07.
- Patients with a poor ECOG PS presented a short time interval until of nail toxicity. the risk being related with the cumulative number of cycles of chemotherapy.
- Age. previous chemotherapy and weight of patients were not associated with the risk of nail toxicity.
- Percentages of patients with no nail toxicity at 1. 2 and 3 months for the control foot were 98. 81 and 67%. respectively.

Nail toxicity of the foot after docetaxel treatment

TOXICITY GRADE	CONTROL FOOT (n = 48) %	CONTROL FOOT (n = 48) [95 % CI]	PROTECTED FOOT (n = 48) %	PROTECTED FOOT (n = 48) [95 % CI]	P
Grade 0	79	[65 - 90]	100	[93 - 100]	0.002
Grade 1	19	[9 - 33]	0	0	
Grade 2	2	[0.1 - 11]	0	0	

Skin toxicity of the foot after docetaxel treatment

TOXICITY GRADE	CONTROL FOOT (n = 48) %	CONTROL FOOT (n = 48) [95 % CI]	PROTECTED FOOT (n = 48) %	PROTECTED FOOT (n = 48) [95 % CI]	P
Grade 0	94	[83 - 99]	98	[89 - 100]	0.18
Grade 1	4	[0.5 - 14]	2	[0.1 - 11]	
Grade 2	2	[0.1 - 11]	0	0	

CI = Confidence Interval ; n = number of patients

Median time to toxicity occurrence

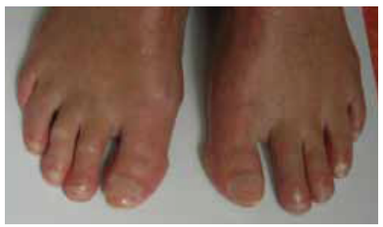
TOXICITY	CONTROL FOOT (days)	PROTECTED FOOT (days)	P
Nail	87	105	N S
Skin	101	101	N S

N S = Not Significant

Frozen Sock Comfort

COMFORT ASSESSMENT	GLOBAL COMFORT (n = 48) %	GLOBAL COMFORT (n = 48) [95 % CI]	COLD TOLERANCE (n = 48) %	COLD TOLERANCE (n = 48) [95 % CI]
Dissatisfied	2	[0.1 - 11]	2	[0.1 - 11]
Satisfied	58	[43 - 72]	35	[22 - 51]
Very satisfied	19	[9 - 33]	17	[8 - 30]
Unknown	21	[11 - 35]	46	[31 - 61]

Nail and skin grade 2 toxicity Protected / Control



CONCLUSIONS

- Less toxicity of the feet vs hands
  - nail : 21 % vs 51 %.
  - skin: 6 % vs 54 %.
- No significant efficacy
  - on skin toxicity: 6% vs 2% (p = 0.18).
- Significant sock protection on nail toxicity
  - no toxicity on protected foot (p = 0.002).

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