BANQUISE

Evaluation of Cryoprotection Induced Nail Toxicity Docetaxel Low Cumulative Dose (BANQUISE)

Controlled, Randomized, Open, Multicentre Prospective.

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Summary

Title of the study	Evaluation of Cryoprotection of Nail Toxicity Induced by Docetaxel Low Cumulative Dose. Controlled, Randomized, Open, Multicentre Prospective.
Keywords	Cryoprevention, Docetaxel, nail toxicity, breast cancer
Sponsor	CHD Vendée
Principal investigator	Dr. Frank PRIOU Onco-haematology Department, CHD Vendée
Number of planned centres	8
Study planning	Recruitment period: 54 months Treatment duration per patient: 4.5 months Duration of follow-up per patient: 12 months Duration of participation for each patient: 16.5 months Total study duration: 70.5 months
Study design	- Multicentric - Randomized - Controlled - Open-label - Prospective
Objectives of the study	Main : The main objective of this study is to evaluate the efficacy of cryoprevention by mittens and slippers on the reduction of onycholysis at 8 weeks post-infusion in a population of patients treated with 3 cycles of adjuvant and neoadjuvant Docetaxel (Tax). Secondary : ❖ Assessing quality of life (EORTC QLQ-C30 and BR-23) ❖ Assessing the tolerability of cryoprevention ➢ Cooling mittens and slippers ➢ Cooling helmet ❖ Assessing at hand and foot level ➢ The incidence of nail toxicity in all grades ➢ The incidence of onychodynia ❖ Evaluate ➢ The incidence of other phanerotic toxicities (eyelashes, eyebrows) ➢ The incidence of neurotoxicity ➢ The incidence of skin toxicity: dyschromias, dyskeratoses ❖ Assessment of the rate and degree of persistent alopecia, at 8 weeks, and at 6 months after the end of chemotherapy ❖ Patient satisfaction at the end of chemotherapy, 8 weeks, 6 months and 12 months after the last treatment

Number of cases (sample size)	288 analysable randomised patients
Schedule of different visits and examinations	- Inclusion - D0, D21, D42 - Randomization - D63, D84, D105 - S8 (=J182) = Visit at 8 weeks post-treatment - M6 (=J309) = 6 month post-treatment visit - M12 (=492) = Visit at 12 months post-treatment
Critères principaux de sélection, d'inclusion, de non-inclusion et d'exclusion	<u>Inclusion Criteria:</u> - upper age to 18 years - mammary adenocarcinoma nonmetastatic and histologically proven - wait under an adjuvant or neoadjuvant chemotherapy according to the following conventional scheme: 3 cycles of F5-Fluorouracil, epirubicin and cyclophosphamide 100 (500 or 5-Fluorouracil 600 mg / m² J1, Epirubicin 100 mg / m² J1, Cyclophosphamide 500 or 600 mg / m² J1 or 3 cycles of Epiribucin and Cyclophosphamide 100) followed by 3 cycles of docetaxel, 100 mg / m², +/- trastuzumab if Her2+++ - patient with the capacity/faculties to understand a newsletter and sign an informed consent - patient receiving social coverage - patient who can be treated and followed in the center for a period of at least one year - WHO scale 0 or 1 <u>Exclusion Criteria:</u> - Age below 18 years - Diseases of the scalp or whatever hair-showing against helmet or alopecia - Using pre nail resin before and per chemotherapy - mammary adenocarcinoma stage IV - Indication of docetaxel for cancer of another organ than breast - Treatment processing or programmed during chemotherapy with an innovative molecule being evaluated - Raynaud syndrome, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia. - Uncontrolled severe arterial disease. - Presence of a device> grade 1 neuropathy before the start of chemotherapy - Patient unable to submit the protocol followed for psychological, social, family or geographical - Patient with an incompatible underlying disease or concomitant with the inclusion in the trial, whether

	psychiatric or somatic - Patient trust, guardianship, under legal protection measure, deprived of freedom - Male <u>- Criteria for non randomization (before the first course of docetaxel) :</u> • Presence of peripheral neuropathy> grade 1 after the first 3 cycles of 5-Fluorouracil, epirubicin and cyclophosphamide 100. • Presence of a nail or skin toxicity> grade 1 after 3 cycles of 5-Fluorouracil, epirubicin and cyclophosphamide 100.
Treatment, medical device, cell therapy product, interventional procedure under study	Patients will be managed according to standard practice and randomised into two groups: ❖ **Standard group (without mittens and slippers)** Proposal to wear a helmet. ❖ **Cryoprevention Group mittens and slippers** Standard management associated with mittens and booties to be put on 15 min before administration and replaced until 15 min after completion of Docetaxel administration. (A minimum of 2-3 pairs of mittens and 2-3 pairs of slippers should be used) (Appendix 4). Whatever the randomisation arm: Any nail care (manicure, varnish, etc.) will be left to the discretion of the investigating centres according to their standard practice. The performance of nail care will be reported in the patient's observation booklet.
Primary endpoint	The primary endpoint was the occurrence of CTAE V4.0 grade 2 nail toxicity assessed at 8 weeks post-docetaxel infusion.
Secondary endpoints	❖ Quality of life (Calculation of EORTC QLQ-C30 and BR-23 scores) ❖ Tolerance of cryoprevention ➢ Overall and specific tolerance of mittens, cooling shoes ❖ Stopping cryoprevention ➢ Reason for discontinuing cryoprevention in the hands ➢ Reason for discontinuing foot cryopreservation ➢ Reason for discontinuing scalp cryoprevention ➢ Number of patients refusing further cryoprevention (cold pack). ❖ Nail toxicity ➢ by DNT score (Centralized comparative digital imaging assessment) ➢ Onychodynia according to CTAE V4.0 ❖ Other toxicity ➢ Skin toxicity (eyelashes, eyebrows) according to CTAE V4.0 and self-questionnaire ➢ Skin toxicity (dyschromias, dyskeratoses) according to CTAE V4.0 and self-questionnaireneurotoxicité.

	❖ Assessment of persistent alopecia according to CTAE V4.0 and self-questionnaire ❖ Patient satisfaction. Analysis of the self-questionnaire
Statistical analysis	The analysis will be conducted on an intention-to-treat basis and will be complemented by a per-protocol analysis. The primary endpoint, defined as the occurrence of grade 2 nail toxicity at 8 weeks post-docetaxel infusion, will be analysed using a generalised linear regression model taking into account the random-effects centre stratification. In each group, the occurrence of nail toxicity will be estimated with a 95% confidence interval. The quality of life scores will be compared using a linear regression model taking into account the random centre effect. In each group, the total score will be estimated with a 95% confidence interval. The evolution of patient satisfaction, evaluated on a VAS, will be compared between the groups using a linear regression model taking into account the baseline data and the time effect in fixed effects and the centre in random effect. The tolerance to the different treatments will be described in each group. Descriptive analyses of the frequency and severity of events will be presented in terms of numbers and percentages.

1 RATIONAL

1.1 Scientific justification

1.1.1 Adjuvant chemotherapy for breast cancer

For a long time it was based on the use of Anthracyclines, Fluorouracil and Cyclophosphamide (FEC protocol). The introduction of Taxanes in the adjuvant setting of breast cancer, and in particular Docetaxel, has improved recurrence-free survival and overall survival. Since the publication in 2006 of the French PACS 011 trial, the sequence of 3 courses of FEC 100 followed by 3 courses of Docetaxel has become a therapeutic standard.

This phase III trial compared the standard regimen (6 courses of FEC 100: 5-FU 500 mg/m2, Epirubicin 100 mg/m2 and Cyclophopshamide 500 mg/m2) with the experimental regimen (3 courses of FEC 100 followed by 3 courses of Docetaxel 100 mg/m2). This trial demonstrated a gain in 5-year recurrence-free survival of 5.2% (p=0.012), and a gain in 5-year overall survival of 4% (p=0.017).
This regimen was validated in the adjuvant and neoadjuvant setting as part of a Temporarily Acceptable Situation (TAS) of the French National Cancer Institute (INCa) in 2009.

1.1.2 Pathophysiology of onycholysis

To date, there is no clear explanation for this onycholysis phenomenon. Predictive factors are not known.

Cancer chemotherapy has an effect on both malignant and normal cells that have high mitotic activity. The rapidly dividing normal cells frequently affected by chemotherapy include those in the bone marrow, the epithelium of the mouth and gastrointestinal tract, and hair follicles and dander. Nail abnormalities result from direct toxicity to several parts of the nail: the matrix, the nail bed, the periungual tissues, but also the blood vessels supplying the fingers2. The degree of chemo-induced onycholysis is both type and cumulative dose dependent. Taxanes are the most toxic to the dander.

Chemotherapy-induced onycholysis is usually reversible after 6 months but can last up to 12 months in the toes after cessation of treatment.

1.1.3 Onycholysis after Docetaxel chemotherapy

The specific pathophysiology of onycholysis induced by Docetaxel is not clearly established. Several studies suggest that the antiangiogenic properties of Taxanes may be involved in this toxicity3,4. 3,4 Others suggest the existence of a neurological pathway via an inflammatory process5.

The incidence of nail changes on Docetaxel was estimated in a review of published studies to be 44% for all grades6. Scotté7 described nail toxicity on the control hand as 29% and 22% grade 1 and 2 respectively. In the PACS 01 study that validated the FEC 100 Docetaxel sequence, 10.3% of nail toxicity of any grade was reported. This can probably be explained by the fact that the cumulative dose of Docetaxel is limited to 300 mg/m², unlike that of Scotté where the cumulative dose was higher (800 mg or 450 mg/m²).

1.1.4 Prevention of onycholysis

Since about 1970, many methods to prevent alopecia have been tried: tourniquets, drugs and scalp cooling8 . Of these, scalp cooling with a cooling helmet is now the most commonly used9. The use of cryoprevention of onycholysis was initially reported by an investigator in a study evaluating the use of Docetaxel in a weekly regimen. He proposed placing a patient's left hand in ice water throughout the administration of the drug during each cycle. He found that there was no onycholysis, whereas the contralateral hand showed this toxicity after two cycles. Scotté7 showed that the use of refrigerated mittens during the administration of Docetaxel (800mg or 450mg/m²) reduced nail toxicity (22.2% and 2.2% grade 1 and 2 respectively against 29% and 22% on the unprotected side). The same author reported similar results when the procedure was applied to the feet10. Sakurai11 reported at SABCS 2009 the results of a case-control study evaluating cryoprevention in patients treated for breast cancer and receiving at least 300 mg/m² of Docetaxel. The nail toxicity observed was 54% versus 74% grade 1, 4.3% versus 18% grade 2 and 3 respectively in the cryoprevention and control groups. No difference was observed in the feet.

The use of hardening or opaque varnishes is proposed by many teams without their effectiveness being clearly demonstrated.

1.1.5 Limitations of cryoprevention

The tolerance of this cryoprevention (-25°C) is not always good, leading a significant proportion of patients to interrupt it before the end of their treatment (11% in F. Scotté's study). H.Ishiguro showed that the use of less cold mittens (-10 to -20) allowed equivalent

control with better tolerance for average cumulative doses of Docetaxel of 570 mg/m². However, 52% complained of discomfort induced by the procedure12 .

The side effects observed in studies evaluating the cooling helmet in the prevention of alopecia were considered mild13. Studies on patient quality of life (very limited in number) show no difference between the two patient groups14.

For this specific population of patients receiving adjuvant and neoadjuvant FEC Docetaxel, the efficacy of cryoprevention has never been demonstrated.

Moreover, this management is cumbersome, requires time for the nurses (several helmet fittings during chemotherapy) and is uncomfortable for the patients.

1.2 Justification of the methodology

For this specific population of patients receiving the Docetaxel FEC sequence (at cumulative dose < 300mg/m2), the use of cryoprevention has never been evaluated.

The efficacy of cryoprevention of onycholysis secondary to Docetaxel is not well established in this population (adjuvant breast cancer) and is based solely on one publication (Scotté) which does not use the same treatment modalities (significantly higher dose). The few studies available have heterogeneous populations, non-randomised, retrospective or with small sample sizes.

By extension with what has been observed with higher cumulative doses of Docetaxel, some teams propose refrigerated mittens and slippers to their patients, a practice that is not the subject of a national consensus.

We are interested in accurately assessing the efficacy of refrigerated mittens and booties, their compliance and their tolerability due to the limited data on this specific population in the literature.

The occurrence of onycholysis is random and can occur during and up to 4 weeks after Docetaxel treatment.

The 8 week visit is the first post-chemotherapy visit performed as standard. If onycholysis is assessed earlier after the last treatment, some onycholysis may not yet have occurred. In addition, onycholysis that appears at the first course of Docetaxel will still be visible at 8 weeks post treatment as this phenomenon usually resolves within 6 months to a year.

This justifies the evaluation of the primary endpoint at 8 weeks post chemotherapy.

Furthermore, patients are familiar with their hair and other body parts (hair, nails) and are therefore able to respond accurately and objectively to the self-administered questionnaires as well as to the quality of life questionnaires (QLQ-C30 and BR-23) given at the initial visit, 8 weeks after the docetaxel treatments, 6 months and 12 months after the last docetaxel infusion. It is the patients' assessment coupled with a medical evaluation that interests us in this study. Moreover, this choice gives them a voice and makes them actors of the project. The nurses also play an important role in the monitoring, the good progress of the procedure of wearing the helmet, the mittens and the slippers but also in the accompaniment and the psychological support of the patients: to involve them in this project will make them also actors of care.

1.3 Benefits / Risks

1.3.1 Benefits

In this context (cumulative dose of 300 mg/m²), demonstrating the effectiveness of cryoprevention of onycholysis will better motivate patients and health care teams despite the cumbersome and uncomfortable procedure.

1.3.2 Risks

The main risk for patients randomised to the control arm is the occurrence of onycholysis at low doses of Docetaxel or a higher incidence of skin toxicities. The published results with this treatment sequence are reassuring but it is possible that these toxicities are underestimated. Exit criteria are provided for in this situation. The proposal of a possible cryoprevention for the remaining courses is left to the investigator's discretion.

1.4 Research perspectives

The 2009-2013 Cancer Plan provides for five major areas in which this study fits perfectly:

- Focus 1 : research
  - measure 1: strengthen the means of multidisciplinary research
  - measure 4: boost clinical research
  - measure 5: make France an international reference
- Focus 2 : observation
  - Produce and communicate
- Focus 4 : care
  - Measure 19: Strengthen the quality of care for all cancer patients
- Focus 5 : living during and after cancer
  - Measure 25: Improve quality of life during and after the disease

The aim of the research is to optimise patient care by improving the quality of life of patients by seeking to demonstrate the usefulness of a procedure that reduces the occurrence of onycholysis (mittens and refrigerated slippers).

This trial will be referenced on the National Cancer Institute (INCa) website, and the data may be disseminated through national and international communications.

1 OBJECTIVES

1.1 Main objective

The main objective of this study is to evaluate the efficacy of cryoprevention by mittens and slippers on the reduction of onycholysis at 8 weeks post-infusion in a population of patients treated with 3 cycles of adjuvant and neoadjuvant Docetaxel (Tax).

1.2 Secondary objectives

- Assessing quality of life (EORTC QLQ-C30 and BR-23)
- Assessing the tolerability of cryoprevention
  - Cooling mittens and slippers
  - Cooling helmet
- Assessing at hand and foot level
  - The incidence of nail toxicity in all grades

- The incidence of onychodynia

- Evaluate
  - The incidence of other phanerotic toxicities (eyelashes, eyebrows)
  - The incidence of neurotoxicity
  - The incidence of skin toxicity: dyschromias, dyskeratoses
- Assessment of the rate and degree of persistent alopecia, at 8 weeks, and at 6 months after the end of chemotherapy
- Patient satisfaction at the end of chemotherapy, 8 weeks, 6 months and 12 months after the last treatment

2 TYPE OF STUDY

This is a randomised, open-label, prospective, multi-centre study in routine care.

3 ELIGIBILITY CRITERIA

3.1 Inclusion criteria

- upper age to 18 years
- mammary adenocarcinoma nonmetastatic and histologically proven
- wait under an adjuvant or neoadjuvant chemotherapy according to the following conventional scheme: 3 cycles of F5-Fluorouracil, epirubicin and cyclophosphamide 100 (500 or 5-Fluorouracil 600 mg / m² J1, Epirubicin 100 mg / m² J1, Cyclophosphamide 500 or 600 mg / m² J1 or 3 cycles of Epiribucin and Cyclophosphamide 100) followed by 3 cycles of docetaxel, 100 mg / m², +/- trastuzumab if Her2+++
- patient with the capacity/faculties to understand a newsletter and sign an informed consent
- patient receiving social coverage
- patient who can be treated and followed in the center for a period of at least one year
- WHO scale 0 or 1

3.2 Exclusion criteria

- Age below 18 years
- Diseases of the scalp or whatever hair-showing against helmet or alopecia
- Using pre nail resin before and per chemotherapy
- mammary adenocarcinoma stage IV
- Indication of docetaxel for cancer of another organ than breast
- Treatment processing or programmed during chemotherapy with an innovative molecule being evaluated
- Raynaud syndrome, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia.
- Uncontrolled severe arterial disease.
- Presence of a device> grade 1 neuropathy before the start of chemotherapy
- Patient unable to submit the protocol followed for psychological, social, family or geographical
- Patient with an incompatible underlying disease or concomitant with the inclusion in the trial, whether psychiatric or somatic

- Patient trust, guardianship, under legal protection measure, deprived of freedom
- Male

3.3 Non-randomisation criteria (before the first course of Docetaxel)

- Presence of peripheral neuropathy > grade 1 after the first 3 cycles of the conventional regimen (EC or FEC 100).
- Presence of skin or nail toxicity > grade 1 after 3 cycles of the conventional regimen (EC or FEC 100).

4 EVALUATION CRITERIA

4.1 Primary endpoint

The primary endpoint was the occurrence of CTAE V4.0 grade 2 nail toxicity assessed at 8 weeks post-docetaxel infusion.

4.2 Secondary endpoint

- Quality of life (Calculation of EORTC QLQ-C30 and BR-23 scores)
- Tolerance of cryoprevention
  - Overall and specific tolerance of mittens, cooling shoes
- Stopping cryoprevention
  - Reason for discontinuing cryoprevention in the hands
  - Reason for discontinuing foot cryopreservation
  - Reason for discontinuing scalp cryoprevention
  - Number of patients refusing further cryoprevention (cold pack).
- Nail toxicity
  - by DNT score (Centralized comparative digital imaging assessment)
  - Onychodynia according to CTAE V4.0
- Other toxicity
  - Skin toxicity (eyelashes, eyebrows) according to CTAE V4.0 and self-questionnaire
  - Skin toxicity (dyschromias, dyskeratoses) according to CTAE V4.0 and self-questionnaireneurotoxicité.
- Assessment of persistent alopecia according to CTAE V4.0 and self-questionnaire
- Patient satisfaction. Analysis of the self-questionnaire

DNT (Docetaxel Nail induced Toxicity) score
Nail toxicity is assessed and graded according to the CTCAE V4.0 toxicity scale. It is assessed before each cycle of Docetaxel, at the end of chemotherapy, at 8 weeks and at 6 months of the last treatment. Nail toxicity is documented by a digital image according to the procedure described in the specific appendix.
The score is established as follows: A nail toxicity of grade 1 gives one point per finger and toe concerned. A grade 2 gives 5 points per affected finger and toe. The total number of points per hand and foot is reported.
This score provides a more global assessment of nail toxicity.

5 CONDUCT OF THE RESEARCH

5.1 Research schedule

The feasibility of this study was assessed by taking the cohort of patients treated with sequential FEC Taxotere chemotherapy during 2011 and 2012. Eighty patients per year were identified. Assuming a participation of 50 patients per year in the CHD Vendée and the seven other centres approached with a treatment period of 4.5 months and a follow-up of twelve months, the following elements were planned:

- Duration of inclusion period: 54 months
- Duration of participation for each patient: 4.5 months (18 weeks) of treatment and 12 months of follow-up for a total of 16.5 months
- Total study duration: 70.5 months

5.2 Experimental design

Patients will be randomised into two groups:

- Standard group (without mittens and booties)
  - Suggested helmet use.
- Mittens and booties cryoprevention group
  - Standard management with mittens and booties to be put on 15 min before administration and replaced until 15 min after the end of Docetaxel administration. (A minimum of 2 pairs of mittens and 2 pairs of slippers should be used) (Appendix 4).

Whatever the randomisation arm: Any nail care (manicure, varnish, etc.) will be left to the discretion of the investigating centres according to their standard practice.
The performance of nail care will be reported in the patient's observation booklet.

5.3 Summary table of patient follow-up

Standard support	**Protocol visits**	**Evaluation in the context of the study**
Consultation before starting chemotherapy	Inclusion	- Checking the inclusion criteria - Proposal to participate in the study - **Signature Informed consent**
Chemotherapy cycles last 21 days		*Between inclusion and D0 :* - Initial self questionnaire (Appendix 3) - Quality of life questionnaire (Appendix 7) - Record of concomitant treatments - Digital picture of hands and feet
1st treatment FEC 100 Or EC 100	D0	
2nd treatment FEC 100 Or EC 100	D21	
3rd treatment FEC 100 Or EC 100	D42	
		Between D42 and D63 : - Verification of randomisation criteria - Randomisation
1st treatment Docetaxel + cryoprevention	D63	- cryoprevention by randomisation arm - Completion of the "BANQUISE plan" document (Appendix 4) (one part by the care assistant, one part by the patient)

		- Digital picture of hands and feet
2nd course of treatment Docetaxel + cryoprevention	D84	- cryoprevention by randomisation arm - Completion of the "BANQUISE plan" document (Appendix 4) (one part by the care assistant, one part by the patient)
3rd treatment Docetaxel + cryoprevention	D105	- cryoprevention by randomisation arm - Completion of the "BANQUISE plan" document (Appendix 4) (one part by the care assistant, one part by the patient)
		End of the last treatment : - Self-questionnaire last treatment (Annex 4) - Quality of life questionnaire (QLQ-C30 and BR-23) Appendix 7
Consultation 8 weeks after last treatment with Docetaxel	W8 (=D182)	- Intermediate self-completion questionnaire at 8 weeks (Appendix 5) - Quality of life questionnaires (QLQ-C30 and BR-23) Appendix 7 - NCI CTC V4 [NCI 2009] toxicity assessment (Appendix 8) - Digital picture of hands and feet
Consultation 6 months after last treatment with Docetaxel	M6 (=D309)	- Self questionnaire at 6 months (Appendix 6) - Quality of Life Questionnaire (QLQ-C30 and BR-23) (Appendix 7) - NCI CTC V4 [NCI 2009] toxicity assessment (Appendix 8) - Digital picture of hands and feet
Consultation 12 months after last treatment with Docetaxel	M12 (=D492)	- Final self-questionnaire (Annex 9)

If grade > 1 onycholysis occurs after D63 or D84. Cryoprevention, if any, is left to the investigator's discretion but should be recorded in the CRF. The patient's file will be analysed according to her randomisation group.

All anonymised digital images of the patients' hands and feet will be collected by the sponsor. A centralized reading of the images will be carried out by a dermatologist of the CHD Vendée.

5.4 Inclusion and follow-up chronology

- Proposal of the study, after verification of eligibility criteria, by the oncologist before the start of any chemotherapy, with delivery of the information letter (Appendix 1) and informed consent (Appendix 2).
- Signature of the informed consent and inclusion of the patient.
- Start of chemotherapy
- Randomisation between D42 and D63 if the patient meets all criteria for randomization

- From inclusion to D0:
  - Patient completion of the initial on-site anonymised self-questionnaire (Appendix 3).
  - Patient completes on-site anonymised quality of life questionnaires (Appendix 7).
  - Indicate concomitant medications (with or without prescription) in the medical record.
  - A digital picture of the hands and feet is taken

- At D63 :
  - Completion of the document entitled "BANQUISE care plan" (Appendix 4). One part is to be completed by the health care team, the other by the patient herself.
  - A digital picture of the hands and feet is taken

- At D84 et D105 :
  - Completion of the BANQUISE care plan document (Caregiver and patient) (Appendix 4).

- After D105 : At the last treatment, the patient will fill in the last treatment self-questionnaire (Appendix 4) and the quality of life questionnaires (QLQ-C30 and BR-23, Appendix 7).

- At W8 :
  - Completion of the intermediate self-questionnaire at 8 weeks (Appendix 5)
  - Completion of quality of life questionnaires (QLQ-C30 and BR-23, Appendix 7)
  - Assessment of toxicities by the investigator according to NCI CTC V4 NCI 2009 (Appendix 8)
  - Completion of a digital picture of the hands and feet

- At M6 :
  - Completion of the anonymised 6-month self-questionnaire at the time of the consultation and to be given to the oncologist (Appendix 6),
  - Completion of the quality of life questionnaires (QLQ-C30 and BR-23) at the time of the consultation and to be given to the oncologist (Appendix 7)
  - Assessment of toxicities by the investigator according to the NCI CTC V4 NCI 2009(Appendix 8)
  - Completion of a digital image of the hands and feet

- At M12: Completion of the final anonymised self-questionnaire at the time of the consultation to be given to the oncologist (Appendix 9)

6.5 Randomisation procedure

Patients who have been informed and have previously signed an informed consent (Appendix 1) will be included in the trial.
After D42, if patients meet the criteria for randomisation, they will be randomised. Randomisation will be centralised and stratified by centre.
As soon as the consent form is signed, the investigator will enter the patient into the e-CRF to create the patient. Electronic randomisation will be performed between D42 and D63.

The randomisation arm will be transmitted to the investigator by automatic edition of an e-mail via the e-CRF.

6 STATISTICAL CONSIDERATIONS

7.1 Number of subjects needed

The only study reporting an assessment of onycholysis with the current French standard treatment regimen in adjuvant and neoadjuvant breast cancer is the PACS 01 study with an incidence of grade 2 onycholysis at 10.3%. With cryoprevention Scotté reported a figure of 0% but with a small number of patients (n= 45), very heterogeneous and including only 11% of breast cancer patients with a higher cumulative dose of Docetaxel Sakurai

reported a figure of 4.3% also with a small number of patients (n= 70) in a retrospective study, without reference to the cumulative dose

Given these data and our experience, a reduction in the onycholysis rate from 10.3% to 2% with cryoprevention seems a realistic and clinically relevant goal given the cumbersome management and patient discomfort and intolerance of this procedure.

With an alpha risk of 5% and a power of 80%, the number of subjects required is 131 patients in each arm, 262 in total. In order to ensure power, it is planned to randomise 288 patients over 54 months.

7.2 Data management

Data will be collected in an electronic case report form (e-CRF) under the responsibility of the principal investigator of each centre.

The data collected from the self-administered questionnaires, quality of life questionnaires, care plans and medical assessments will constitute source data that will not be transcribed into the patient's medical record but reported in the e-CRF.

7.3 Statistical analysis

Person in charge of the statistical analysis: Ms Lucie PLANCHE

The statistical analyses will be carried out using SAS v.9.4 software.

The analysis will be carried out on an intention-to-treat basis and will be completed by a Per-Protocol analysis.

The alpha risk is set at 5%.

All variables will be described globally and by group. The description will include the numbers and percentages of the modalities for the qualitative variables and the minimum, maximum, mean, standard deviation and median for the quantitative variables.

Primary endpoint

The primary endpoint, defined as the occurrence of grade 2 nail toxicity at 8 weeks post-docetaxel infusion, will be analysed using a generalised linear regression model taking into account the randomised centre of effect stratification. In each group, the occurrence of nail toxicity will be estimated with a 95% confidence interval.

Secondary endpoints

The quality of life scores will be compared using a linear regression model taking into account the randomised centre effect. In each group, the total score will be estimated with a 95% confidence interval.

The evolution of patient satisfaction, evaluated on a VAS, will be compared between the groups using a linear regression model taking into account the baseline data and the time effect in fixed effects and the centre in random effect.

The tolerance to the different treatments will be described in each group. Descriptive analyses of the frequency and severity of events will be presented in terms of numbers and percentages.

Method of accounting for missing, unused or invalid data
All missing data and their reasons will be described in each group.

For the analysis of the primary endpoint, missing data will be imputed as treatment failure.

For the secondary endpoint analysis, no imputation will be made.

7 ETHICAL CONSIDERATIONS

7.1 Patient information

The investigator must, in a personal interview, give understandable and fair explanations to the patients, explaining the interest, the advantages and the risks of the study.

A letter of information will be given to each patient, informing her of the objectives, course, duration and constraints of the study, and the possibility of refusing to participate in the research. This letter will also indicate the nature of the information transmitted, the natural or legal persons to whom the data will be sent, the right of access, rectification and opposition in accordance with laws n° 78-17 of 6 January 1978 and n° 94-548 of 1 July 1994. In case of acceptance, the patient will sign the informed consent.

The opinion of the Committee for the Protection of Individuals (CPP) will be sought regarding the information transmitted to patients in written form (information letter, care plan to be completed, self-questionnaires).

Applications for authorisation specific to this type of research will be made in accordance with the laws in force. The information collected about the patients during the study will remain strictly confidential in accordance with the French Data Protection Act (Loi Informatique et Liberté), but may be consulted by the sponsor's representatives, the monitors, the legal authorities and by the doctors themselves. The data from this study will be computerised and used anonymously in a final report on the results observed. According to the law of 4 March 2002 on patients' rights, patients will be informed, if they so wish, of the overall results of the research by the investigating doctor.

7.2 Confidentiality

In accordance with article R.5121-13 of the Public Health Code, the investigators and all persons called upon to collaborate in the study are bound by professional secrecy.

The investigating centre will ensure that the confidentiality of information and the anonymity of patients are strictly respected.

On all documents (including observation books) used for the study and containing specific information (questionnaires), patients will only be mentioned by an identification code and initials.

8 PUBLICATION RULES

The publication is under the responsibility of the Editorial Board. The list of authors will depend on the number of inclusions.

9 BIBLIOGRAPHY

1. Henri Roché, Pierre Fumoleau, Marc Spielmann, Jean-Luc Canon, Thierry Delozier, Daniel Serin, Michel Symann, Pierre Kerbrat, Patrick Soulié, Franc¸oise Eichler, Patrice Viens, Alain Monnier, Anita Vindevoghel, Mario Campone, Marie-Josèphe Goudier, Jacques Bonneterre, Jean-Marc Ferrero, Anne-Laure Martin, Jean Genève, and Bernard Asselain. Sequential Adjuvant Epirubicin-Based and Docetaxel Chemotherapy for Node-Positive Breast Cancer Patients: The FNCLCC PACS 01 Trial. *J Clin Onco (2006) 24:5664-567.*
2. Piraccini BM, Iorizzo M, Antonucci A, et al: Drug-induced nail abnormalities. Expert Opin Drug Saf 3:57-65, 2004**.**
3. Battegay EJ: Angiogenesis: Mechanistic insights, neovascular diseases, and therapeutic prospects. J Mol Med 73:333-346, 1995.
4. Spadaro P, Maisano R, Mare M: Is there any correlation between decreased serum vascular endothelial growth factor (sVEGF) levels and nail toxicity in responsive metastatic breast cancer (MBC) patients treated with weekly docetaxel ? Preliminary data of a phase II study. Proc Am Soc Clin Oncol 20:2002 (abstr 1952)**.**
5. Wasner G, Hilpert F, Schattschneider J, et al: Docetaxel-induced nail changes: A neurogenic mechanism—A case report. J Neurooncol 58: 167-174, 2002**.**
6. Minisini AM, Tosti A, Sobrero AF, et al : Taxane-induced nail changes: Incidence, clinical presentation and outcome. Ann Oncol 14:333- 337, 2003**.**
7. Scotté F, Tourani JM, Banu E, Peyromaure M, Levy E, Marsan S, Magherini E, Fabre-Guillevin E, Andrieu JM, Oudard S (2005) Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. J Clin Oncol (2005) 23 :4424–4429.
8. Randall, J. et Ream, E. - Hair loss with chemotherapy: at a loss over its management? European journal of cancer care (2005), vol. 14, n° 3, p. 223-231.
9. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. Ann Oncol. 2005 Mar;16(3):352-8. Epub 2005 Jan 10.
10. Scotté F, Banu E, Mzdioni J et al. Frozen sock use in the prevention of docetaxel-induced nails and skin toxicities.Results of a case-control study. J Clin Oncol 2007;25 (suppl.18) : abstract 9059.
11. Sakurai M, Todaka K, Takada N, Kamigaki S, Anami S, Shikata A, Ueno H, Iseki C, Fujii C, Fujino M, Yamamura J, Masuda H, Ishitobi M, Nakayama T, Masuda N (2008) Multicenter phase II study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity for the breast cancer patients (Kinki Multidisciplinary Breast Oncology Group: KMBOG-0605). San Antonio Breast Cancer Symposium, San Antonio.
12. Degree of freezing does not affect efficacy of frozen gloves for prevention of docetaxel-induced nail toxicity in breast cancer patients. H. Ishiguro & S. Takashima & K. Yoshimura & I. Yano & T. Yamamoto & M. Niimi & H. Yamashiro & T. Ueno & M. Takeuchi & T. Sugie & K. Yanagihara & M. Toi & M. Fukushima Support Care Cancer (2012) 20:2017–2024.
13. Lemenager M, Lecomte S, Bonneterre ME, Bessa E, Dauba J, Bonneterre J (1997) Effectiveness of cold cap in the prevention of docetaxel-induced alopecia. Eur J Cancer 33 (2):297–300.
14. Lemieux, Desbiens C, Hogue JC. Breast cancer scalp metastasis as first metastatic site after scalp cooling: two cases of occurrence after 7- and 9-year follow-up.) Breast Cancer Res Treat. 2011 Jul;128(2):563-6. Epub 2011 Mar 24.