**Case Series**

**Capsaicin 8% patch as therapy for neuropathic chronic postsurgical pain after melanoma excision surgery: A single center case series**

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**Key words:** capsaicin; melanoma; neuropathic pain.

**INTRODUCTION**

Chronic postsurgical pain (CPSP) is defined as pain that develops or increases in intensity after a surgical procedure and persists 3 months after the surgery.1,2 Neuropathic postsurgical pain is related to an intraoperative nerve injury or impaired pain modulation with central sensitization and has a considerable impact on quality of life.3 The International Association for the Study of Pain has recommended tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors as first line treatment in neuropathic pain. Lidocaine patches, capsaicin patches, and tramadol are the second-line treatments.4

The capsaicin 8% patch (CP8), (Qutenza, Grunenthal GmbH) is labeled for use in peripheral Neuropathic Pain (NP) in adults, administered every 3 months.

CP8 is available in the USA and Europe, and received first Food and Drug Administration approval in 2009 for management of neuropathic pain associated with postherpetic neuralgia and second Food and Drug Administration approval in 2020 for treatment of neuropathic pain associated with diabetic peripheral neuropathy of the feet in adults. It delivers a high concentration of capsaicin, a highly selective agonist of transient receptor potential vanilloid-1, impaired in pain perception. Activation of transient receptor potential vanilloid-1 expressing nociceptor on skin causes loss of function of the sensory nerve fibers by loss of membrane potential and inability to transport neurotrophic factors, leading to an altered phenotype and reversible retraction of epidermal and dermal nerve fiber terminals.5

Advantages of CP8 include a longer-lasting effect, patient compliance, and low risk for systemic effects or drug–drug interactions, unlike treatments usually recommended for NP.6

We report 13 patients with neuropathic CPSP after excision of a skin melanoma treated with CP8 at a single academic institution over a 40-month period. Response to treatment and adverse effects are presented.

**Abbreviations used:**

- CP8: Capsaicin 8% patch
- CPSP: chronic post-surgical pain
- IASP: International Association for the Study of Pain
- NP: Neuropathic Pain
- NPRS: Numeric Pain Rating Scale
- TRPV-1: Transient Receptor Potential Vanilloid-1
- NSAIDs: non-steroidal anti-inflammatory drugs

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METHOD

Participants

Patients from Amiens-Picardie University Hospital with CPSP on a skin melanoma excision site area with CP8 treatment between January 2018 and June 2021 were included. The Amiens-Picardie University Health Sciences Investigational Review Board approved this case series study (Registration PI2021_843_0043).

Patients were eligible for inclusion if they had surgical removal of cutaneous melanoma with histological diagnosis and CPSP according to International Association for the Study of Pain, with neuropathic features according to the Douleur Neuropathique 4 Questions (DN4).

DN4 is a screening tool for neuropathic pain, consisting of interview questions and physical tests. This score validated in clinical practice, allows the diagnosis of neuropathic pain with 4 questions divided into 10 items. DN4 is positive if $\geq 4$.

Patients with cognitive impairment and patients with uncontrolled hypertension were excluded.

Patients who took long-term pain medications were included if they had been on stable doses of these medications for at least 21 days before CP8 treatment, and stayed on a stable dose during the study period. Long-term pain medications could include oral or transdermal opioids.

Therapeutic procedure

Each patient was being managed by the same dermatologist and pain specialist.

Patients were treated with CP8 administered transcutaneously, under the supervision of the chronic pain physician and a nurse.

All patients received from 2 to 5 administrations of CP8 with an interval of 3 months between each treatment. The allodynic area to be treated was determined by the pain physician in the presence of stimulus-evoked pain of the skin using a quantitative sensory testing with Von Frey monofilament. Allodynia was considered present if touching the skin with Von Frey monofilament evoked a clear sensation of pain. The borders of the allodynic area were traced on the skin and reported on a transparent plastic sheet. Then, CP8 patch was cut to cover the allodynic area (Fig 1). CP8 was used as per the manufacturer’s recommendations as follows: pretreatment topical anesthetic cream (lidocaine 2.5%/prilocaine 2.5%) for 60 minutes and CP8 for 60 minutes on the painful area, with tolerability control (blood pressure, intensity of pain, and dermal reaction) until 20 minutes after patch removal.

A standardized measurement tool was used for pain evaluation. Pain levels were assessed using the 11-point Numeric Pain Rating Scale (NPRS).
### Table I. Patient characteristics and capsaicin 8% patch therapy

| Patient | Age, y | Sex | Location | Excision margin, cm | Time from surgery to pain, months | Time from pain to CP8 initiation, months | Systemic analgesics before CP8 | Concomitant systemic analgesics with CP8 | Systemic analgesics after CP8 | Initial pain, NPRS | Number of CP8 administrations | Pain after CP8 week 12, NPRS |
|---------|--------|-----|----------|---------------------|----------------------------------|------------------------------------------|-------------------------------------|--------------------------------------|--------------------------------|----------------|---------------------------------|-----------------------------|
| 1       | 65     | F   | Arm      | 1                   | 0                                | 120                                      | Hypnotic Local anesthetics           | Hypnotic                             |                                | 0              | 6                              | 3                           | 0                           |
| 2       | 55     | M   | Foot     | 2                   | 12                               | 15                                       | Acetaminophen Antidepressant         | Benzodiazepine                       |                                | 5              | 2                              | 3                           |
| 3       | 37     | M   | Leg      | 2                   | 0                                | 33                                       | Acetaminophen Opioid                |                                      |                                | 0              | 6                              | 5                           | 0                           |
| 4       | 65     | F   | Leg      | 2                   | 36                               | 5                                        | Acetaminophen Antidepressant         | 0                                    | 0                              | 3              | 2                              | 0                           |
| 5       | 59     | M   | Arm      | 2                   | 14                               | 7                                        | Acetaminophen Antidepressant         | 0                                    | 0                              | 7              | 4                              | 0                           |
| 6       | 72     | F   | Leg      | 2                   | 104                              | 5                                        | Acetaminophen Antidepressant         | 0                                    | 0                              | 8              | 5                              | 1                           |
| 7       | 37     | F   | Leg      | 2                   | 0                                | 18                                       | Antidepressant Antiepileptic         | 0                                    | 0                              | 9              | 4                              | 6                           |
| 8       | 65     | M   | Shoulder | 2                   | 80                               | 20                                       | Antidepressant Antiepileptic         | Antidepressant Antiepileptic         |                                | 7              | 2                              | 1                           |
| 9       | 61     | M   | Pectoral | 1                   | 0                                | 21                                       | Acetaminophen, Antidepressant        | Antidepressant                       |                                | 0              | 5                              | 2                           | 0                           |
| 10      | 59     | M   | Leg      | 1                   | 0                                | 87                                       | Acetaminophen Antidepressant         | 0                                    | 0                              | 7              | 2                              | 0                           |
| 11      | 56     | F   | Leg      | 2                   | 3                                | 9                                        | Acetaminophen Antidepressant         | 0                                    | 0                              | 6              | 2                              | 5                           |
| 12      | 50     | F   | Leg      | 2                   | 0                                | 13                                       | Acetaminophen Antidepressant         | 0                                    | 0                              | 6              | 2                              | 5                           |
| 13      | 33     | M   | Heel     | 2                   | 0                                | 45                                       | Acetaminophen Opioid                |                                      |                                | 0              | 6                              | 2                           | 5                           |

CP8, Capsaicin 8% patch; F, female; M, male; NPRS, Numeric Pain Rating Scale; NSAID, non-steroidal anti-inflammatory drugs.
Judgment criteria
The primary endpoint was the response rate at week 12 after the last administration. Patients were considered to be responding if they reported $\geq 30\%$ pain reduction compared to baseline pain score in NPRS. Complete remission is defined as the absence of pain at the end of treatment (NPRS 0). The secondary endpoints were the reduction of the allodynic area, the change in the impact of pain on health-related quality of life, and the number of concomitant medications.

The impact of pain on health-related quality of life was measured using the EuroQol Five Dimensions Questionnaire (EQ-5D-5L) (Registration ID 38457). The EQ-5D-5L is a standardized self-completed instrument developed in Europe and widely used for measuring health related quality of life. It includes 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 response levels as follows: level 1 (no problems) to level 5 (extreme problems). The instrument also includes the EQ-VAS, a vertical visual analog scale that takes values between 100 (best imaginable health) and 0 (worst imaginable health), on which patients provide a global assessment of their health.

RESULTS
Patient characteristics
We identified 13 patients (6 women, 7 men) with neuropathic CPSP on a melanoma excision site area who were treated with 2 to 5 applications of CP8 (Table I). The mean age (standard deviation) of the patients was 54.9 years and the mean pain score before treatment was 6.4 (1.6).

The resection margins of melanoma were 1 or 2 cm for all patients, (2 cm for 10 patients, 1 cm for 3 patients). The painful area was always in contact with the melanoma excision scar line.

The topography involved a lower limb for most patients as follows: 6 on the leg (46.2%), 1 on the thigh (7.7%), 2 on the foot (15.4%), 2 on the arm (15.4%), 1 on the scapula (7.7%) and 1 on the pectoral (7.7%).

The median pain duration before CP8 was 18 months (range 5-120). Time to onset of pain from surgery varied from immediately after surgery for 8 patients (61.5%) to 9 years.

The mean number of pain therapies prior to treatment with CP8 was 2.7 (range 0-8). At the initiation of CP8, 9 (69.3%) patients were taking concomitant antalgic medication (average number of antalgics per patient 1.7, range 0-6). Previous treatments included acetaminophen, non-steroidal anti-inflammatory drugs, opioids, antiepileptics, antidepressant, local anesthetics, benzodiazepines, and hypnotics. These treatments were ineffective or insufficiently effective (pain reduction of less than 30% or less than 2 points on NPRS) and often caused side effects (especially for antidepressants and anti-epileptics, including nausea, constipation, drowsiness, dizziness, weight gain, etc).

Response to CP8
The primary endpoint defined as $\geq 30\%$ reduction in NPRS score from baseline to week 12 after last administration was achieved for 84.6% patients (11 of 13 patients), after a mean number of 3.5 administrations.

For 9 patients (69.2%), the pain decreased by at least 70% after the last administration, and 6 complete remissions were reported. The mean pain 12 weeks after the end of treatment was 2 (2.4) on NPRS.

One relapse was detected during the follow-up, with reappearance of NP in the area previously treated with CP8 (Patient 3). This relapse occurred 16 months after the fourth patch, which resulted in a complete remission. This patient benefitted from a reintroduction of CP8 and obtained a complete remission after a single patch application. Pain area decreased for 12 patients (92.3%) with an average decrease of 38% in the allodynic surface as follows: mean allodynic surface was 205 cm² before CP8 (range 24-502), 120 cm² (range 5-302) before the last administration. Data were missing for 2 patients concerning health-related quality of life in EQ-5D-5L; we present the results of 11 patients (Table II).

Except pain, the most frequently reported problem among these 11 patients were anxiety/depression (100%) followed by usual activities problems (91%), mobility problems (82%), and self-care problems (82%). At week 12 after the last administration patients reported improvements in health-related quality of life in EQ-5D-5L as follows: 4 patients (36%) had no anxiety/depression, 7 (64%) had no problems in self-care, 7 (64%) reported no problems in mobility, and 7 (64%) no problems in usual activities. The mean improvement in EQ-VAS score was 28.4% (mean EQ VAS 55.9/100 before CP8, 71.8/100 after CP8).

We also reported a reduction in analgesic intake with only 3 patients who were still receiving analgesic treatment after the last CP8 administration.

All patients completed 100% of the intended CP8 application time. All patients had redness at the patch application area that resolved within 48 hours. Within days of treatment, 5 patients (38.5%) applied ice to the treated area, 1 patient (7.7%) used acetaminophen, and 1 patient (7.7%) used tramadol.
because of pain. These adjunctive analgesic treatments were taken for a maximum of 72 hours.

One case of hypertension during application was reported and one case of hypertension occurring after the patch was removed. In both cases, the blood pressure spontaneously normalized and did not require treatment. No adverse events were reported or documented in patient medical records. No patients discontinued treatment due to adverse events.

DISCUSSION

We report a cohort of 13 patients treated with CP8 for neuropathic CPSP after excision of cutaneous melanoma with a good efficacy and tolerance without systemic effects reported. The 13 patients with a follow-up of ≥6 months demonstrated a 91.4% mean reduction in their NPRS score from baseline to week 12 after treatment, including 6 complete remissions. Only one relapse occurred during the follow-up and was effectively treated with a new CP8 administration. We observed a decrease in the surface of the allodynic area after treatment, in use of other analgesics and an overall improvement in the patients’ health related quality of life. CP8 treatment was effective regardless duration of preexisting pain.

CPSP is experienced by 10% to 50% of individuals after classical operations.10,11

Chronic pain has the following individual physical, psychological, and social consequences: Sleep quality, cognitive processes, mental health, cardiovascular health, sexual function, and overall quality of life are affected as found in our patients. It has also economic consequences related to health care cost (pharmaceuticals, primary consultations, emergency department visits, and hospitalizations) and loss of productivity (absenteeism from work, incapacity, and disability).12

The price of CP8 is $741 per patch, representing an average cost to our patients of $2223 (for 3 patches) has to be interpreted according to a cost-effectiveness analysis.

Qutenza showed to be the less expensive option in comparison with pregabalin or lidocaine, independent of the area of administration (Primary or Secondary Care).9

The risk factors for chronic scar pain are as follows: age <50 years, female gender, smoking, anxiety, preoperative pain, and acute postoperative pain, factors related to the surgery (long duration, technique at risk of nerve damage).10,13 Surgical reinterventions induce a higher risk of CPSP than the initial surgery in cases of visceral surgery, cardiac surgery, cesarean section, andinguinal hernia recurrence.11

After melanoma excision, to the best of our knowledge, only one publication has evaluated the occurrence of pain around the surgical scar in 350 patients at the Department of Plastic Surgery in Aalborg (Denmark) as follows: 31.5% of patients described sensory disturbances (21.8% hypoesthesia, 12.5% hyperesthesia). Daily discomfort induced by these sensory disturbances was reported by 60.2% of patients with hypoesthesia and 95.3% of patients with hyperesthesia. Pain around the surgical scar affected 9.7% with 8.6% of chronic pain (persisting 2 years after melanoma excision).14

Melanoma surgery is neither considered long surgery nor high risk for nerve damage but sensory changes (hyposensitivity and hypersensitivity) are a strong predictor of pain after melanoma surgery, suggesting that nerve damage may play a role in some patients.14

Table II. Euroqol five dimensions questionnaire EQ-5D-5L

| Dimension                  | Baseline | Week 12 after last administration |
|----------------------------|----------|-----------------------------------|
| Mobilitiy problems         |          |                                   |
| None                       | 2 (18.2) | 7 (63.6)                          |
| Slight                     | 1 (9.1)  | 1 (9.1)                           |
| Moderate                   | 5 (41.7) | 0                                 |
| Severe                     | 3 (27.3) | 3 (27.3)                          |
| Unable to walk             | 0        | 0                                 |
| Self-care problems         |          |                                   |
| None                       | 1 (9.1)  | 7 (63.6)                          |
| Slight                     | 5 (41.7) | 2 (18.2)                          |
| Moderate                   | 3 (27.3) | 2 (18.2)                          |
| Severe                     | 2 (18.2) | 0                                 |
| Unable to wash or dress    | 0        | 0                                 |
| Usual activities problems  |          |                                   |
| None                       | 2 (18.2) | 7 (63.6)                          |
| Slight                     | 2 (18.2) | 1 (9.1)                           |
| Moderate                   | 3 (27.3) | 2 (18.2)                          |
| Severe                     | 4 (36.4) | 1 (9.1)                           |
| Unable to do usual activities | 0     | 0                                 |
| Pain/discomfort            |          |                                   |
| None                       | 0        | 4 (36.4)                          |
| Slight                     | 1 (9.1)  | 2 (18.2)                          |
| Moderate                   | 2 (18.2) | 3 (27.3)                          |
| Severe                     | 7 (63.6) | 2 (18.2)                          |
| Extreme                    | 1 (9.1)  | 0                                 |
| Anxiety/depression         |          |                                   |
| Not anxious/depresses      | 0        | 4 (36.4)                          |
| Slightly                   | 4 (36.4) | 4 (36.4)                          |
| Moderately                 | 1 (9.1)  | 2 (18.2)                          |
| Severely                   | 5 (41.7) | 1 (9.1)                           |
| Extremely                  | 1 (9.1)  | 0                                 |
Only young age showed a significant association with the occurrence of postoperative pain after melanoma excision. In the present study, the proportion of smokers (6 patients, 46.1%) was higher than the regional average and patients were younger than patients diagnosed with melanoma in France. Sex ratio was balanced which corresponds to the distribution of melanoma in France.

We have chosen to focus our study only on melanoma because the surgery is well standardized regarding the lateral and deep margins of excision down to the muscle fascia, which allows a comparison. We did not include other surgeries such as carcinoma because the margins are less standardized.

In the present study patients had improvement in pain with repeated applications. In the French prospective observational study QAPSA (Post-marketing surveillance of CP8 for long-term use in patients with Peripheral Neuropathic Pain in France), in which NP was mostly of post-traumatic or postsurgical origin (76.3%), the efficacy of CP8 also increased with the number of patches applied.

Limitations of our study include a small sample size and the lack of a control group.

Furthermore, our population represents a selected group of patients compared to general melanoma patients because of hospital-based recruitment in a specialized institution.

CONCLUSIONS
CP8 may be an additional effective and well tolerated treatment for high neuropathic CPSP with a very impaired quality of life after melanoma surgery.

This treatment could be included in the therapeutic arsenal if prospective randomized controlled study confirms its effectiveness.

Conflicts of interest
None disclosed.

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