Evolution de la PACC Intrathécal Douleurs & Cancers

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The Polyanalgesic Consensus Conference (PACC)®: Updates on Clinical Pharmacology and Comorbidity Management in Intrathecal Drug Delivery for Cancer Pain

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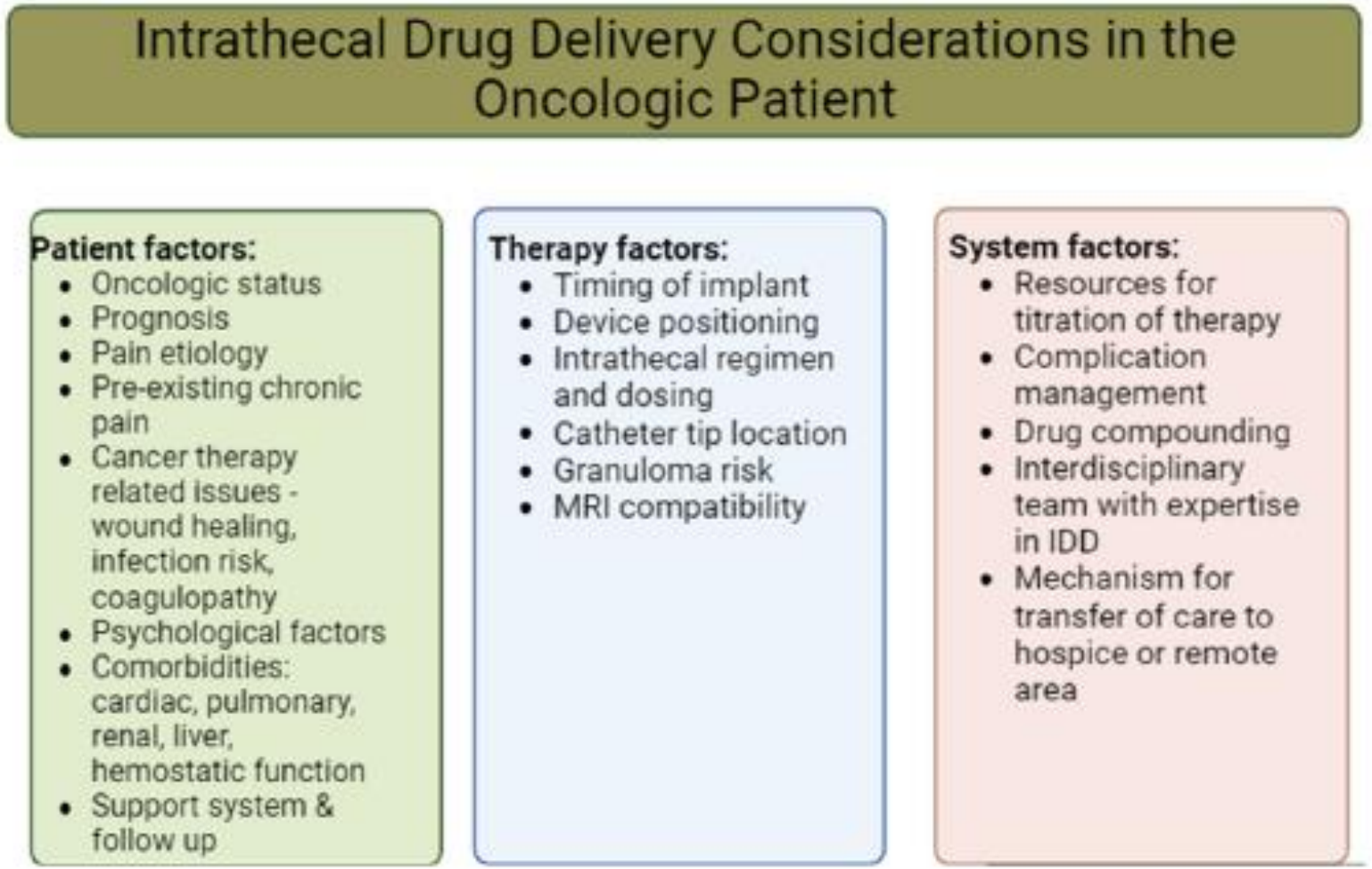

Facteurs qui affectent l'efficience et la sécurité de IDD en cancérologie

Evaluation psychologique

Psychologic Assessment and Support

The psychologic status of the patient with cancer pain should be considered before pump implantation and in the period after implantation. Unique considerations related to cancer pain include cancer prognosis, the possibility of terminal disease, loss of independence, changes in family and other social relationships, and morbidity from cancer treatments. It is essential to recognize when psychologic distress in cancer is driven by poorly controlled symptoms or medication side effects, or a combination of both. When successful, the superior analgesia provided by IDD may produce improved functional status and psychologic well-being. Although precancer comorbidities such as depression, anxiety, and substance misuse may complicate IDD, they should not preclude the implementation of IDD to control pain and minimize the analgesic side-effect burden.

Psychologic factors are less likely to play a major role in the pain of patients with cancer than in that of patients with noncancer pain.[23,24] Nonetheless, a review of the literature found that nearly 73% of patients with cancer reported an association between pain and psychologic distress.[25] A study found that preimplantation psychologic evaluations occur in approximately 11% of cases with cancer-related pain and 89% of cases with noncancer pain.[26]

Consensus Point 2

The PACC recommends that in cancer pain, psychologic assessment and treatment continue to be important to evaluate and counsel the patient on issues such as cancer prognosis, death and dying, and anxiety or depression, but should not unreasonably delay IDD. USPSTF Grade B; Level of certainty low; Quality of evidence II.

Gestion des comorbidités

Consensus Point 3

The PACC recommends consideration of pulmonary disease and status when choosing IT drugs and during both initial dosing and dosing adjustments with opioids. USPSTF Grade B; Level of certainty low; Quality of evidence II.

Consensus Point 4

The PACC recommends that consideration be given to the choice of IT medications, with particular attention paid to clonidine, when treating patients with cardiovascular disease, with special consideration of clinically significant hypotension and/or rebound hypertension. USPSTF Grade A; Level of certainty low; Quality of evidence 1-C.

Traitements intrathecaux

- Baclofene

- Ziconotide

Clinical Studies

Although no direct study for ITB in the oncologic population is known in the literature Spasticity In Stroke-Randomised Study (SISTERS), the largest and most recent multicenter RCT of ITB therapy, evaluated the efficacy and safety of ITB administration vs conventional medical management (CMM) for poststroke spasticity.[114] The study found that the ITB therapy group had significantly more improvement in spastic hypertonia and muscle tone than did the CMM group. Although AEs were more frequent among the ITB group, these events were mild or moderate and were attributed to the nature of the therapy, given it involves surgical implantation.

Combination Drug Regimens

Although lacking good prospective data, most recent clinical studies of IDD used combination drug regimens. According to a recent analysis of data from the Medtronic Implantable Systems Performance Registry data base, >97% of pumps for cancer pain are used with off-label drugs.[135] In vitro evidence of the efficacy of combination approaches includes a study showing that IT ziconotide and morphine produce synergistic analgesic effects in rats because activation of mu-opioid receptors by morphine leads to inhibition of N-type calcium channels through a G-protein.[136] A prospective study in humans ($N = 20$) showed that a slow titration of ziconotide to a dose of 4.8 μg/d with morphine effectively controlled cancer pain and caused just four mild AEs, which did not require treatment.[137]

Avantages et inconvenients / drogue

Table 5. Commonly Used IT Drugs in Cancer Pain: Practical Issues Driving Regimen Selection.

Agent	Factors favoring use	Factors complicating use
Morphine	• FDA approved • Inexpensive	• At higher doses, neurotoxicity may be observed.
Hydromorphone	• Higher potency and higher maximum compounded recommendations allow longer refill intervals.	
Fentanyl and sufentanil	• With an appropriately positioned catheter, higher lipophilicity may exert a more localized effect. • Sometimes added to morphine or hydromorphone (3rd line)	
Ziconotide	• FDA approved. • Unique mechanism of action, useful when extreme opioid tolerance is encountered or when pain seems poorly opioid responsive. • No withdrawal phenomenon—can be easily removed from the regimen if adverse effects.	• Expensive. • Will not be covered by hospice agencies in US. • Rapid dose titration impractical in patient with limited life expectancy. • Unavailable in many countries.
Bupivacaine/ ropivacaine	• Catheter tip location is important. • Evidence of synergy with opioids. • Patient controlled IT analgesia permits bolus of local anesthetic, facilitating rapid control of breakthrough pain	• Motor weakness may be observed at higher doses. • In patients at high risk of neurologic injury from spinal disease, local anesthetic may mimic neurologic symptoms and signs.
Clonidine	• Consider in complex neuropathic pain.	• Dose titration may be challenging in the patient with limited life expectancy. • Withdrawal syndrome is possible
Baclofen	• FDA approved for spasticity. • Consider when spinal cord injury and spasticity is present. • Consider in complex neuropathic pain.	• Dose titration may be challenging in the patient with limited life expectancy. • Withdrawal syndrome is life-threatening.

FDA = Food and Drug Administration.

Patient survie limitée

Table 3. Cancer Pain Treatment in a Patient with Limited Life Expectancy.

Line 1	Morphine or hydromorphone ± bupivacaine		Fentanyl ± bupivacaine			
Line 2	Morphine or hydromorphone or fentanyl + low-dose ziconotide ± bupivacaine					
Line 3	Hydromorphone or morphine or fentanyl + clonidine ± bupivacaine	Ziconotide + bupivacaine	Ziconotide + clonidine		Clonidine as secondary or tertiary adjuvant	Sufentanil as primary or secondary (along with morphine or hydromorphone) opioid
Line 4	Opioid + ziconotide	Sufentanil + bupivacaine	Baclofen as secondary or tertiary adjuvant	Sufentanil + clonidine	Bupivacaine + clonidine + ziconotide	Bupivacaine + clonidine
Line 5	Refractory pain – consider complex regimen including combination of multiple drug classes					

In a patient with limited life expectancy (<six months), aggressive dose titration is implemented to obtain satisfactory analgesia. Regimen selection also should be based on pain characteristics, catheter tip location, and the individual drug factors presented in Table 5.

Patient survie prolongée > 6 mois

Table 4. Chronic Cancer Pain Treatment With Favorable Prognosis (Six Months to Years).

Line 1	Morphine or hydromorphone or fentanyl ± bupivacaine		Ziconotide	
Line 2	Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide		Hydromorphone or morphine or fentanyl + clonidine	
Line 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine	Ziconotide + bupivacaine	Ziconotide + clonidine	Sufentanil
Line 4	Refractory pain – consider complex regimen including combination of multiple drug classes			

Emphasis is on attaining improvement in pain and function, while considering durability and safety of therapy for a long period. Regimen selection should also be based on the patient's condition and individual drug factors.

Introducing dosage

Table 8. Starting and Dose Increases for IT Pain Medications in Patients Naïve to or on Low Doses of Opioids.

Drug	Starting dose for opioid-naive patients/24 h
Morphine	0.1–0.5 mg
Hydromorphone	0.02–0.1 mg
Fentanyl	25–75 µg
Sufentanil	10–20 µg
Ziconotide	0.5–1 µg
Bupivacaine	1–4 mg
Clonidine	40–100 µg
Baclofen	25 µg (50 µg for spasticity)

Trialing

Table 6. Disadvantages and Advantages of IT Trialing in Cancer Pain.

Disadvantages of trialing	Advantages of trialing
• Delays definitive therapy in a population with limited life expectancy • Many patients with cancer are on anticoagulation. Trialing requires an additional discontinuation of anticoagulation therapy and increased risk of thromboembolic events. • Additional procedural risk of trial (postdural puncture headache, infection, etc) in immuno-compromised population • Additional burden for patient for trial and associated posttrial monitoring • Additional cost • Inpatient trials are laborious • Ethical conflict if trial "fails" in patient with limited life expectancy and intolerance of opioids and/or severe pain despite opioid dose escalation • IT opioid dose requirement unpredictable in patients using high-dose oral opioids	• Payor authorization • Allow patients to experience potential efficacy of IDD • May spare a small percentage of patients going through the implant process if there would be lack of efficacy or inability to access the IT space

IDD = intrathecal drug delivery; IT = intrathecal.

Catheter tip location

Table 7. IT Catheter Tip Location Based on Pain Location.

Pain location	Vertebral body catheter tip location
Face	C1–2
Brachial plexus	C3–5
Arm	C3–5
Breast	T1–2
Upper chest wall	T3–4
Visceral abdomen	T5–6
Lower chest wall	T6–7
Abdominal wall	T6–7
Back	T8–11
Pelvis	T9–12
Leg	T10
Sacrum	Vertebral body level corresponding to conus medullaris

Conclusion

PACC plus clinique

Moins « americano – centrée »

Système de soins differents en Europe

- Recommendations Européennes ?