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Treatment of pruritus in malignant diseases

Abstract

Severe pruritus is a rare complication of cancer. Although many patients with or without cancer suffer of mild pruritus due to generic causes like dry skin, *candida* infections and local inflammation, very few suffer severe pruritus. Similarly to the concept of "cancer pain", there is nothing like "pruritus of cancer", no common mechanism and no common treatment. Thorough analysis and deduction as well as laboratory and image investigations are necessary to unravel possible cause and help choose appropriate treatment. Many treatments, appear to be effective against pruritus judging from the number of case reports, but render ineffective in controlled clinical trials.

Key words: pruritus, cancer, treatment

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Introduction

Severe pruritus is a rare complication of cancer [1]. Although many patients with or without cancer suffer of mild pruritus due to generic causes like dry skin, candida infections and local inflammation, very few suffer severe pruritus [2]. Similarly to the concept of "cancer pain", there is nothing like "pruritus of cancer", no common mechanism and no common treatment. Thorough analysis and deduction as well as laboratory and image investigations are necessary to unravel possible cause and help choose appropriate treatment [3]. As the knowledge of "pruritus in cancer" conditions is limited, typical treatment plan would be organised in three or more steps which should be tried after each other. Sometimes combination of several modalities is necessary to satisfactorily control pruritus [4].

Mechanisms of pruritus in cancer

Most of the cancer patients experiencing severe itch can be classified as patients with cholestasis. This cholestasis is usually due to extra- or intrahepatic bile retention due to bile duct and pancreas tumours or, more often, intrahepatic metastases of other distant tumours. Itch of cholestasis may also result from an ill understood paraneoplastic phenomenon and in this kind of patients drainage of the bile by insertion of bile duct stent will relieve jaundice, but not pruritus. Cholestasis may also result from hepatotoxic drugs. As in advanced disease, patients may become more vulnerable for this mechanism as in general their resilience decreases. Simple discontinuation of the suspected drugs, one by one, may lead to resolution of the itch.

There may be some patients who will suffer of paraneoplastic itch, unrelated to cholestasis. In

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these patients it is typical that suppression of the tumour growth will suppress itch, but recurrence of this symptoms may herald recurrence of the tumour. This type of itch frequently preceded diagnosis of cancer by months and sometimes by years [5]. In this context lymphomas are notorious [6].

Finally, many patients will experience localized itch due to neuropathy. This neuropathy may result from localized tumour growth and damage to the nerves [7–9]. Neuropathy may result from neural shingles infection [10, 11] or from damage to the nerves by the treatment of cancer. In this latter category one can find all kind of neurotoxic effects of chemotherapy [12–14] and radiotherapy [15]. New therapies, like biologic response modifiers may also be toxic and cause persistent itch [16–18].

The specific mechanisms and available treatments will be now discussed in more details.

Cholestasis and cholestyramine

Bile acids are metabolites of cholesterol and their accumulation was thought for a long time as patognomonic for pruritus in liver diseases [19]. Injection of bile acids intracutaneously causes itch [20, 21]. However, patients with cholestasis advance into hepatic failure stop itching despite accumulation of bile acids [22]. This happens when androgens are used to treat itch: itch is decreasing despite the surge of bile acids in blood [22]. Removal of bile acids from the plasma by ion exchange resin cholestyramine used to treat hypercholesterolaemia helps only for some time. Although this therapy is known for many years, rigorous clinical trials are still missing. Above all cholestyramine may adsorb many other things, also potential pruritogens, so this drug is not selective at all. Adsorption of vitamin K may cause serious bleeding in patients with cancer. Cholestyramine helps also in cases of pruritus due to policythaemia vera which has nothing to do with cholestasis and bile acids [23]. In the context of cancer and cholestasis due to obstruction of external bile duct it is important to state that cholestyramine will not help in case of jaundice when the bile is not pouring into the duodenum. In this context it is interesting that nasobiliary drainage was found useful in several pruritic patients [24, 25].

Interesting aspect of cholestyramine is that it is associated with release of cholecystokinin [26] and endogenous opioids [27]. In this way cholestyramine may influence opioidergic tone. And this is the clue to understand pruritus of cholestasis.

Cholestasis and opioids

Cholestatic rodents subjected to resection of their bile ducts present with a naloxone reversible analgesia and pruritus [28–30]. Increase of activity of mu-specific opioids increases itch transmission and induces analgesia while treatment with kappa-opioid agonists U50488H [31, 32] reduces itch. Also well known is antipruritic effect of opioids antagonists like naloxone and naltrexone [33, 34]. In non-malignant diseases naloxone and naltrexone is the treatment of choice of pruritus [34–37]. However, in malignant disease there is a need of a different approach. Rapid reversal of opioids analgesia, which we believe is present in many patients with cholestasis may on one side control itch but may also induce pain. Juby et al. proposed in 1994 treatment with buprenorphine [38]. This opioids drug has a high affinity to the opioids receptors and my make them unavailable to the pruritogenic endogenous opioids [35]. This approach had been tried in a clinical trial in time when only high dose sublingual preparations of buprenorphine were available [38]. Not surprising that this drug was found very toxic and the trial was prematurely discontinued. Several patients responded to this therapy with decrease of itch. Recently buprenorphine became available in patches and made titration to effect, avoiding toxicity possible. Single successful cases of antipruritic activity of this drug were reported [39–41].

Pruritus and serotoninergic system

We do not know exactly how serotoninergic system is connected to the opioids. However, some patients with cholestatic pruritus, but also with a plethora of other conditions may respond to administration of SSRIs. It appears that paroxetine and probably also sertraline are especially effective in the treatment of paraneoplastic itch. Administration of paroxetine in patient with cholestasis may evoke reaction that clinically is indistinguishable to opioids abstinence syndrome evoked by naloxone (Zylicz — unpublished). Also, after failure of naltrexone to relieve itch, paroxetine is usually ineffective too (Zylicz — unpublished). Use of SSRIs for relieve of itch was observed empirically [42]. Later several clinical trials were performed, all of them confirming the original observation [43–46]. Nausea and vomiting observed in patients treated with paroxetine [43] can best be avoided by careful increments of the dose [44]. In this context it is interesting to note that some patients with cholestasis will present with a codeine resistant dry cough [47,

48]. This cough responds very well to administration of any type of SSRIs [48]. Clinical trials are on their way to confirm this interesting observation.

Several years ago a lot of attention was paid to the use of ondansetron in the treatment of itch, especially itch of cholestasis [49–51]. However, controlled trial did not confirm this effect [52]. In this context it is interesting to state that ondansetron may have a potential to control fatigue accompanying cholestasis [53, 54]. Author uses from time to time subcutaneus tropisetron to relieve itch in a patient who can not take medicines orally, with remarkable effect. The difference between poor response in clinical trial and reported cases can be explained by variable bioavailability of ondansetron. The HT_3 receptor antagonists appeared to be antipruritic only in opioids induced itch [55, 56].

Among other drugs interacting with serotoninergic system mirtazapine warrants further investigations [57, 58].

Rifampicin

Rifampicin is an antibiotic but it also induces liver enzymes. Although the antipruritic mechanism of rifampicin is still unknown, many people think that inducing the metabolic mashine of the liver will speed the metabolism of an unknown pruritogen(s) in the liver [59]. In a double blind trial rifampicin appeared to be effective as an antipruritic agent in the dose of 300–450 mg per day [60]. Although rifampicin is present in almost all guidelines to treat itch it must be pointed out that this drug is hepatotoxic and close monitoring of the liver panel is advisable. Treatment with the low dose, 75 mg is advisable initially and the dose can be gradualny increased. Because of this rifampicin can not be given chronically, something which is needed by many patients suffering from this condition.

Treatment of neuropathic itch

Neuropathic itch can be best treated in the same way as neuropathic pain. Gabapentin is effective against some form of this itch [61–63]. However, this therapy appears to be effective also in pruritus unrelated to neuropathy [64–67]. Antidepressants, including SSRIs may be tried, but there is an insufficient body of evidence to advocate this. Epidural clonidine may be tried too as it was effective in several cases of pruritus due to herpes zoster [68]. Other options are discussed in the recent article by Yosipovitch [69].

Opioid induced pruritus

Opioid induced pruritus is rare after oral or parenterally administration of opioids. It is so rare that its presence may indicate reaction to other than opioids component of the medication. Itch following systemic opioids administration responds well to antihistamines which suggest an allergic reaction. It is different in case of opioids administered spinally. The prevalence of itch in spinal opioids administration is very high [70]. Especially in women before Caesarian section, spinal opioids induce always itch. Bupivacaine added to spinal opioids nearly always ameliorates itch [71–73]. Interestingly diclofenac and other NSAIDs are able to reduce itch due to spinal opioids suggesting that prostaglandines but not histamine are involved in this mechanism [74, 75].

Conclusion

Severe itch can be very annoying to the patients with malignancies. Although the direct effect of tumour growth on itch is still under investigation, cancer patients suffer most often of itch due to cholestasis. This condition is best treated with bile drainage but sometimes this is impossible due to advanced disease. Other measures, among which buprenorphine patches should be investigated. Also the use of SSRIs is promising in this context. Many treatments, like ondansetron, appear to be effective against pruritus judging from the number of case reports, but render ineffective in controlled clinical trials.

References

1. Krajnik M., Zylicz Z. Pruritus accompanying solid tumors. In: Zylicz Z, Twycross R, Jones E.A. (eds). Pruritus in advanced disease. 1st ed. Oxford University Press, Oxford 2004: 97–106.
2. Cormia F.E. Pruritus, an Uncommon but Important Symptom of Systemic Carcinoma. Arch. Dermatol. 1965; 92: 36–39.
3. Krajnik M., Zylicz Z. Pruritus in advanced internal diseases. Pathogenesis and treatment. Neth. J. Med. 2001; 58: 27–40.
4. Zylicz Z., Stork N., Krajnik M. Severe pruritus of cholestasis in disseminated cancer: developing a rational treatment strategy. A case report. J. Pain Symptom Manage 2005; 29: 100–103.
5. Bosonnet L. Pruritis: scratching the surface. Eur. J. Cancer Care (Engl) 2003; 12: 162–165.
6. Paul R., Jansen C.T. Itch and malignancy prognosis in generalized pruritus: a 6-year follow-up of 125 patients. J. Am. Acad. Dermatol. 1987; 16: 1179–182.
7. Cohen A.D., Vander T., Medvendovsky E. et al. Neuropathic scrotal pruritus: anogenital pruritus is a symptom

of lumbosacral radiculopathy. J. Am. Acad. Dermatol. 2005; 52: 61–66.
8. McMichael J. Localized itching as a harbinger of breast cancer? J. Fam. Pract. 2004; 53: 562.
9. Welsh B., Howard A., Cook K. Vulval itch. Aust. Fam. Physician 2004; 33: 505–510.
10. Oaklander A.L., Bowsher D., Galer B., Haanpaa M., Jensen M.P. Herpes zoster itch: preliminary epidemiologic data. J. Pain 2003; 4: 338–343.
11. Oaklander A.L. Mechanisms of pain and itch caused by herpes zoster (shingles). J. Pain 2008; 9: S10–S18.
12. Hejna M., Valencak J., Raderer M. Anal pruritus after cancer chemotherapy with gemcitabine. N. Engl. J. Med. 1999; 340: 655-–656.
13. Dunagin W.G. Clinical toxicity of chemotherapeutic agents: dermatologic toxicity. Semin. Oncol. 1982; 9: 14–22.
14. Hood A.F. Cutaneous side effects of cancer chemotherapy. Med. Clin. North Am. 1986; 70: 187–209.
15. Hassey K.M. Skin care for patients receiving radiation therapy for rectal cancer. J. Enterostomal Ther. 1987; 14: 197–200.
16. Krown S.E. Interferons and interferon inducers in cancer treatment. Semin. Oncol. 1986; 13: 207–217.
17. Irwin M.M. Patients receiving biological response modifiers: overview of nursing care. Oncol. Nurs. Forum 1987; 14: 32–37.
18. Sullivan K.M., Deeg H.J., Sanders J.E. et al. Late complications after marrow transplantation. Semin. Hematol. 1984; 21: 53–63.
19. Jones E.A., Bergasa N.V. The pruritus of cholestasis: from bile acids to opiate agonists. Hepatology 1990; 11: 884–887.
20. Kirby J., Heaton K.W., Burton J.L. Pruritic effect of bile salts. Br. Med. J. 1974; 4: 693–695.
21. Varadi D.P. Pruritus induced by crude bile and purified bile acids. Experimental production of pruritus in human skin. Arch. Dermatol. 1974; 109: 678–681.
22. Lloyd-Thomas H.G., Sherlock S. Testosterone therapy for the pruritus of obstructive jaundice. Br. Med. J. 1952; 2: 1289–1291.
23. Chanarin I., Szur L. Letter: Relief of intractable pruritis in polycythaemia rubra vera with cholestyramine. Br. J. Haematol. 1975; 29: 669–670.
24. Beuers U., Gerken G., Pusl T. Biliary drainage transiently relieves intractable pruritus in primary biliary cirrhosis. Hepatology 2006; 44: 280–281.
25. Stapelbroek J.M., van Erpecum K.J., Klomp L.W. et al. Nasobiliary drainage induces long-lasting remission in benign recurrent intrahepatic cholestasis. Hepatology 2006; 43: 51–53.
26. Koop I., Fellgiebel A., Koop H., Schafmayer A., Arnold R. Effect of cholestyramine on plasma cholecystokinin and pancreatic polypeptide levels, and exocrine pancreatic secretion. Eur. J. Clin Invest. 1988; 18: 517–523.
27. Wiertelak E.P., Maier S.F., Watkins L.R. Cholecystokinin antianalgesia: safety cues abolish morphine analgesia. Science 1992; 256: 830–833.
28. Bergasa N.V., Alling D.W., Vergalla J., Jones E.A. Cholestasis in the male rat is associated with naloxone-reversible antinociception. J. Hepatol. 1994; 20: 85–90.
29. Dehpour A.R., Akbarloo N., Ghafourifar P. Endogenous nitric oxide modulates naloxone-precipitated withdrawal signs in a mouse model with acute cholestasis. Behav. Pharmacol. 1998; 9: 77–80.
30. Ghafourifar P., Dehpour A.R., Akbarloo N. Inhibition by L-NA, a nitric oxide synthase inhibitor, of naloxone-precipitated withdrawal signs in a mouse model of cholestasis. Life Sci. 1997; 60: PL 265–270.
31. Ko M.C., Lee H., Song M.S. et al. Activation of kappa-opioid receptors inhibits pruritus evoked by subcutaneous or intrathecal administration of morphine in monkeys. J. Pharmacol. Exp. Ther. 2003; 305: 173–179.
32. Kuraishi Y., Yamaguchi T., Miyamoto T. Itch-scratch responses induced by opioids through central mu opioid receptors in mice. J. Biomed. Sci. 2000; 7: 248–252.
33. Jones E.A., Neuberger J., Bergasa N.V. Opiate antagonist therapy for the pruritus of cholestasis: the avoidance of opioid withdrawal-like reactions. QJM 2002; 95: 547–552.
34. Bernstein J.E., Swift R. Relief of intractable pruritus with naloxone. Arch. Dermatol. 1979; 115: 1366–1367.
35. Thornton J.R., Losowsky M.S. Opioid peptides and primary biliary cirrhosis. BMJ 1988; 297: 1501–1504.
36. Bergasa N.V., Alling D.W., Talbot T.L. et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. Ann. Intern. Med. 1995; 123: 161–167.
37. Carson K.L., Tran T.T., Cotton P., Sharara A.I, Hunt C.M. Pilot study of the use of naltrexone to treat the severe pruritus of cholestatic liver disease. Am. J. Gastroenterol. 1996; 91: 1022–1023.
38. Juby L.D., Wong V.S., Losowsky M.S. Buprenorphine and hepatic pruritus. Br. J. Clin. Pract. 1994; 48: 331.
39. Reddy L., Krajnik M., Zylicz Z. Transdermal buprenorphine may be effective in the treatment of pruritus in primary biliary cirrhosis. J. Pain Symptom Manage 2007; 34: 455–456.
40. Jones E.A., Zylicz Z. Treatment of pruritus caused by cholestasis with opioid antagonists. J. Palliat. Med. 2005; 8: 1290–1294.
41. Krajnik M., Adamczyk A., Zylicz Z. Transdermal buprenorphine ameliorated pruritus complicating advanced hepatocellular cancer. Adv. Palliative Medicine 2007; 6: 83–86.
42. Zylicz Z., Smits C., Krajnik M. Paroxetine for pruritus in advanced cancer. J. Pain Symptom Manage 1998; 16: 121–124.
43. Zylicz Z., Krajnik M., Sorge A.A., Costantini M. Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. J. Pain Symptom Manage 2003; 26: 1105–1112.
44. Mayo M.J., Handem I., Saldana S., Jacobe H., Getachew Y., Rush A.J. Sertraline as a first-line treatment for cholestatic pruritus. Hepatology 2007; 45: 666–674.
45. Diehn F., Tefferi A. Pruritus in polycythaemia vera: prevalence, laboratory correlates and management. Br. J. Haematol. 2001; 115: 619–621.
46. Tefferi A., Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. Blood 2002; 99: 2627.
47. Chatila R., Bergasa N.V, Lagarde S., West A.B. Intractable cough and abnormal pulmonary function in benign recurrent intrahepatic cholestasis. Am. J. Gastroenterol. 1996; 91: 2215–2219.
48. Zylicz Z., Krajnik M. What has dry cough in common with pruritus? Treatment of dry cough with paroxetine. J. Pain Symptom Manage 2004; 27: 180–184.
49. Schworer H., Ramadori G. Treatment of pruritus: a new indication for serotonin type 3 receptor antagonists. Clin. Investig. 1993; 71: 659–662.
50. Raderer M., Muller C., Scheithauer W. Ondansetron for pruritus due to cholestasis. N. Engl. J. Med. 1994; 330: 1540.
51. Quigley C. 5HT3 receptor antagonists and pruritus due to cholestasis. Palliat. Med. 1996; 10: 54.
52. O'Donohue J.W., Pereira S.P., Ashdown A.C., Haigh C.G.,

Wilkinson J.R., Williams R. A controlled trial of ondansetron in the pruritus of cholestasis. Aliment. Pharmacol. Ther. 2005; 21: 1041–1045.
53. Jones E.A. Pruritus and fatigue associated with liver disease: is there a role for ondansetron? Expert Opin. Pharmacother. 2008; 9: 645–651.
54. Jones E.A., Bergasa N.V. The pathogenesis and treatment of pruritus and fatigue in patients with PBC. Eur. J. Gastroenterol. Hepatol. 1999; 11: 623–631.
55. Pirat A., Tuncay S.F., Torgay A., Candan S., Arslan G. Ondansetron, orally disintegrating tablets versus intravenous injection for prevention of intrathecal morphine-induced nausea, vomiting, and pruritus in young males. Anesth. Analg. 2005; 101: 1330–1336.
56. Kyriakides K., Hussain S.K., Hobbs G.J. Management of opioid-induced pruritus: a role for 5-HT3 antagonists? Br. J. Anaesth. 1999; 82: 439–441.
57. Davis M.P., Frandsen J.L., Walsh D., Andresen S., Taylor S. Mirtazapine for pruritus. J. Pain Symptom Manage 2003; 25: 288–291.
58. Van Gool A.R., Bannink M., Stronks D.L., Vos M.S. Re: Mirtazapine in cancer patients. J. Pain Symptom Manage 2003; 25: 7–8.
59. Hoensch H.P., Balzer K., Dylewizc P., Kirch W., Goebell H., Ohnhaus E.E. Effect of rifampicin treatment on hepatic drug metabolism and serum bile acids in patients with primary biliary cirrhosis. Eur. J. Clin. Pharmacol. 1985; 28: 475–457.
60. Ghent C.N., Carruthers S.G. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. Gastroenterology 1988; 94: 488–493.
61. Bueller H.A., Bernhard J.D., Dubroff L.M. Gabapentin treatment for brachioradial pruritus. J. Eur. Acad. Dermatol. Venereol. 1999; 13: 227–228.
62. Stander S., Weisshaar E., Luger T.A. Neurophysiological and neurochemical basis of modern pruritus treatment. Exp. Dermatol. 2008; 17: 161–169.
63. Winhoven S.M., Coulson I.H., Bottomley W.W. Brachioradial pruritus: response to treatment with gabapentin. Br. J. Dermatol. 2004; 150: 786–787.
64. Demierre M.F., Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. J. Am. Acad. Dermatol. 2006; 55: 543–544.
65. Manenti L., Vaglio A. Gabapentin for uraemic pruritus. Nephrol. Dial. Transplant. 2005; 20: 1278–1279.
66. Manenti L., Vaglio A., Borgatti P.P. Gabapentin as a therapeutic option in uremic pruritus. Kidney Int. 2008; 73: 512, author reply — 3.
67. Yesudian P.D., Wilson N.J. Efficacy of gabapentin in the management of pruritus of unknown origin. Arch. Dermatol. 2005; 141: 1507–1509.
68. Elkersh M.A., Simopoulos T.T., Malik A.B., Cho E.H., Bajwa Z.H. Epidural clonidine relieves intractable neuropathic itch associated with herpes zoster-related pain. Reg. Anesth. Pain. Med. 2003; 28: 344–346.
69. Yosipovitch G., Samuel L.S. Neuropathic and psychogenic itch. Dermatol. Ther. 2008; 21: 32–41.
70. Twycross R., Greaves M.W., Handwerker H. et al. Itch: scratching more than the surface. QJM 2003; 96: 7–26.
71. Dahl V., Hagen I., Koss K.S., Nordentoft J., Raeder J.C. Bupivacaine 2.5 mg/ml versus bupivacaine 0.625 mg/ml and sufentanil l microg/ml with or without epinephrine 1 microg/ml for epidural analgesia in labour. Int. J. Obstet. Anesth. 1999; 8: 155–160.
72. Eriksson S.L., Frykholm P., Stenlund P.M., Olofsson C. A comparison of three doses of sufentanil in combination with bupivacaine-adrenaline in continuous epidural analgesia during labour. Acta Anaesthesiol. Scand 2000; 44: 919–923.
73. Alhashemi J.A., Crosby E.T., Grodecki W., Duffy P.J., Hull K.A., Gallant C. Treatment of intrathecal morphine-induced pruritus following caesarean section. Can. J. Anaesth. 1997; 44: 1060–1065.
74. Sun H.L., Wu C.C., Lin M.S., Chang C.F. Effects of epidural morphine and intramuscular diclofenac combination in postcesarean analgesia: a dose-range study. Anesth. Analg. 1993; 76: 284–288.
75. Cardoso M.M., Carvalho J.C., Amaro A.R., Prado A.A., Cappelli E.L. Small doses of intrathecal morphine combined with systemic diclofenac for postoperative pain control after cesarean delivery. Anesth. Analg. 1998; 86: 538–541.