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

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
may influence opioidergic tone. And this is the clue to understanding opioidergic tone. Endogenous opioids [27]. In this way cholestyramine can be toxic and cause persistent itch [16–18].

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 pathognomonic 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 policythemia 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 serotonergic system**

We do not know exactly how serotonergic 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,
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 subcutaneous 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 HT3 receptor antagonists appeared to be anti-pruritic 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 machine 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 the dose can be gradually 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 spinaly. 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.

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