Case report

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Itraconazole therapy in a pancreatic adenocarcinoma patient: A case report

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Abstract

Objective: To report the case of a patient receiving itraconazole for the treatment of histoplasmosis and his subsequent reduction in pancreatic tumor size.

Case summary: A 64-year-old male was diagnosed with Stage III locally advanced unresectable pancreatic adenocarcinoma. The patient was administered radiation plus chemotherapy, which included cisplatin and capecitabine. Upon restaging, the patient's tumor was again determined to be unresectable; therefore, palliative chemotherapy treatments were initiated, which included gemcitabine and erlotinib. After two gemcitabine cycles, he was admitted to the hospital because of loss of motor function due to spinal cord hemisection. After the surgery, the patient became neutropenic because of previous chemotherapy cycle and developed disseminated histoplasmosis. After he received his nine-month course of itraconazole, the pancreatic cancer was readdressed and he was then deemed to be resectable and had a Whipple procedure. Over the next several years, he showed no evidence of pancreatic metastases or relapse.

Discussion: Itraconazole has been shown to have many mechanisms by which it could potentially suppress tumor cell growth, which includes inhibition of the Hedgehog pathway, vascular endothelial growth factor receptor-2, and P-glycoprotein efflux pump. This azole antifungal has been studied in small patient populations with various types of cancers. Studies of basal cell carcinoma, nonsmall cell lung cancer, ovarian cancer, and malignant pleural mesothelioma have shown favorable results suggesting that more study of itraconazole is warranted to decide its clinical utility.

Conclusion: There would need to be much more research performed to determine if this agent had a role as a chemotherapy agent; however, health care professionals should be aware of itraconazole's potential antineoplastic mechanisms.

Keywords

Cancer, oncology, itraconazole, antifungal, histoplasmosis, infection

Introduction/objective

Pancreatic adenocarcinoma is the fourth most common cancer-related death in the US among both men and women.[1] Pancreatic cancer carries a reputation of a poor prognosis because of its difficulty to manage successfully with the present treatment modalities. Tumors that are determined to be resectable are often associated with a better prognosis; however, most pancreatic cancers are not symptomatic until they are in advanced stages and are less likely to be removed successfully by surgery.[1]

For patients with locally advanced unresectable pancreatic adenocarcinoma, capecitabine is indicated for use in patients without metastases[1,2] and cisplatin is suggested as a preferred option if the cancer has a potential hereditary link.[1,3] It has been widely studied that gemcitabine is a backbone in many treatment regimens for pancreatic cancer[4] and has been shown to be superior in improving overall survival when used in combination with erlotinib.[5,6] For the significance of

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this particular case report, it is noted that there are no azole antifungal agents that are included anywhere in the potential treatment of any stage of pancreatic adenocarcinoma.[1]

Itraconazole is an oral azole antifungal agent that has broad coverage that includes infections, such as aspergillosis, blastomycosis, and histoplasmosis. There is no labeled or unlabeled indication for this medication that is related to cancer. Itraconazole has a relatively benign side effect profile, with nausea and diarrhea being the most common issues patients' experience. It does have significant drug interactions due to its strong inhibition of CYP3A4 and P-glycoprotein efflux pump.[7]

The purpose of the following case report is to describe a patient who was treated for histoplasmosis with itraconazole therapy and subsequently saw a reduction in size of his pancreatic tumor without additional chemotherapy. A literature search was conducted in PubMed from 1950 to present with the following MeSH terms used in various combinations: pancreatic cancer, azole antifungals, itraconazole, Hedgehog pathway, cancer, and ketoconazole. The National Comprehensive Cancer Network (NCCN) guidelines were also examined for pancreatic adenocarcinoma. Although potentially plausible for an azole antifungal, like itraconazole, to be effective in the treatment of pancreatic cancer because of its mechanisms of action, there was no specific literature found that would support this idea.

Case description

A 64-year-old white male patient presented to a PCP office visit after developing vague upper abdominal epigastric discomfort, primarily after eating. He complained of increased gas and alternating constipation with diarrhea. His past medical history included hypertension, type II diabetes, peripheral neuropathy, and hyperlipidemia. His surgical history is significant for laminectomy of the lumbar spine and left inguinal hernia repair seven years prior. Pertinent family history is a brother who died at the age of 64 of pancreatic cancer, a father who died at 95 following complications from a hip fracture, and a mother who died at 76 with renal failure. Besides an aunt with ovarian cancer, there is no other history of malignancy within the family. He was a retired mechanic from a large fire department, married, with three kids, with an approximately 50-pack year smoking history but did not smoke at presentation.

Due to the patient's insistence based on his brother's passing, a computed tomography (CT) scan of the abdomen and pelvis was performed, revealing a 3 cm × 4 cm mass on the pancreatic head with dilation of the pancreatic duct. A fine needle biopsy was performed and resulted in pancreatic adenocarcinoma. At initial staging, he was Stage III, T4, N1, M0. His Carbohydrate Antigen 19-9 level was 189 units/ml (0–37 units/ml). His Karnofsky performance status was 80, but the pancreatic mass was deemed unresectable at this time, so preoperative radiation therapy with capecitabine and cisplatin was initiated. After 25 radiation treatments over five weeks with 4500 centiGray to the tumor, daily capecitabine, and two cycles of cisplatin, restaging was performed and still considered to be unresectable pancreatic cancer. At this point, the patient began palliation treatment with gemcitabine and erlotinib.

Approximately one month after starting palliative treatments, an MRI was done that showed spondylosis of the thoracic spine and severe cord compression at the C6–C7 vertebrae. Nearly one month after the scan, he presented to the emergency department with complaints of weakness in the left upper and lower extremities and a fever. At this point, the patient was transferred to another facility where he had an emergent anterior cervical discectomy and interbody fusion of the C6–C7 vertebrae because of cervical myelopathy with stenosis. This was considered an episode of Brown-Sequard Syndrome.

Status post surgery, the patient is still febrile and neutropenic from recent cycle of gemcitabine and, therefore, is placed on broad-spectrum antimicrobial coverage. Initially, he was placed on vancomycin, cefepime, and ciprofloxacin, but this was later changed to vancomycin, merropenem, ciprofloxacin, and fluconazole to include fungal and more resistant bacterial pathogens. A more complete listing of his medications during his hospital stay is located in Table 1. After several days of fever and no significant clinical improvement, a CT scan of the abdomen shows evidence of an atypical or fungal infectious process in the left lower lobes of the lungs. At this point, he became septic with sinus tachycardia and a fever. A bronchoalveolar lavage was subsequently performed and the respiratory culture tested positive for histoplasmosis. From this culture, he was placed on itraconazole 200 mg PO daily. For the remaining 21 days of this hospital stay, he saw clinical improvement to a stable condition. He did experience some elevation in his liver function enzymes, but they were returning to normal upon discharge. At discharge, he was expected to complete a nine-month course of itraconazole 200 mg PO daily to treat the disseminated histoplasmosis.

Through the months of treating the histoplasmosis infection, treating the pancreatic cancer was put on hold. When it was finally readdressed, PET/CT showed that the tumor on the head of the pancreas had shrunk and was now considered resectable. He subsequently had a Whipple procedure done to

Table 1. Medication therapy of this patient during his hospital stay.

Drug	Dose/route/ frequency	Duration (hospital days)
Amphotericin B lipid complex	390 mg IV q24h	Day 16–29
Caspofungin	70 mg IV ×1 dose	Day 10
	50 mg IV q24h	Day 11–13
Cefazolin	1 g IV ×1 dose	Day 5
Cefepime	2 g IV q8h	Day 5–6
Ciprofloxacin	400 mg IV q12h	Day 5–20
Demeclocycline	300 mg PO q6h	Day 12–39
Erlotinib	50 mg PO BID	Day 2–5
Neupogen	480 mcg SC daily	Day 6–12
Fluconazole	400 mg IV ×1 dose	Day 6
	200 mg IV daily	Day 7–10
Hydrocortisone	100 mg TID	Day 20–22
	100 mg BID	Day 23
	50 mg BID	Day 24
	50 mg daily	Day 25–26
Itraconazole	200 mg PO daily	Day 15–16, 29–41
Meropenem	1 g IV q8h	Day 6–20
Vancomycin	1 g IV q12h	Day 5–11
	1.5 g IV q12h	Day 11–15
Voriconazole	470 mg IV q12h	Day 13–14
	310 mg IV q12h	Day 14–15

remove the tumor. Regular PET/CT scans have shown no relapse or metastases until approximately four years later when the patient reported new complaints of weight loss. This scan showed a new finding of left lower lobe pulmonary nodule, previously negative on PET/CT. This was suspected to be metastatic pancreatic disease or a second primary lung cancer tumor. Upon biopsy, this nodule was determined to be a left lower lung bronchoalveolar nonsmall cell lung cancer Stage pT2b, pN0, M0, Stage IIA, not a pancreatic cancer metastasis. Soon after the diagnosis, the patient had a left lower lungectomy showing a 6 cm × 4 cm nodule with margins negative within 1 cm of incision. The patient at that point did not wish to pursue adjuvant chemotherapy.

Discussion/literature review

The objective of this unique case is to describe a patient who was receiving palliative treatment for locally advanced, unresectable pancreatic cancer with gemcitabine and erlotinib. He became neutropenic following his third gemcitabine cycle and subsequently developed disseminated histoplasmosis. His chemotherapy treatments were put on hold while he was treated with a nine-month course of itraconazole. Upon restaging of pancreatic cancer, his tumor had shrunk and he was considered eligible for resection with a Whipple procedure. This is suspected to be due to the itraconazole treatment, since his chemotherapy was stopped during the histoplasmosis treatment and the inhibitory mechanisms of itraconazole.

As the genetic mechanisms that control different cancers are better understood, the options for treating these cancers have the potential to broaden. One particular instance of this type of research comes by examining the effects of azole antifungals, such as ketoconazole and itraconazole, on specific cancers and the suspected mechanisms by which they work.

For many years, ketoconazole has played an effective role in advanced stage castration-recurrent prostate cancer as an androgen synthesis inhibitor.[8] Because of the unexpected use of ketoconazole here and new information that has been published, the use of another azole antifungal, itraconazole, and its potential antineoplastic effects are being examined further. Itraconazole has been shown to inhibit the Hedgehog pathway, which is a critical signaling pathway for some progenitor cells that are active in tumors.[9–12] Inhibiting the Hedgehog pathway may assist in halting cancer stem cells from overproduction. Itraconazole has also been shown to have another possible mechanism for suppressing solid tumors, which is its inhibition of angiogenesis[10,13,14] by inhibiting the vascular endothelial growth factor receptor-2 (VEGFR2).[15] By inhibiting VEGFR2, itraconazole could possess the ability to stop the generation of new blood vessels to the growing tumor, therefore, disrupting its supply of nutrients. It has been suggested that itraconazole has the potential to enhance the efficacy of other cytotoxic chemotherapy[13] via reversal of P-glycoprotein-mediated resistance to specific chemotherapy agents, such as docetaxel, paclitaxel, doxorubicin, daunorubicin, and vinblastine.[14] P-glycoprotein is an efflux pump by which some cancer cells are able to actively pump the cytotoxic agents outside of the cell. Since itraconazole is a P-glycoprotein inhibitor, it has the potential to disrupt the efflux of the chemotherapy agent, hence, increasing its efficacy.

Itraconazole has been through some preliminary testing in small cancer patient subsets and has shown potential in the clinical setting. Some foundational work was conducted in 2010 by showing that itraconazole antagonizes Hedgehog signaling, which suppressed the growth of medulloblastoma in murine models.[16] This led to a a Phase II trial using itraconazole in basal cell carcinoma, which showed that one month of itraconazole therapy gave a reduction in size of the tumors via inhibition of the Hedgehog pathway.[9] In 2012, research at John Hopkins University was published on itraconazole showing that it demonstrated

multiple modalities of inhibiting angiogenic stimulatory pathways in vitro and in vivo,[17] which resulted in another Phase II trial comparing pemetrexed versus pemetrexed plus itraconazole as second-line therapy in metastatic nonsquamous nonsmall cell lung cancer. This trial showed trends suggestive of improved disease control in the pemetrexed plus itraconazole arm of the study.[13] Another study attempted to examine itraconazole treatment for advanced prostate cancer, but was only successful in showing that high dose (600 mg daily) had modest activity.[10] Another study looked at chemotherapy versus chemotherapy plus itraconazole in patients with refractory ovarian cancer. They were able to show promising statistically significant results for these patients with adjunct itraconazole.[14] One last in vitro study looks at itraconazole plus arsenic trioxide activity for the Hedgehog pathway against malignant pleural mesothelioma cells and suggests that this is an effective combination that could be used clinically.[18]

Case summary/conclusion

This case study depicts a patient who developed Stage III pancreatic adenocarcinoma that was considered unresectable and after palliative chemotherapy became immunocompromised. He had a hospital stay that included complex spinal complications and disseminated histoplasmosis, which was treated with nine months of itraconazole therapy. At completion of his itraconazole therapy, the pancreatic tumor was now resectable. This reduction in size of his pancreatic adenocarcinoma was decided to be due to the inhibition of the Hedgehog pathway by the itraconazole. This Hedgehog pathway inhibition is an understood mechanism of itraconazole, but the use of this azole antifungal in pancreatic cancer is not currently documented in the literature. There is still much research remaining to determine if itraconazole may have a place in cancer chemotherapy, but the potential of this agent has been demonstrated in this particular case report.

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Conflict of interests

None declared.

References

1. Tempero MA, Malafa MP, Behrman SW, et al. Pancreatic adenocarcinoma. National Comprehensive Cancer Network (NCCN) guidelines. Version 2.2014, nccn.org (accessed 29 August 2014).
2. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; 27: 5513–5518. DOI: 10.1200/JCO.2009.24.2446.
3. Oliver GR, Sugar E, Laheru D, et al. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma [abstract]. *Presented at 2010 ASCO Gastrointestinal Cancer Symposium*, 22–24 January 2010. Orlando, FL. Abstract 180.
4. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000–01 FFCD/SFRO study. *Ann Oncol* 2008; 19: 1592–1599. DOI: 10.1093/annonc/mdn281.
5. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; 25: 1960–1966. DOI: 10.1200/JCO.2006.07.9525.
6. Lee JN, Waddell JA and Solimando DA. Cancer chemotherapy update: gemcitabine and erlotinib (GE) regimen for pancreatic cancer. *Hosp Pharm* 2012; 47: 19–23. DOI: 10.1310/hpj4701-19.
7. Itraconazole: Drug information. LexiComp Online (accessed 5 August 2014).
8. Mohler JL, Kantoff PW, Armstrong AJ, et al. Prostate cancer. National Comprehensive Cancer Network (NCCN) guidelines. Version 2.2014, nccn.org (accessed 29 August 2014).
9. Kim DJ, Kim J, Spaunhurst K, et al. Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. *J Clin Oncol* 2014; 32: 745–751. DOI: 10.1200/JCO.2013.49.9525.
10. Antonarakis ES, Heath EI, Smith DC, et al. Repurposing itraconazole as a treatment for advanced prostate cancer: a noncomparative randomized phase II trial in men with metastatic castration-resistant prostate cancer. *The Oncologist* 2013; 18: 163–173. DOI: 10.1634/theoncologist.2012-314.
11. Kim J, Aftab BT, Tang JY, et al. Itraconazole and arsenic trioxide inhibit Hedgehog pathway activation and tumor growth associated with acquired resistance to smoothened antagonists. *Cancer Cell* 2013; 23: 23–34. DOI: 10.1016/j.ccr.2012.11.017.
12. Merchant AA and Matsui W. Targeting Hedgehog—a cancer stem cell pathway. *Clin Cancer Res* 2010; 16: 3130–3140. DOI: 10.1158/1078-0432.CCR-09-2846.
13. Rudin CM, Brahmer JR, Juergens RA, et al. Phase 2 study of pemetrexed and itraconazole as second-line therapy for metastatic nonsquamous non-small-cell lung cancer. *J Thoracic Oncol* 2013; 8: 619–623. DOI: 10.1097/JTO.0b013e31828c3950.
14. Tsubamoto H, Sonoda T, Yamasaki M, et al. Impact of combination chemotherapy with itraconazole on survival

of patients with refractory ovarian cancer. *Anticancer Res* 2014; 34: 2481–2488.
15. Nacev BA, Grassi P, Dell A, et al. The antifungal drug itraconazole inhibits vascular epithelial growth factor receptor 2 (VEGFR2) glycosylation, trafficking, and signaling in endothelial cells. *J Biol Chem* 2011; 286: 44045–44056. DOI: 10.1074/jbc.M111.278754.
16. Kim J, Tang JY, Gong R, et al. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer Cell* 2010; 17: 388–399. DOI: 10.1016/j.ccr.2010.02.027.
17. Aftab BT, Dobromilskaya I, Liu JO, et al. Itraconazole inhibits angiogenesis and tumor growth in non-small cell lung cancer. *Cancer Res* 2011; 71: 6764–6772. DOI: 10.1158/0008-5472.CAN-11-0691.
18. You M, Varona-Santos J, Singh S, et al. Targeting of the Hedgehog signal transduction pathway suppresses survival of malignant pleural mesothelioma cells in vitro. *J Thoracic Cardiovasc Surg* 2014; 147: 508–516. DOI: 10.1016/j.jtcvs.2013.08.035.