Case Report

Near 5-year survival in metastatic pancreatic cancer patient with ROS1 rearrangement, HER2 amplification, and KRAS G12C mutation—a case report

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Background: Pancreatic cancer is a significant cause of cancer-related deaths in Canada. Although it is less common than other cancers, the mortality rate has remained high and stable since 1984, with a five-year net survival rate being the lowest of 23 reported cancers. The limited options for detection and treatment contribute to the high mortality rate. A developing area of treatment is tumour site agnostic targeted therapy, where patients' cancer is treated based on genomic alterations that are amenable to targeted agents, regardless of where the tumour originated.

Case Description: A 52-year-old man with no prior medical history presented with anemia, intermittent fatigue, post-prandial indigestion, and bloating, and 8–10 lbs of unintentional weight loss over a 1-year period. A computed tomography scan of the abdomen revealed pancreatic ductal adenocarcinoma and diffuse liver metastasis. He received multiple local and non-targeted systemic therapies. Serial genomic analyses sequentially revealed c-ros oncogene 1 (ROS1) receptor tyrosine kinase rearrangement, human epidermal growth factor receptor 2 (HER2) amplification, and Kirsten rat sarcoma virus (KRAS) G12C mutation throughout his journey, none of which were present at diagnosis. Each new genomic alteration prompted treatment change. Concurrent with systemic therapy, the patient also received numerous local treatments, including hepatic transarterial chemoembolization, Yttrium 90, Whipple procedure, stereotactic body radiation therapy, and CyberKnife. Over the course of the disease, metastases were found in the lungs, brain, and kidneys. Despite this, the patient had periods of remarkable response and quality of life evidenced by his cycling tour of France. However, nearly five years from diagnosis, the patient elected to pursue supportive care and died from his cancer.

Conclusions: This case report demonstrates the importance of repeat genomic analyses in the treatment of advanced cancer and timely access to targeted therapy. The clinical impact of utilizing a tumor-agnostic treatment approach based on these genomic alterations has the potential to yield a strong response both in survival and quality of life.

Keywords: Metastatic pancreatic cancer; genomic analysis; c-ros oncogene 1 (ROS1); human epidermal growth factor receptor 2 (HER2); Kirsten rat sarcoma virus (KRAS); case report

Submitted May 10, 2023. Accepted for publication Aug 31, 2023. Published online Sep 25, 2023.
doi: 10.21037/jgo-23-190
View this article at: https://dx.doi.org/10.21037/jgo-23-190

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Introduction

Background

Pancreatic cancer is the third leading cause of cancer-related death in Canada, with an incidence rate of 14.2 per 100,000 and a mortality risk of 12.2 per 100,000 in 2022 (1,2). Although it is relatively less commonly diagnosed compared to other cancers, such as lung, breast, and prostate, the annual percent change in age standardized mortality rate has remained high and stagnant between 1984 and 2019, only changing 0.1 and –0.1 for men and women, respectively (1). The five-year net survival for pancreatic cancer is 10%, the lowest of 23 reported cancers in the Canadian Cancer Registry database (1).

Rationale and knowledge gap

Contributing to the high mortality rate are the limited options for detection and treatment. Anatomically, the pancreas is deep within the abdomen, which can allow the cancer to progress until the patient presents with symptoms (3,4). Often, when signs and symptoms are present, the cancer has progressed to a stage where surgical resection with curative intent is not possible (3). When it is diagnosed, the cancer is often metastatic, commonly to the liver (3). For patients with metastatic disease, there is a dichotomy of competing interests between prolonging life and maintaining quality of life. As an example, chemotherapy with gemcitabine and nab-paclitaxel offers a modest median survival benefit of 8.7 months, while the regimen of 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) offers greater median survival benefit of 11.1 months but is associated with increased toxicity (5,6).

An area of research and clinical trial interest is tumour site agnostic treatment based on tumor genomics. An example of such a trial is the Targeted Agent and Profiling Utilization Registry (TAPUR) Study that aims to investigate FDA-approved treatments that may have activity in non-approved tumor sites based on tumor genomics (7). Similarly, the Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR/PM.1) is an open-label basket trial seeking to match patients with their genetic variants to their respective commercially available targeted agents (8). Another basket trial is the MyPathway trial investigating targeted agents administered to patients with a variety of cancers where agents are paired to patients' genetic profiles, as an example using anti-human epidermal growth factor receptor 2 (HER2) treatments traditionally used in breast cancers for HER2-amplified metastatic colorectal cancer (9). This approach to advanced cancers can be applied for patients with metastatic pancreatic cancer who have targetable genetic biomarkers.

Objective

Given the limited therapeutic options combined with the poor prognosis of metastatic pancreatic cancer, we sought to document a unique case report of a patient who elected an arduous journey of aggressive therapy that encompasses over 30 treatments including transhepatic arterial chemoembolization (TACE), Whipple's, radiofrequency ablation (RFA) to the kidney, liver wedge resection, CyberKnife neurosurgery, numerous monoclonal antibodies, as well as traditional chemotherapies. The culmination of the procedures and treatments offered the patient nearly 5 years survival from initial diagnosis with pancreatic ductal adenocarcinoma with diffuse liver metastasis. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-190/rc).

Highlight box

Key findings

- Repeat genomic analyses in the treatment of advanced pancreatic cancer and timely access to targeted therapy has yielded a strong response, survival, and quality of life.

What is known and what is new?

- The five-year net survival for all pancreatic cancer is 10%, the lowest of 23 reported cancers in the Canadian Cancer Registry database.
- This case report describes a personalized treatment approach to pancreatic ductal adenocarcinoma with diffuse liver metastasis that offered nearly 5 years survival from initial diagnosis.

What is the implication, and what should change now?

- Tumour site agnostic treatment exploiting genomic alterations can potentially offer improved survival and quality of life.

Case presentation

A 52-year-old Caucasian man with no prior medical history, beyond arthroscopic surgery on his knee, was found to have normocytic normochromic anemia on routine full physical, accompanied with intermittent fatigue, indigestion and

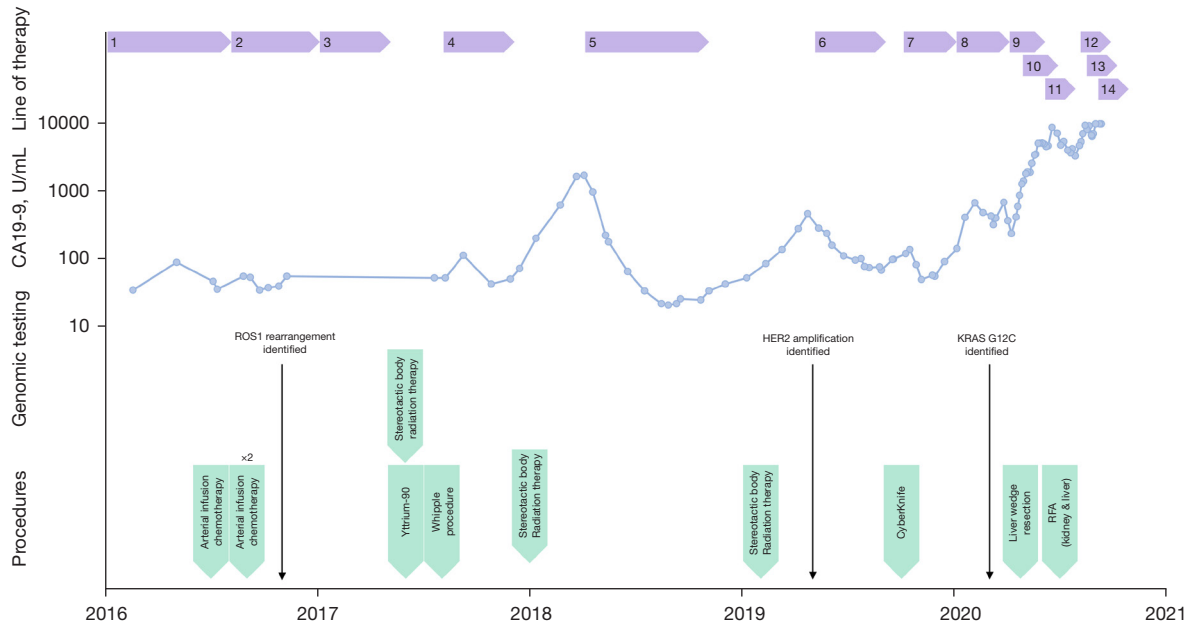

Figure 1 Timeline describing the patient's line of therapy, tumour marker response, genomic testing, and local procedures. Line of therapy: 1, gemcitabine, nab-paclitaxel, demcizumab/placebo; 2, FOLFIRINOX; 3, entrectinib; 4, brigatinib; 5, lorlatinib; 6, trastuzumab, pembrolizumab, capecitabine, oxaliplatin; 7, lorlatinib, trastuzumab, pemetrexed; 8, lorlatinib, trastuzumab, gemcitabine, docetaxel, capecitabine; 9, KRAS G12C inhibitor; 10, trastuzumab, pertuzumab, capecitabine, oxaliplatin; 11, bevacizumab, capecitabine, oxaliplatin, pembrolizumab, trastuzumab; 12, trastuzumab, capecitabine, docetaxel; 13, osimertinib; 14, trastuzumab deruxtecan. CA19-9, carbohydrate antigen; ROS1, c-ros oncogene 1; HER2, human epidermal growth factor receptor 2; KRAS, Kristen rat sarcoma virus; G, guanine; C, cytosine; RFA, radiofrequency ablation; FOLFIRINOX, 5-fluorouracil, irinotecan and oxaliplatin.

bloating after meals, and 8–10 lbs of unintentional weight loss over a 1-year period. A colonoscopy and an upper gastrointestinal endoscopy were performed yielding no explanation for anemia; thus, a computerized tomography (CT) scan of his abdomen was ordered. The scan revealed a large pancreatic head tumor mass with diffuse liver metastasis with approximately 30% of liver replaced by tumor. Gemcitabine, nab paclitaxel, demcizumab/placebo, a monoclonal antibody targeting Delta-like ligand 4, was initiated as first line treatment (10) (*Figure 1*). At the end of 5 months, the treatment was stopped due to progressive disease evidenced on CT. The patient then began full dose FOLFIRINOX therapy and received three rounds of TACE overseas (mitomycin, gemcitabine, cisplatin, lipiodol, embocept).

Five months into his second line treatment, a subsequent genomic analysis revealed a c-ros oncogene 1 (ROS1), receptor tyrosine kinase rearrangement. The new genomic analysis coupled with only a minor tumor response from FOLFIRINOX prompted a therapy switch to target ROS1 using entrectinib. The patient tolerated the new treatment well, however a CT showed evidence of subtle progression at 5 months. This prompted the initiation of aggressive local treatment using Yttrium 90 for the liver and stereotactic body radiation therapy for the pancreas. The left liver received 22.1 Gy, right liver received 33.7 Gy. This was followed two months later by Whipple's procedure. A block specimen collected during the Whipple's procedure confirmed a solute carrier family 4 member 4 (SLC4A4)-ROS1 fusion prompting re-initiation of a targeted therapy using brigatinib, an inhibitor of multiple tyrosine kinases including ROS1 and anaplastic lymphoma kinase (ALK). Notably, the analysis did not detect KRAS mutation nor HER2 amplification. Cyclin-dependent kinase inhibitor 2A (*CDKN2A)* $p16^{INK4a}$ H83Y and $p14^{ARF}$ A97V mutations were detected at this analysis but did not affect the treatment plan. Brigatinib was well tolerated, and the patient retained a remarkably excellent performance status, being able to keep up with instrumental activities of regular living and with hobbies, such as playing squash and cycling.

However, in the coming 4–5 months, he developed a new mild chest pain that prompted a CT revealing a central 1 cm nodule in the right middle lobe. The 1 cm nodule was treated with stereotactic ablative radiotherapy of 60 Gy in 8 fractions. Over the next months, the patient's carbohydrate antigen (CA19-9) steadily increased, and CT revealed progressive disease prompting a switch to a novel therapy, lorlatinib, which is a selective inhibitor of ALK and ROS1 tyrosine kinases (11). The patient's response to lorlatinib was remarkable, showing a precipitous decline of CA19-9 and shrinking tumours. He remained on this monotherapy for 8 months, at the end of which positron emission tomography CT (PET/CT) revealed growing lung nodules. A lower left paratracheal lymph node was biopsied and a HER2 amplification was detected by fluorescence *in situ* hybridization (FISH) with a ratio of 4.7 HER2 to centromeric region of chromosome 17 (CEP17). At this time, the patient was discussed at multidisciplinary rounds, and an approach of systemic therapy with gentle local treatment was recommended. Following the recommendation, a new combination therapy was initiated consisting of capecitabine, oxaliplatin, pembrolizumab, and trastuzumab. He responded well with minimal impact to his quality of life, keeping up with an active lifestyle by going on a one-week cycling tour abroad a month after initiating treatment.

This regimen was continued for 6 months until a new focal metastasis in the brain developed. This was a 6 mm lesion in the right parietal cortex just anterior to the central sulcus evidenced on magnetic resonance imaging (MRI). The lesion was treated with CyberKnife radiosurgery. This new brain metastasis also prompted a change of therapy reintroducing lorlatinib, due to its high central nervous system penetrance, in combination with trastuzumab and pemetrexed (11). After three months of this treatment, two new liver metastases were found on CT prompting a slight modification removing pemetrexed and adding gemcitabine and capecitabine while retaining lorlatinib and trastuzumab. However, on day 11 of the new regimen, the patient developed pancytopenia and the treatment was stopped. Genomic analysis of cell-free deoxyribonucleic acid (cfDNA) was repeated using peripheral blood, revealing a 21.5% cfDNA KRAS G12C mutation and 2.5 plasma copies of KRAS amplification. These alterations were investigated previously and only were found to be positive at the present analysis. Interestingly, this peripheral blood genomic analysis was unable to detect any ROS1 rearrangement or HER2 amplification. With these new genomic alterations identified the patient was initiated on an experimental KRAS G12C inhibitor. Unfortunately, despite a stark decrease of his CA19-9 from 692 to 240 in less than 2 weeks, the patient experienced drug-induced liver injury with marked elevation of his transaminases and treatment was discontinued. Over the following months, numerous local procedures and systemic therapies were initiated. A liver wedge resection and RFA of a renal mass were undertaken. The KRAS G12C inhibitor was re-initiated and promptly discontinued due to intolerable liver injury. A combination of capecitabine, oxaliplatin, trastuzumab, pertuzumab, and bevacizumab was attempted with no objective response seen. Osimertinib and trastuzumab deruxtecan treatments were also initiated without any objective response seen. Simultaneously, optimal supportive care efforts were undertaken including a celiac plexus nerve block and pleural catheter for reactive pleural effusion post renal ablation. Ultimately, the patient decided to focus on quality of life and passed from the cancer with family at his side shortly after discontinuing systemic therapies.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The five-year net survival for pancreatic cancer is 10%, the lowest of 23 reported cancers in the Canadian Cancer Registry database (1). This case report features a patient who uniquely was able to access a vast multitude of systemic and locally aggressive treatments that offered nearly a 5-year survival from diagnosis of pancreatic ductal adenocarcinoma with diffuse liver metastasis at initial presentation. Normally in the case of metastatic disease, a patient will be ineligible for surgical resection and will instead begin their palliative journey with medical management. Standard medical therapy in our institution is either FOLFIRINOX or gemcitabine and nab-paclitaxel, which are both chemotherapy-based regimens. In the literature, randomized controlled trials show median survival benefit of 11.1 months, and 8.7 months for these regimens respectively, which is far less than is documented in this case report (5,6). Targeted therapy is a separate class of anti-cancer agents that selectively bind to protein targets

that contribute to the proliferation, evasion, or spread of cancerous cells. In recent years, targeted non-cytotoxic-based therapy has become increasingly prevalent; yet, the advances seen in lung, colorectal, and breast cancers for example have not been observed in the pancreatic setting. Nonetheless, targeted therapeutics have been used in pan solid tumor settings given that cancer has an identified and targetable genomic marker, such as ROS1 rearrangement, KRAS G12C, and HER2 amplification as observed in this case report. The ROS1 gene, a proto-oncogene, is a well-reported marker found in a multitude of tumour lines including lung and pancreas (12). Presently, there are numerous Health Canada approved ROS1 targeting agents used to treat non-small cell lung cancer (NSCLC) including entrectinib, brigatinib, and lorlatinib, yet none are approved with a tumour agnostic indication or specifically for pancreatic cancer (13-15). Similarly, KRAS G12C and HER2 amplification are also proto-oncogene alterations that are observed in a variety of solid tumours and have existing targeted therapeutics; yet none are presently approved or funded for use in pancreatic cancer patients with the respective genomic alteration (16-18). This presents a unique difficulty of accessing personalized therapy for many Canadians.

This case also highlights the importance of repeat genomic analyses. The ROS1, KRAS G12C, and HER2 alterations were not present at diagnosis, but were all individually revealed upon subsequent analyses that prompted treatment change. Only while targeting the ROS1 mutation did the patient achieve his longest remission while maintaining excellent quality of life. Although the patient twice failed anti-ROS1 therapy, he reached his longest period of stability while utilizing a third anti-ROS1 agent. Access to multiple successive anti-ROS1 agents likely contributed to his remarkable response. This case highlights how having access to repeat testing and targeted therapies can dramatically impact quality of life and survival. It describes an approach to advanced cancer that is tumor agnostic, but with a focus towards treating based on genomic alterations yielding a strong response.

Conclusions

Ultimately, this case presents a patient diagnosed with metastatic pancreatic cancer with a rare survival that is nearly 5 years. The remarkable journey of this patient showcases the importance of being able to rapidly change management plans after favourable targetable mutations are uncovered on repeat genomic analyses.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-190/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-190/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-190/coif). SW reports honoraria fees and advisory boards from GlaxoSmithKline, Eisai, and Merck. MV reports consulting fees from Seagen, honoraria from Eli Lilly, AstraZeneca, Merck, and Bristol Myers Squibb; payment for expert testimony from the Canadian Medical Protective Association; advisory boards for AstraZeneca, Bristol Myers Squibb, Hoffmann-La Roche, Pfizer, Amgen, Apotex, Novartis, Abbvie, Sanofi, Merck, Johnson & Jonson, and Bayer; independent director and stock in Aptose Biosciences Inc.; CEO and president of Sarissa Inc. and patents planned, issued or pending 16/065,641, 09/509,418, 2,865,468, 15/161,424, 14/004/416, 62/646,147, WO 2022/140860 A1. DB reports consulting fees from Bristol Myers Squibb, Takeda, and Amgen; and honoraria from AstraZeneca, Merck, Amgen, and Bayer. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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Cite this article as: Balta KY, Welch S, Vincent M, Breadner D. Near 5-year survival in metastatic pancreatic cancer patient with ROS1 rearrangement, HER2 amplification, and KRAS G12C mutation—a case report. J Gastrointest Oncol 2023;14(5):2273-2278. doi: 10.21037/jgo-23-190

