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Durable Response of Induction Sequential Chemotherapy Combined With Nimotuzumab and Consolidative Carbon Ion Radiotherapy With Non-V600 BRAF Mutation Locally Advanced Pancreatic Cancer

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Case report

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Abstract

Background: Pancreatic cancer remains a highly fatal malignancy among the most common cancers. Multidisciplinary systemic treatment is the vital method to prolong the survival of patients with locally advanced and advanced disease.

Case presentation: We report a patient presented to the hospital with upper abdominal pain with occasional diarrhea for 6 months, diagnosed as locally advanced pancreatic cancer (LAPC). The patient was detected carrying with BRAF p.N486_P490del mutation and positive EGFR expression, receiving induction sequential chemotherapy of gemcitabine plus nab-paclitaxel and modified fluorouracil plus leucovorin, oxaliplatin and irinotecan, combined with nimotuzumab, followed by consolidative carbon ion radiotherapy. After the sequential treatment, the efficacy evaluation was partial response and progression-free survival was at least 20 months.

Conclusions: LAPC patients with non-V600 BRAF mutation and positive EGFR expression might benefit from induction sequential chemotherapy combined with nimotuzumab and consolidative carbon ion radiotherapy. It is possible for patient with locally advanced disease to obtain better local control and further survival.

Introducion

Pancreatic cancer (PC) remains a highly fatal malignancy among the most common cancers. Based on demographic data and survival projections, PC is predicted to become a major leading cause of cancer death in the future. [1–2] Approximately 80% of patients are diagnosed either unresectable or advanced disease at the time of initial diagnosis, and the 5-year survival rate is less than 10%. For the few patients who can be resected surgically, the 5-year survival rate is only 20%. [3–4] Therefore, multidisciplinary systemic treatment is the vital method to prolong the survival of PC patients.

The first-line chemotherapy regimens recommended by National Comprehensive Cancer Network (NCCN) are gemcitabine plus nab-paclitaxel (AG) or fluorouracil plus leucovorin, oxaliplatin and irinotecan (FOLFIRINOX). [5] The FIRGEMAX strategy with gemcitabine + nab-paclitaxel alternating with irinotecan, leucovorin and fluorouracil (FOLFIRI.3) every 2 months, appears feasible and effective, with manageable toxicities, in patients able to reach > 2 months of treatment. [6] During phase II, AG and FOLFIRINOX were administered sequentially, each AG cycle followed by 2 FOLFIRINOX cycles. The objective response rate (ORR) reached to 63.2%. [7] The monoclonal antibody nimotuzumab combined with chemotherapy is an active regimen in KRAS wildtype patients with locally advanced pancreatic cancer (LAPC) or advanced pancreatic cancer (APC). But for those with BRAF mutations, it is not clear that nimotuzumab will benefit. Photon radiation therapy can be an option for unresectable locally advanced disease, but its role remains controversial. [8] As the most advanced radiation technique, carbon ion radiotherapy (CIRT) offers significant physical and radiobiological advantages over photon due to the Bragg peak effect and enhanced relative biological effectiveness, which may be able to better spare the critical organs and

accurately deliver higher radiation dose, leading to increased tumor killing capacity and improved local control rate. [9] Here, we report a case diagnosed as LAPC who was successfully treated with induction sequential chemotherapy combined with nimotuzumab and consolidative CIRT, indicating a gratifying survival.

Case Report

A 29-year-old woman presented to the hospital with upper abdominal pain with occasional diarrhea for 6 months. computed tomography (CT) examination revealed a low perfusion area in body and tail of pancreas, local vascular structures invasion, and celiac as well as retroperitoneal enlarged lymph nodes. Serum tumor marker carbohydrate antigen (CA) 19 − 9 level was 887.3 U/mL. She underwent laparoscopic exploration + pancreatic tumor biopsy. A hard mass was detected at the tail of the pancreas. Postoperative pathology indicated ductal adenocarcinoma (Fig. 1), and the immunohistochemical staining of EGFR demonstrated positive expression. The result of gene expression revealed somatic mutations at BRAF p.N486_P490del Exon 12 (17%) and TP53 p.E286K Exon8 (24.53%). There was no germline or DNA damage repair genes mutation. PD-1 was positive (TPS = 1%, CPS = 1). Tumor mutational burden was 2.79Muts/Mb. Microsatellite stable and EBV negative were detected. The analysis of HLA-I typing was heterozygous. The patient was diagnosed as LAPC with celiac and retroperitoneal lymph node metastasis (cT4N + M1, stage IV).

After accepted one cycle of modified FOLFIRINOX (mFOLFIRINOX) in other hospital, the patient came to our hospital for further treatment and performed the baselined CT (Fig. 2A). Considering the young age and good performance status of the patient, the induction sequential chemotherapy combined with targeted therapy before surgery or local radiotherapy was recommended after multidisciplinary discussion. The 5 cycles of mFOLFIRINOX (oxaliplatin 140mg d1 + irinotecan 240mg d1 + leucovorin 0.66g d1 + fluorouracil 2000mg civ23h d1-2, q2w) plus nimotuzumab (400mg, qw) were practiced. During the treatment, grade 3 neutropenia and rash were recorded. The corresponding symptomatic treatments were effective. The efficacy evaluation was stable disease (SD) (reduced 7%) according to Response Evaluation Criteria in Solid Tumors (RECIST) version1.1 (Fig. 2B). Then, the 4 cycles of GA (gemcitabine 1600mg + nab-paclitaxel 200mg, d1, d8, d15, q4w) plus nimotuzumab (400mg, qw) were arranged. In the meanwhile, there was no indication of surgery in the surgical evaluation. Thus, the consolidative CIRT was considered for better control of the local disease. CIRT was performed from August 10 to August 31, 2020. The patient was treated in prone position with three non-coplanar 45° beams. Respiratory gating and image guidance techniques were used to account for tumor motion. The prescription dose of planning target volume (PTV) was 67.5 Gy (RBE) in 15 fractions over 3 weeks. The dose distribution and radiation doses received by organs at risk were presented (Fig. 3). No adverse events were observed during the CIRT. CT scan revealed shrinkage of the pancreatic tumor. After multidisciplinary systemic treatment, the efficacy evaluation reached partial response (PR) (Fig. 2C). For now, the patient is taking S-1 as maintenance treatment, and there is no tumor progression observed. The progression-free survival (PFS) was at least 20 months. This case report was approved by the Institutional Review Board of West China Hospital.

Discussion

While the GA and FOLFIRINOX regimens have improved the efficacy of chemotherapy for PC and showed the incredible clinical benefit, new approaches are still required to further patients` survival and improve the quality of life. [5, 10–12] The significance of sequential chemotherapy is to increase ORR and prolong survival for advanced disease. Compared with AG alone, the FIRGEMAX strategy showed a higher response rate. The ORR reached 40.3%, versus 26.7% for AG alone. [6] The GABRINOX study applied sequential AG and FOLFIRINOX as well, with the ORR of 63.2%. [7] Both studies mentioned above had acceptable toxicity. It is suggested that the result of this sequential treatment regimen combining the two kinds of chemotherapy is meaningful and worth for further exploration. In this case, we practiced the idea of sequential chemotherapy. The result reported in this case is consistent with above studies.

BRAF is one of the most common mutated kinases in human cancer. BRAF mutations promote tumorigenesis by activating the MAPK signaling pathway. [17] The most common mutation site is V600. There are 3 types of BRAF mutations. Class I is a V600 BRAF mutation. Class II and class III are non-V600 BRAF mutations. [18] There was a meta-analysis demonstrated that metastatic colorectal cancer (mCRC) patients with BRAF V600E mutation may not benefit from anti-EGFR therapy. [19] However, it has also been confirmed that mCRC patients with BRAF class III mutations can benefit from EGFR inhibitors. [20] The controversial studies described above suggest heterogeneity existing in different classes of BRAF mutations on anti-EGFR therapy. The result of gene expression of this patient revealed that BARF p.N486_P490del mutation, which is a pathogenic non-V600 BRAF mutation. What`s more, there is no research indicated that BRAF p.N486_P490del mutation was resistant to EGFR inhibitors. Considering patient's immunohistochemical staining of EGFR demonstrated positive expression, we chose to apply nimotuzumab. The treatment result indicated that nimotuzumab may have therapeutic effect on non-V600 BARF mutations. Combined with induction sequential chemotherapy and consolidative CIRT, the best efficacy evaluation of our systemic treatment reached PR. Although grade 3 neutropenia and rash were documented twice during the treatment, the corresponding symptomatic treatments was effective without interfering the therapy.

CIRT was initiated by the Heavy Ion Medical Accelerator in Chiba, Japan, in 1993. It is a more effective technology for use in patients with deeply located malignant tumors compared with photon due to its unique physical and radiobiological characteristics. [13–14] The sharp lateral penumbra and rapid fall-off of dose at the end of range of carbon beam allow for an excellent dose distribution in the target, while sparing adjacent normal tissues with a lower risk of radiation-related complications. Its radiobiological properties (high linear energy transfer, enhanced relative biological effectiveness and low oxygen enhancement ratio) result in more effective against photon resistant tumors. [14–15] The results of J-CROS revealed that the 1-year overall survival (OS) rate was 73%, median OS was 21.5 months, and 1-year distant metastasis-free survival (DMFS) rate was 41%, suggesting that CIRT yielded quite favorable outcomes for LAPC. [16] It is expected that the strategy of optimizing local control will be beneficial in the multimodal treatment of PC.

Conclusions

Patient with LAPC carrying non-V600 BRAF mutation and positive EGFR expression might benefit from induction sequential chemotherapy of AG and FOLFIRINOX, combined with nimotuzumab and consolidative carbon ion radiotherapy, which may improve local control rate and prolong survival time.

Abbreviations

PC: Pancreatic Cancer; NCCN: National Comprehensive Cancer Network; AG: gemcitabine plus nab-paclitaxel; FOLFIRINOX: fluorouracil plus leucovorin, oxaliplatin and irinotecan; FOLFIRI.3: irinotecan, leucovorin and fluorouracil; ORR: Objective Response Rate; LAPC: Locally Advanced Pancreatic Cancer; APC: Advanced Pancreatic Cancer; CIRT: Carbon Ion Radiotherapy; CT: Computed Tomography; CA: Carbohydrate Antigen; mFOLFIRINOX: modified FOLFIRINOX; SD: Stable Disease; RECIST: Response Evaluation Criteria in Solid Tumors; PTV: Planning Target Volume; PR: Partial Response; PFS: progression-free survival; mCRC: metastatic Colorectal Cancer; OS: Overall Survival; DMFS: Distant Metastasis-Free Survival

Declarations

AUTHOR CONTRIBUTIONS

CD conceived and designed the study. CC, LLJ, and HD drafted the manuscript. ZYQ, WZ, LXF, CK, and DRH provided super-vision. CD critically revised the manuscript for important intellectual content. All authors provided substantial contributions to conception, acquisition of data, and interpretation of data. Everyone took part in drafting this article or revising it critically for important content, gave final approval of the version to be published, and is willing to be accountable for all aspects of this work.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

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AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during this study are available from the corresponding author within reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was granted an exemption from providing written informed consent by the Institutional Review Board of West China Hospital (2020[962]).

CONSENT FOR PUBLICATION

Not applicable. All identifying information is removed.

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Figures

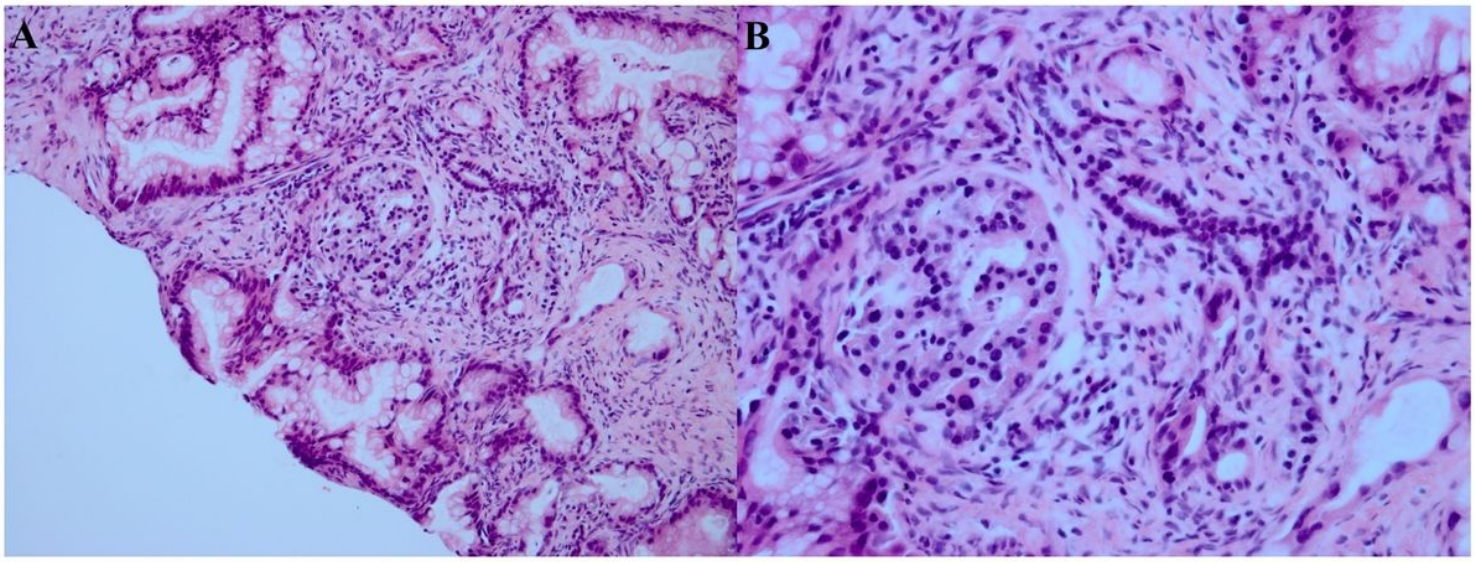

Figure 1

Postoperative pathology indicated ductal adenocarcinoma (A, ×200; B, ×400).

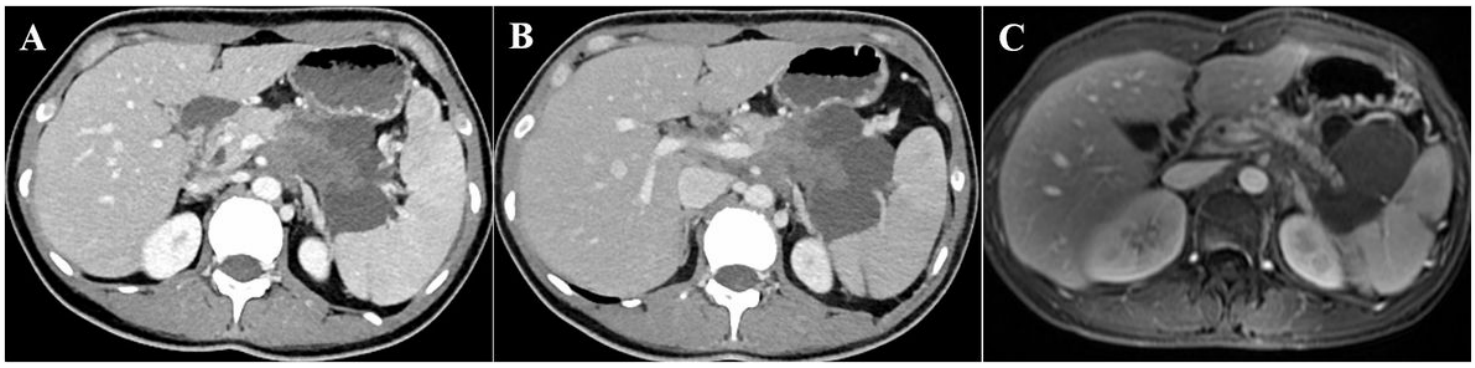

Figure 2

The baselined CT (A, Feb 11,2020) showed cysticsolid and solid tumor in body and tail of pancreas. The solid content accounts for the majority. The efficacy evaluation was SD (reduced 7%) after 5 cycles of mFOLFIRINOX (B, Apr 15,2020). The latest MRI showed that the solid tumor had shrunk 46.7%, and the efficacy evaluation reached PR. (C, Oct 14,2020).

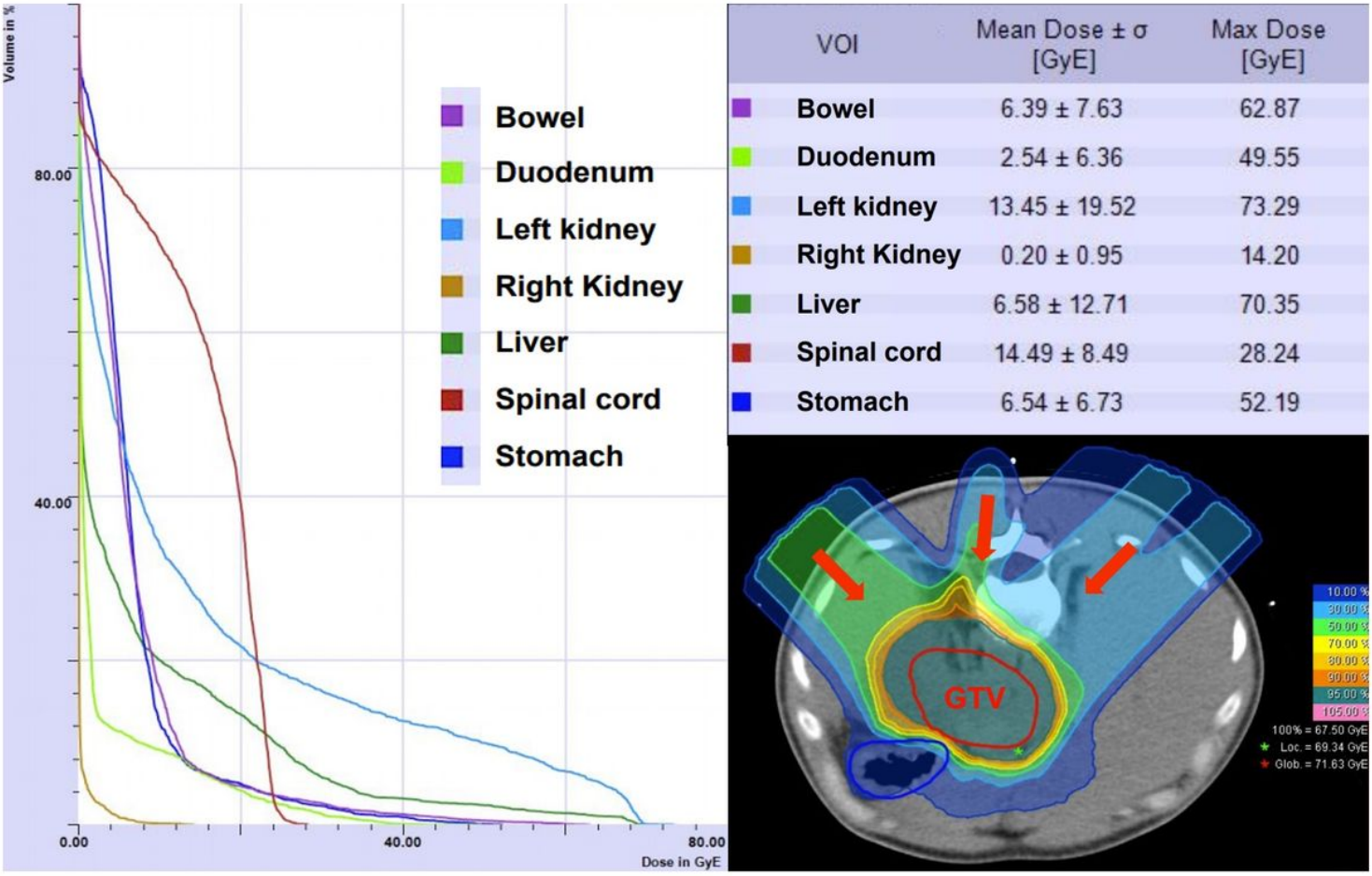

Figure 3

Dose distribution images of CIRT in the case. A total dose of 67.5Gy (RBE) was applied to the tumor in 15 fractions for 22 days. The organs at risk were received extremely low radiation dose.