Indian J Med Res 148, September 2018, pp 254-257
DOI: 10.4103/ijmr.IJMR_615_18

Quick Response Code:

Commentary

Pancreatic ductal adenocarcinoma: Role of chemotherapy & future perspectives

The management of pancreatic ductal adenocarcinoma (PDAC) is a therapeutic challenge. Locally advanced/metastatic disease at presentation and significant genetic heterogeneity, a potential reason for resistance to cytotoxic chemotherapy are major barriers[1]. Incidence (per 100,000) of PDAC is low in India, 1.4 in males and 1.0 among females, compared to North America where corresponding figures are 7.5 and 6.5, respectively[2]. This burden of PDAC is likely to increase further in India with increase in longevity, changing lifestyle, increase in smoking/tobacco consumption, obesity and lack of physical activity/exercise - the key risk factors for this disease[3,4].

The current treatment approach for PDCA patients with advanced/metastatic disease is to use chemotherapy; the choice of the regimen is based on the patient's fitness [Eastern Cooperative Oncology Group (ECOG) performance status], organ function, comorbidities, individual preference and psychosocial issues. Leucovorin plus short-term infusional fluorouracil plus oxaliplatin and irinotecan (FOLFIRINOX) is the preferred regimen for the young and fit patients [ECOG performance status (ECOG PS) 0, 1] with serum bilirubin <1.5 mg/dl[5]. FOLFIRINOX was compared to single-agent gemcitabine in a randomized phase III trial, which included patients with metastatic pancreatic cancer with ECOG PS 0, 1 and serum bilirubin <1.5 mg/dl. The patients received single-agent gemcitabine (1000 mg/m^2 weekly 7 of 8 wk and then for 3 of 4 wk) and FOLFIRINOX (oxaliplatin, 85 mg/m^2; irinotecan, 180 mg/m^2; leucovorin, 400 mg/m^2 and fluorouracil, 400 mg/m^2 given as a bolus followed by 2400 mg/m^2 as a 46 h continuous infusion, every 2 wk). The use of FOLFIRINOX was associated with a better overall response rate (ORR) (32 vs. 9%), progression-free survival (PFS) (6.4 vs. 3.3 months) and overall survival (OS) (11.1 vs. 6.8 months). Patients in combination arm had higher Grade 3/4 toxicity including febrile neutropenia, thrombocytopenia, neuropathy and diarrhoea[5]. It should be pointed out that only minorities of patients with metastatic pancreatic cancer are candidates for FOLFIRINOX due to older age and poor general condition. Patients who are candidates for intensive regimen and have serum bilirubin <1.5 mg/m^2 but not a candidate for FOLFIRINOX are treated with a combination of gemcitabine and nab (nanoparticle albumin-bound) paclitaxel. In a phase III randomized controlled trial, MPACT, the combination of nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) for 3 wk every 4 weekly was compared to single-agent gemcitabine (1000 mg/m^2 weekly 7 of 8 wk and then for 3 of 4 wk). The combination regimen was associated with a higher ORR (23 vs. 7%), PFS (5.5 vs. 3.7 months) and OS (8.5 vs. 6.7 months) and higher toxicity[6]. This study included patients older than 75 yr and with ECOG PS 2 which are not represented in the studies evaluating FOLFIRINOX. It has been suggested that nab-paclitaxel may deplete the tumour stroma through the binding of albumin to fibroblasts containing secreted protein acidic and rich in cysteine[7].

In this issue Ostwal *et al*[8] report a retrospective study evaluating the response and treatment outcome of patients with metastatic/locally advanced pancreatic cancer treated with a combination of gemcitabine and non-cremophor paclitaxel [abraxane (Abraxis BioScience, Inc., Los Angeles, CA, USA) or nanoxel (Dabur Pharma Ltd., India)]. The conventional paclitaxel is insoluble in water and hence cremophor; a castor oil-based surfactant is used to make it soluble. Cremophor contributes to the hypersensitivity reactions associated with paclitaxel infusion. The non-cremophor paclitaxel, abraxane is albumin-bound nanoparticles of paclitaxel while nanoxel is a polymeric-micelle formulation. The use of non-cremophor paclitaxel compared to conventional paclitaxel has an added advantage of lesser hypersensitivity reaction and lesser need for pre-medications. The authors report

an ORR of 30.8 per cent, median PFS of 5.6 months [95% confidence interval (CI) 3.7-7.4] and a median OS of 11.6 months (95% CI 8.8-14.3) months. The OS and PFS in this study are comparable to that in the MPACT trial[6]. There was no significant difference in the OS and PFS among patients treated with gemcitabine-abraxane and gemcitabine-nanoxel combination. There was no difference in the treatment outcomes of these two-drug combinations as the study was not designed or powered to answer this question. Although it is undoubted that availability of nanoxel gives a cheaper option for patients who are to be treated with non-cremophor paclitaxel, which may be an important factor in a resource-limited setting. The other interesting point was that the grade III/IV toxicity in this study was lower than that reported in another phase III study[6] evaluating this combination, which as per authors could be due to the dose modification incorporated in the treatment protocol. This gives a useful insight into means of limiting toxicity without affecting the efficacy and treatment outcome by tailoring the dose of chemotherapy regimen for an individual patient in a palliative setting. Other means have also been used to reduce the toxicity of this regimen, for example, administering gemcitabine (1000 mg/m^2) and nab-paclitaxel (125 mg/m^2) every two weeks. This regimen has comparable efficacy and reduced toxicity as compared to standard dosing schedule of nab-paclitaxel-gemcitabine[9]. Patients who are fit for combination chemotherapy but who continue to have bilirubin >1.5 mg/dl despite biliary stenting can be treated with FOLFOX regimen[10]. Other combination regimens have also been evaluated, for example, gemcitabine-5-fluorouracil and gemcitabine-capecitabine which have a doubtful benefit over single-agent gemcitabine[11-14].

In view of the dismal outcome of patients with advanced pancreatic cancer several novel approaches have been evaluated. Pancreatic cancer has been shown to express epidermal growth factor receptor[15]. The vascular endothelial growth factor (VEGF) is also deemed important in the pathogenesis and spread of pancreatic cancer[16]. In keeping with these findings, a phase III study compared the gemcitabine (1000 mg/m^2 weekly) with or without erlotinib (100 mg daily)[17]. Patients in the combination arm (gemcitabine and erlotinib) had a significant though small OS benefit of two weeks (6.2 vs. 5.9 months). This clinically insignificant benefit comes at a greater financial cost and toxicity. The combination of gemcitabine with VEGF inhibitor, for example, bevacizumab, or multikinase inhibitors, for example, axitinib or sorafenib, on the other hand, failed to show any benefit over single-agent gemcitabine[17,18].

The patients who are not candidate for intensive chemotherapy and ECOG PS ≤2 can be offered single-agent gemcitabine (1000 mg/m^2 weekly 7 of 8 wk and then for 3 of 4 wk)[19]. The use of single-agent gemcitabine is associated with low ORR (11%) with clinical benefit observed in nearly 30 per cent of the patients[19]. Clinical benefit was defined by decrease in pain, analgesic use and weight gain. This discordance between response assessed by response evaluation criteria in solid tumors (RECIST) criteria (*recist.eortc.org*)[19] and clinical benefit may be due to the extensive desmoplastic reaction seen in pancreatic cancer which makes assessment of response at primary site difficult. Immunotherapy is another option for patients with metastatic pancreatic cancer with high microsatellite instability[20].

Palliative care forms the bedrock for an appropriate management of metastatic/locally advanced metastatic PDAC. Care must be taken for adequate analgesia, nutrition, management of obstructive jaundice, gastric outlet obstruction and psychosocial well-being of these patients. Patients with significant comorbidities and a poor performance status should be referred for palliative care.

Genetically, PDAC is a very heterogeneous disease[1]; important mutations are KRAS (>90%), p53 (60-70%), CDKN2A, (>50%), SMAD4 (approximately 50%). About 4-5 per cent of patients have mutations in *BRCA1/2*; these cases have enhanced sensitivity to platinum-based chemotherapy as well as poly (ADP-ribose) polymerase (PARP) inhibition[1]. This improved understanding has led to initiation of a number of clinical trials (*https://www.cancer.gov/types/pancreatic*). Several new drugs such as methyl ethyl ketone (MEK) inhibitors, pegvorhyaluronidase alpha (PEGH20) which degrades hyaluronic acid in tumour microenvironment (TME), napabucasin (BBI-608), which inhibits cancer stem cells, and AM0010, a PEGylated interleukin-10 are at various stages of drug development and are being evaluated in combination with various agents[21-24]. Similarly, poly(ADP-ribose) polymerase (PARP) inhibitors are being evaluated as single-agent or as maintenance therapy in breast cancer (BRCA)-mutated patients with metastatic pancreatic cancer who have had a stable disease or objective response to chemotherapy[25].

In PDCA, the stroma is very dense, fibrotic and heterogeneous and is possibly responsible for resistance to therapy. Recent progress in the field of immunotherapy and checkpoint inhibitors have shown promise in a number of cancers particularly in melanoma, lung cancer, urinary bladder cancer, renal cancer and head and neck cancer. Results of single-agent checkpoint inhibitors have not met with success. Possibly lower levels of neoantigens, the unique immunosuppressive TME and low levels of intratumoral infiltrating T-lymphocytes are some of the barriers[26]. Currently, a number of phase I/II trials are underway to evaluate the use of checkpoint inhibitors along with gemcitabine or targeted therapies for modulating and enhancing T-cell immunity[26]. Results of these trials are awaited with hope.

***Conflicts of Interest*:** None.

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Received March 28, 2018

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