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Mini-review

Tackling pancreatic cancer with metronomic chemotherapy

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ABSTRACT

Pancreatic tumours, the majority of which arise from the exocrine pancreas, have recently shown an increasing incidence in western countries. Over the past few years more and more new selective molecules directed against specific cellular targets have become available for cancer therapy, leading to significant improvements. However, despite such advances in therapy, prognosis of pancreatic cancer remains disappointing. Metronomic chemotherapy (MCT), which consists in the administration of continuous, low-dose anticancer drugs, has demonstrated the ability to suppress tumour growth. Thus, it may provide an additional therapeutic opportunity for counteracting the progression of the tumour. Here we discuss evidence arising from preclinical and clinical studies regarding the use of MCT in pancreatic cancer. Good results have generally been achieved in preclinical studies, particularly when MCT was combined with standard dose chemotherapy or antinflammatory, antiangiogenic and immunostimolatory agents. The few available clinical experiences, which mainly refer to retrospective data, have reported good tolerability though mild activity of metronomic schedules. Further studies are therefore awaited to confirm both preclinical findings and the preliminary clinical data.

Introduction

Pancreatic cancer (PC), with an increasing incidence in western countries around 20:100,000 new cases per year, ranks as 12th among cancer types worldwide. The majority of pancreatic malignancies pertain to the exocrine pancreas and of these pancreatic ductal adenocarcinoma (PDAC) is by far the most common type of PC.

At a metastatic stage, therapy mainly consists of chemotherapy, while gemcitabine for Westerners and S-1 for East Asian populations are regarded as backbone drugs [1,2]. Combination regimens such as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) [3], gemcitabine plus nab-paclitaxel [4] and erlotinib plus gemcitabine [5] represent new standards in the first-line therapy of patients that show a good performance status. There is also evidence for the benefits of second-line chemotherapy as compared to best supportive care alone even though in randomized studies only limited results were reported [6–15].

Pancreatic cancer characterized by both a 5-year survival rate below 10% [16] and a mortality rate that nearly overlaps the incidence [17] represents a great challenge for cancer therapy. Undoubtedly, the strong commitment of recent research has provided a deeper knowledge concerning molecular pathways underlying tumour development and yielded positive clinical achievements [18]. High levels of secreted protein acidic and rich in cysteine (SPARC), which are observed in about 50% of PC, have been recognised to correlate with better survival following nab-paclitaxel [19–21].

Epidermal growth factor receptor (EGFR) amplification and KRAS mutations, which lead to a permanent activation of the signalling pathway below the EGFR molecule, are frequently detected in PC cells. However, only the combination of gemcitabine plus erlotinib, which is an EGFR tyrosin-kinase inhibitor, was associated with a modest but statistically significant increase in survival when compared to gemcitabine alone [5]. Early studies testing other molecular targeted therapies showed marginal outcomes [22–24]. Even, strategies aimed at overcoming drug resistance are currently being investigated [21]. Particularly, the hedgehog signalling activation through stroma proliferation [25], hypoperfusion and impaired drug delivery, determined resistance to gemcitabine in animal models while the use of hedgehog inhibitor increased intratumoral concentration of the drug [26]. Moreover, the inhibition of the epithelial to mesenchymal transition in a genetically engineered mouse model enhanced sensitivity to gemcitabine [27].

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Future perspectives of PC therapy certainly involve a more accurate recognition of genetic and hystopathological features [28] as well as the support of immunotherapy [15].

Furthermore, metronomic chemotherapy (MCT), by demonstrating that repetitive low-doses of antiproliferative agents can suppress tumour growth with acceptable toxicity, provides an additional therapeutic chance of tackling PC [29]. Here we consider reports from preclinical and clinical studies about MCT in PC. The search strategy and selection criteria are reported in Table 1(supplementary material).

Metronomic chemotherapy: preclinical studies

Effects of metronomic chemotherapy on cancer cells and the tumour microenvironment

The choice of experimental model is essential in the evaluation of drugs, particularly those targeting the tumour microenvironment [30]. Unlike in the case of pancreatic neuroendocrine tumours (PNET), which are dependent on angiogenic factors, tumours arising from the exocrine pancreas show apparently limited dependence on an excess of angiogenesis. Indeed, PDAC is essentially characterized by an extensive stromal reaction resulting in a hypovascular and hypoxic microenvironment, which supports tumour growth. Moreover, the rigidity of the extracellular matrix of PDAC by disrupting the normal architectural vasculature could influence therapeutic response by preventing the delivery of drugs to neoplastic cells [30]. Notwithstanding, targeting tumour vasculature remains an attractive strategy also in PC, aimed at further impairing perfusion or, alternatively, at improving intra-tumour drug delivery. For this reason, MCT, which is endowed with multiple anti-tumour functions including antiangiogenic properties [29,31], is proposed for the role of targeting both PC cells and their microenvironment (Fig. 1).

An early set of preclinical studies has investigated the feasibility of delivering metronomic cyclophosphamide (CTX) in human PNET xenografts of mice [32–34] (Table 1). In the first study, the chronic administration of CTX at low doses on a daily basis through the drinking water of mice proved safe, reasonably efficacious and potentially applicable to chronic treatment [32]. This protocol further demonstrated itself to be particularly well suited for integration with antiangiogenic drugs. The second study has provided the evidence for enhanced efficacy of metronomic CTX using imatinib [33]. This receptor tyrosine kinase inhibitor was used to disrupt platelet-derived growth factor receptor (PDGFR) mediated pericyte support of tumour endothelial cells. CTX at maximum tolerated dose (MTD) prompted transitory regression followed by rapid regrowth of tumours, in contrast to metronomic CTX plus imatinib, which produced stable disease along with increased endothelial cell apoptosis. Moreover, a "chemo-switch" (C-S) protocol, using sequential MTD and MCT by means of a multitargeted inhibition of PDGFR and vascular endothelial growth factor receptor (VEGFR) produced enduring responses and improved survival. The third study, evaluating the cysteine cathepsin inhibitor JPM-OEt, alone or in combination with CTX, supplied further evidence in favour of the C-S strategy [34]. Three dosing schedules for CTX, MTD regimen, a metronomic continuous low-dose regimen or a C-S regimen consisting of MTD followed by metronomic dosing, were compared. The cathepsin inhibitor in combination with two distinct regimens of chemotherapy administration (MTD or C-S) resulted in tumour regression, decreased tumour invasiveness and increased survival. The cathepsin inhibitor plus the C-S regimen of CTX led to the most pronounced reduction in tumour burden and the greatest increase in OS. These results indicate that the initial MTD chemotherapy is able to debulk the tumour, whereas the metronomic therapy evidently reduces regrowth/relapse and tumour progression. Notably, the addition of JPM-OEt to the C-S regimen led to an even further regression in tumour burden. Conversely, metronomic CTX administered either alone or in combination with JPM-OEt did not significantly affect total tumour volume.

Aimed at targeting various components of the tumour microenvironment to relieve vessel compression and aid drug delivery in a xenograft model of PC, lenalidomide, an immunomodulatory agent, sunitinib and low dose metronomic CTX, alone and in combination have been tested [35]. The combination strategy was shown to significantly inhibit the growth of primary tumours in

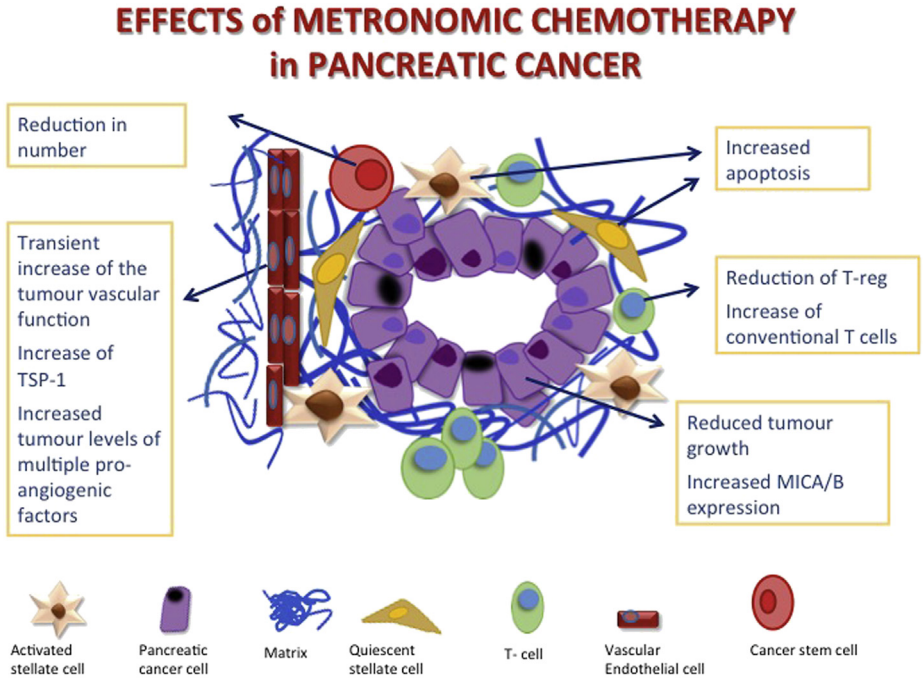

Fig. 1. Effects of metronomic chemotherapy on pancreatic cancer cells and tumour microenvironment.