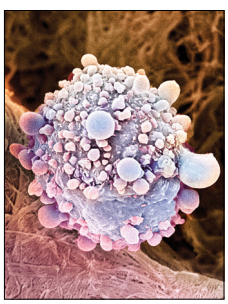
Metformin for pancreatic cancer



Metformin is the most widely used oral anti-diabetic drug worldwide. It inhibits hepatic gluconeogenesis and increases insulin sensitivity in peripheral tissues, leading to reduced blood glucose and insulin concentrations. The observation from retrospective studies[1,2] that metformin might decrease the risk of cancer and mortality in patients with diabetes has prompted the initiation of numerous preclinical and clinical studies to investigate its anticancer activity.

In *The Lancet Oncology*, Sil Kordes and colleagues[3] report one of the first results from a prospective study of metformin. Their randomised phase 2 study assessed metformin combined with gemcitabine and erlotinib in patients with advanced pancreatic cancer with a primary survival endpoint. The study was ambitious. It was designed to look for a significant benefit from the use of metformin in pancreatic cancer—one of the most lethal and aggressive of all malignancies. The sample size (120 patients) was defined based on the detection of a 50% increase in survival at 6 months—from 50% to 75%—with 80% power. This exceeds the degree of benefit seen with FOLFIRINOX compared with gemcitabine (58% to 75%)[4] and that of gemcitabine plus nab-paclitaxel compared with gemcitabine (58% to 70%).[3] With a total study cohort of 121 patients, the trial was underpowered to detect a small but still clinically meaningful benefit from metformin. Nevertheless, the study is important and the results raise several points for consideration.

Reassuringly, metformin was reasonably well tolerated when combined with gemcitabine and erlotinib. No increase in reported grade 3 or 4 toxic effects occurred and no non-diabetic patient treated with metformin developed hypoglycaemia. Nonetheless, treatment discontinuation because of toxic effects was more common in patients treated with metformin compared with patients receiving placebo (13 [22%] of 60 *vs* eight [13%] of 61), which might have contributed to the fact that the median duration of treatment was shorter in the metformin group; however, progressive disease was still the most common reason for treatment discontinuation. Overall survival at 6 months was 63·9% (95% CI 51·9–75·9) in the placebo group and 56·7% (44·1–69·2) in the metformin group; hazard ratio [HR] 1·056 [95% CI 0·72–1·55]; p=0·78). The fact that the study did not meet the primary endpoint of a 50% increase in overall survival is disappointing, but not surprising. Pancreatic cancer is a complex disease and the addition of targeted drugs to gemcitabine has not produced a clinically significant survival benefit in a non-selected population.[5] Metformin, which putatively targets cancer cell metabolism, was unlikely to be an exception.

One of the main mechanisms of action for the antineoplastic activity of metformin is thought to be downregulation of insulin receptor signalling.[6] To investigate this, the correlation between dynamic changes in blood concentrations of insulin, IGF-1, and IGFBP-3 and patient survival was examined in the study. Although patients with a reduction in insulin concentration after treatment with metformin seemed to have an improved survival outcome, the results were too preliminary to draw a conclusion. The lack of tumour tissues for correlative studies hampered opportunities to identify patient subgroups that might potentially derive clinical benefit from metformin.

Metformin inhibits complex I in the mitochondria respiratory chain, thereby reducing oxidative phosphorylation and ATP production in cells.[7] This inhibition creates energy stress and could potentially lead to cancer cell arrest or death, especially in cells dependent on oxidative phosphorylation to fulfill the energy requirement[8] or under certain conditions such as kinase inhibition-induced reduction in glycolysis.[9] However, whether metformin produces a cytostatic or cytotoxic response in cancer cells, or any response at all, is likely to be dependent on many factors, including how they derive energy, the state of their microenvironment, the interaction between glycolytic and oxidative phosphorylation pathways, and the intracellular concentration of metformin. Tumour heterogeneity is also important in this context, and the mutational landscape of tumours needs to be taken into consideration, especially *STK11* (LKB1) and *TP53* mutation status[10,11] and mitochondrial DNA mutations.[12]

Despite this disappointing outcome, attempts to repurpose metformin for treating cancer should not be abandoned. More than 100 studies assessing metformin in various stages and types of cancer are currently

underway, and the findings of additional trials with translational endpoints are yet to be reported. Careful patient selection and translational studies will be crucial to determine the success of these attempts to bring metformin into cancer therapy.

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