

Building the clinical evidence on metformin and cancer

Population studies, mouse models, and mechanistic studies all show that metformin, a cheap well-tolerated diabetes drug, impacts in some way on how some cancers develop and progress. **Anna Wagstaff** talks to clinicians and researchers building the evidence on what it can deliver in the clinic.

In the early 2000s diabetologists began reporting an unusually low rate of cancer among their patients who were treated with metformin.

What happened next seemed to follow a ‘false-dawn’ pattern that has become all too familiar in the history of cancer research. A series of epidemiological studies came out showing large effect sizes, some showing cancer rates more than halved in metformin users – results that wiser heads cautioned were simply “too good to be true”. But then attempts to back up the find-

ings with lab studies confounded the sceptics: whether used against cancer cells in petri dishes or against tumours in mice models, metformin did indeed inhibit cancer growth.

“That was the golden period,” says Michael Pollak, whose lab at the McGill translational research centre in Montreal, Quebec, was one of those tasked with carrying out the research. “It appeared that we had independent evidence from population studies and lab studies that projected that metformin had a bright future in treating cancer, at least in diabetics and even in

patients without diabetes.”

As the excitement rose, so did the number of studies. But then uncertainty began to creep in. Research done to confirm the early epidemiological reports found no evidence, or conflicting evidence, of a protective effect. And while the findings of the lab studies were found to be robust, questions emerged about dosing levels: was the anticancer activity occurring at drug levels higher than those that are – or ever could be – achieved in humans?

In 2015, hotly awaited results from one of the few robust ran-

domised controlled trials of metformin, used in patients with advanced pancreatic cancer, showed no impact on survival (*Lancet Oncol* 2015, 16:839–847). The golden period was over.

Metformin is special

The discovery of new anticancer agents is always welcome, but in the case of metformin, there were additional reasons for excitement. The drug is off patent, simple to manufacture and therefore cheap, so global access would not be a problem. Its side effects are known from decades of use by people with diabetes, and they are well-tolerated. Indeed some ‘side-effects’ – if that is the right term in the context of cancer treatment – may be positively beneficial. This is because the drug is active against metabolic syndrome, which is associated with chronic conditions such as diabetes, obesity, atherosclerosis and cardiovascular disease. This aspect takes on particular importance when seen in the context of the changing diets and lifestyles, and consequential rising rates of obesity and metabolic syndrome, that are thought to be a factor in the current global cancer epidemic.

All of that may be irrelevant to oncology if the drug does not actually work against cancer in humans. Yet the way that metformin performs in restricting cancer cell proliferation in preclinical tests cannot be ignored.

Metformin seems to work at a whole organism level principally by lowering the insulin levels. This could be relevant for the subset of cancers that are growth-stimulated by insulin. But it also works directly on the tumour, by modifying the characteristic energy metabolism of cancer cells in a way that Pollak says

is “very, very interesting” – not least because energy metabolism is one of the characteristics that distinguishes cancerous from normal cells, and is important in sustaining their ability to survive and proliferate.

In short, despite the disappointing results of the pancreatic cancer trial, the mechanisms and potential clinical benefit of this drug deserve to be explored further. As Pollak says, “Pancreatic cancer is a pretty hard nut to crack. That doesn’t mean there is no area where it may be of some use. But the best case scenario – that metformin will be effective against a wide range of cancers – is unlikely to be achieved... The overarching message is that we are now into the subtleties.”

He suggests that there could be a rationale for conducting trials that focus on areas like the colon and the liver (including prevention of liver metastases), because metformin is known to accumulate in higher levels in these organs – indeed it has already been shown to decrease polyp growth in a phase III trial of people who had undergone polypectomy (*Lancet Oncol* 2016, 17:475–83). Focusing metformin trials more generally on cancer types associated with metabolic syndrome and obesity could also make sense, says Pollak.

Would an adjuvant trial make sense?

Ruth Langley, a medical oncologist and programme leader at the UK Medical Research Council clinical trials unit, spends much of her time amassing and analysing different types of evidence to assess whether it is strong enough to justify running a clinical trial.

She is the key instigator behind the Add-Aspirin trial, which is following

up evidence from clinical, preclinical and mechanistic studies to try to get a clear answer on whether taking low-dose aspirin as an adjuvant therapy can lower the risk of recurrence in people treated for a range of common cancers.

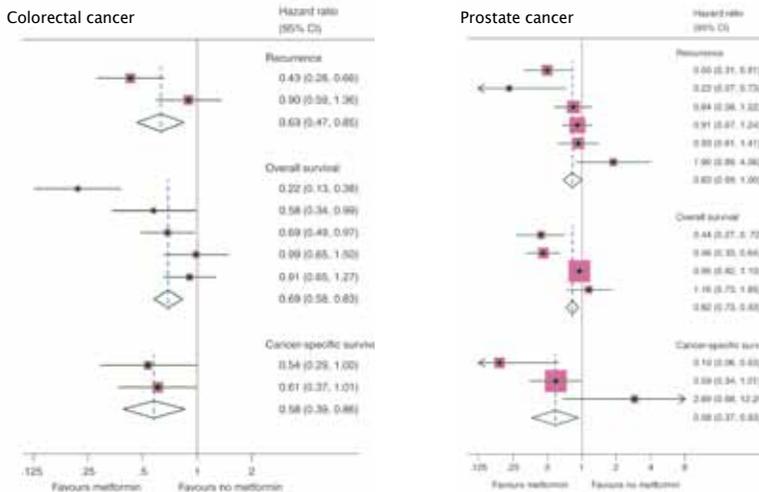
Most recently, she and her team have been examining the evidence around metformin, to assess whether there is sufficient evidence – and enough support among clinicians and funders – to think about trialling the drug in a similar, adjuvant, setting.

Their ‘homework’ included carrying out a meta-analysis of research reporting cancer outcomes for individual tumour types in metformin users compared with non-users – focusing on the results for patients with early-stage cancers (*Ann Oncol* 2016, 27:2184–95). The findings come with all the usual caveats about observational studies, with some additional ones – not least that the metformin users will all have been suffering from diabetes, which could affect cancer outcomes independently of the metformin.

The results do nonetheless add to the total body of evidence available. They indicate that, taken in an adjuvant setting by patients treated for early-stage colorectal cancer, metformin appears to be associated with significantly better recurrence-free, overall and cancer-specific survival. Significant or borderline significant benefit for all three measures was also seen among patients treated for early prostate cancer, particularly those treated with radiotherapy, though there was a lot of heterogeneity between studies (see figure overleaf).

No significant benefits were seen in either urothelial or breast cancer. The latter finding may temper expectations around the outcomes of the MA.32 Canadian Cancer Trials Group phase III randomised trial of metformin vs

Could metformin work as an adjuvant?



A meta-analysis of studies comparing outcomes between metformin users and non-metformin users for cancers treated curatively at an early stage found that, in colorectal cancer (*above left*), metformin use was associated with longer recurrence free survival, overall survival and cancer-specific survival. For men with early-stage prostate cancer, metformin was also associated with significant, or borderline significant, benefits in all three outcomes, but there was significant heterogeneity between the studies (*above right*). The data also suggest that prostate cancer patients treated with radical radiotherapy may benefit more from metformin. In breast and urothelial cancer, no significant benefits were identified.

Source: C Coyle et al (2016) *Ann Oncol* 27:2184–95. Republished under a Creative Commons licence

placebo in early-stage breast cancer, which is one of the few robust trials of metformin in an adjuvant setting, and is due to report sometime in 2020. Langley is keen to emphasise that epidemiological studies are often not confirmed in clinical trials.

The MRC clinical trials unit has not taken any decision yet on whether or not to try to launch a trial of metformin in an adjuvant setting, but Langley, with her experience of the aspirin story, believes there may be some good arguments for doing so.

“One of the things I feel about these potential repurposed agents is that we know, because most of them are used every day – metformin for diabetes, aspirin for heart disease –

that they don’t make a large amount of tumour disappear. But it is plausible that they affect the microenvironment such that, if you have a very, very small volume of cancer – right at the beginning of a primary cancer or one or two cells from a metastasis – they change the microenvironment such that the growth isn’t established.”

This seems to be what is happening in the case of aspirin, Langley argues, because the doses used in most of the epidemiological studies supporting the Add-Aspirin trial “suggest it is acting on platelets, and the microenvironment, not directly on the tumour.”

Another reason that could tip the balance in favour of trialling metformin as an adjuvant treatment is that

a large platform study is already up and running. The Add-Aspirin trial has been randomising patients treated for early breast, colorectal, prostate, and gastro-oesophageal cancer to aspirin (100mg or 300mg) or placebo for two years now (bit.ly/AddAspirin-protocol). If an additional metformin arm – or arms – were to be run on the same trial platform, in at least some of the same cancers, this would be an efficient use of resources.

This ‘smarter’ approach to conducting clinical trials, using a single platform to evaluate multiple primary treatment hypotheses, was developed by the Director of the MRC clinical trials unit, Mahesh Parmar, and has always been part of the strategic concept behind the Add-Aspirin trial, says Langley (*Clin Trials* 2017, 14:451–61).

“Despite calling the trial Add-Aspirin, we always thought we might evaluate other agents.” If they do add further arms (metformin is only one of a number of possibilities), they’ll have to change the name to ‘the Add trial’ or the ‘Adjuvant trial’ she says.

The fact that the Add-Aspirin trial is now opening up in India could be seen as a third argument in favour of adding a metformin arm. Cancer prevention, including secondary prevention, needs to be a priority in countries where expensive high-tech treatments are accessible to only a privileged few. Collaborating with the trials network run by India’s recently established National Cancer Grid (*Indian J Med Paediatr Oncol* 2014, 35:226–7), to explore the value of cheap generics like aspirin and metformin in that population, makes obvious sense in terms of global cancer control.

None of which, Langley emphasises, rules out the possibility that metformin could also be of interest in other settings, including advanced disease. She mentions as an example the

STAMPEDE trial – one of the great success stories of the MRC clinical trials unit’s ‘multi-arm, multistage’ trial platforms, for patients with prostate cancer who are starting on androgen deprivation therapy. The trial compares a single standard-of-care arm against a rolling panel of exploratory treatments added to standard of care, and has recently started randomising patients to added metformin.

Can metformin perform in advanced prostate cancer?

Finding better solutions for men with advanced prostate cancer has become something of a speciality for Silke Gillesen, who is co-lead of the STAMPEDE metformin comparison.

Like Langley, Gillesen and all the STAMPEDE trialists spend a lot of time weighing up evidence to make intelligent decisions about the most likely options to move into large clinical trials – and with some notable successes. The metformin arm of STAMPEDE is the tenth arm to run against a single continuously recruiting control arm, in a trial that has already notched up two important changes in the standard of care for men with advanced prostate cancer, first with docetaxel and more recently with abiraterone (*Eur Urology* 2016, 70:906–8).

Gillesen believes that prostate cancer is a likely place to see a benefit from metformin, not least because it reduces insulin levels, which could be important for a number of reasons. “Insulin has been shown to upregulate intracellular testosterone levels and secreted androgens sufficient to activate the androgen receptor – a very important receptor in prostate cancer,” says Gillesen, “It acts directly on prostate cancer cells and can also activate pathways involved in progres-

Mechanisms of anti-cancer action

Metformin affects multiple key processes related to cell growth, proliferation, and survival. The drug’s effects on these processes stem from both metabolic and intracellular-signaling activity. First, metformin decreases the amount of glucose produced by the liver and reduces the bloodstream level and cellular uptake of insulin. In turn, the reduced insulin stimulation results in reduced activation of insulin receptors on cell membranes, triggering a cascade of intracellular molecular effects, such as the downregulation of the Ras/Raf/MEK/ ERK and PI3K/AKT/ mTOR signaling pathways. One or both of these pathways are often activated in many types of cancer cells. In addition, metformin appears to upregulate AMP-activated protein kinase, a key molecule in glucose and insulin regulation and also an inhibitor of mTOR.



© Maddalena Carrai

For further information see, for instance: I Pernicova & M Korbonits (2014) Metformin—mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol* 10: 143–156

sion to castration resistance.”

Hyperinsulinaemia also causes activation of insulin-like growth factor (IGF) signalling pathways, which has been associated with prostate cancer progression in preclinical models, she adds, while metformin has been shown to block AMP kinase, which is involved in a signalling pathway known to be important for prostate cancer. “So there is a lot of preclinical evidence to suggest that metformin has anti-proliferative effects in prostate cancer.”

These findings, she argues, are backed up by the overall weight of evidence from population studies, including a relatively recent study of almost 4,000 diabetic men who were diagnosed with prostate cancer, which found that “cumulative duration of metformin treatment after prostate cancer diagnosis was associated with a significant decreased risk of prostate cancer-specific and all-cause mortality in a dose-dependent fashion,” (*JCO* 2013, 31:3069–75). Those findings, says Gillesen, support the idea that

metformin can work in patients who already have cancer, and not just in a prevention or adjuvant setting.

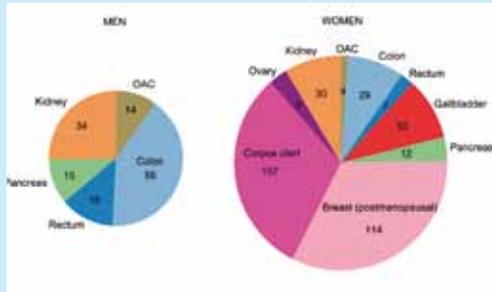
Whether or not that anti-cancer benefit shows up in the clinical trial only time will tell. But even if it doesn’t, Gillesen believes that metformin could still improve both quality and length of life for her patients. This is because the androgen deprivation therapy that is the standard of care is believed to raise their risk of developing insulin resistance, high blood sugar levels, obesity, and high cholesterol, which may in turn raise their risk of diabetes and cardiovascular disease.

So potentially metformin could do “two really fantastic things,” says Gillesen. “one is the anti-cancer effect, and the other is mitigating the metabolic effects of androgen deprivation therapy.” Unlike the other STAMPEDE arms, the primary outcome measure by which metformin will be judged is all-cause survival, to capture both the anti-cancer effects and the wider health benefits.

Obesity, insulin resistance, metabolic syndrome and cancer incidence

A population-based study led by the International Agency for Cancer Research (*Lancet Oncol* 2015, 16:36–46) showed that 3.6%, or almost 481,000, of all new cancer cases in 2012 were attributable to excess BMI (BMI $\geq 25\text{kg/m}^2$).

Cancers attributable to excess BMI accounted for 5.4% of all cancers in women – almost one third of which were postmenopausal breast cancer, with another one third cancers of the corpus uteri.



Estimate of the number of cancers (in thousands) attributable to excess BMI in 2012

OAC – oesophageal cancer

Source: M Arnold et al. (2015) *Lancet Oncol* 16:36–46.

© 2015 World Health Organization. Published by Elsevier. All rights reserved. Republished under a Creative Commons licence

Among men, cancers attributable to excess BMI accounted for almost 2% of all cancers, with colon cancer accounting for a little under half (43%). A review of the evidence on the links between insulin resistance, diabetes and cancer (*Curr Diab Rep* 2013, 13:213–22) cited “multiple meta-analyses and other large cohort studies published over the past year”, supporting an association between the presence of insulin resistance (type 2 diabetes and metabolic syndrome) and an increased incidence of many types of cancer, including colorectal, hepatic, pancreatic, breast, endometrial, and urinary tract malignancies.

Michael Pollak, who has led preclinical work exploring the impact of metformin on cancer, argues that focusing metformin trials on cancer types associated with metabolic syndrome and obesity could be a sensible way to go in developing clinical evidence.

Not surprisingly perhaps, the trial is proving a hit with patients, and Gillessen is confident they will accrue their target of 1,800 patients by the end of 2019 – greatly helped by the multi-arm, multi-stage design, “which means we can open several arms and lose fewer patients onto a control arm.” She hopes to be able to report early results by the end of 2024.

Is radiotherapy where metformin will prove its value?

Alan Dal Pra, assistant professor of radiation oncology at the University of Miami Miller School of Medicine, shares Gillessen’s enthusiasm for learning more about what metformin can do for men with prostate cancer.

His priority is to follow up intriguing results from population and preclinical studies that seem to indicate a particular benefit when the drug is used in combination with radiotherapy.

He too mentions the 2013 *JCO*

study of 4,000 diabetic men treated for prostate cancer, which showed an association between cumulative dose of metformin and a significantly decreased risk of dying of that cancer, but points out that the decrease was a lot higher among the one in four men who had been treated with radiotherapy. “For the radiotherapy cohort, there was a 48% decrease in prostate-cancer specific mortality,” says Dal Pra.

Those results form part of a body of evidence that has convinced him and colleagues at SAKK (Swiss Group for Clinical Cancer Research) to launch PROMET, a randomised phase II trial that will look at the benefit (measured by time to progression) of adding metformin to salvage radiotherapy for patients whose PSA rate has started to rise after radical prostatectomy. The trial will be carried out in collaboration with the GETUG group (Groupe d’Etudes des Tumeurs Uro-Génitales).

A more recent study of 2,500 patients with local or locally advanced disease treated with curative radiother-

apy (including diabetics on metformin, diabetics not on metformin and non-diabetics) showed that metformin was associated with improved biochemical (PSA) control and decreased incidence of castrate-resistant prostate cancer, distant metastases and prostate-specific cancer mortality (*Eur Urol* 2013, 63:709–16).

These and other epidemiological studies – with all the many caveats – are backed up by evidence from mechanistic studies, including one conducted by Dal Pra and colleagues in the Koritzinsky Lab in Toronto, looking *inter alia* at the impact metformin has on cancer cell metabolism, and potential therapeutic implications (*Clin Cancer Res* 2013, 19:6741–50).

“We showed, in preclinical cells and animal models, that metformin results in tumour reoxygenation, leading to increased radiotherapy response,” says Dal Pra. The relationship between hypoxia and resistance to radiotherapy has been known about for many years, he adds, but so far efforts to address

the problem by increasing oxygen delivery to the cells have not gained significant clinical traction. Metformin, by contrast, changes the way the cells consume oxygen, and may be more effective at combatting radio-resistance, he suggests.

Interestingly, when the impact of metformin on oxygen consumption was assessed *in vitro* in a panel of different cancer cells, says Dal Pra, “while there was a significant dose- and time-dependent decrease in oxygen consumption in all cell lines, the prostate cancer cell line showed the biggest impact.”

We’ll know more about what this could mean for patients undergoing salvage radiotherapy after prostatectomy when the findings are reported from Dal Pra’s SAKK 08/15-PROMET trial, which has recently started recruiting.

He worries, however, that the efforts of people like himself and his trial colleagues to learn more about exactly how and where metformin could play its most effective role in treating cancer may be hampered by lack of co-ordination.

Who will take the lead?

Alan Dal Pra says he is aware of more than 20 phase II trials currently looking at metformin and radiotherapy, including one in non-small-cell lung cancer, and others in cervical cancer, brain tumours, rectal cancer (as a neoadjuvant) and more. Searching the terms cancer+metformin on clinicaltrials.gov throws up 68 phase II or phase III studies currently recruiting.

If this were a patentable new drug, says Dal Pra, these trials would probably be part of a joined up strategy designed to learn about what would be the best way to prove its value in cancer. In the absence of such a joined up

strategy, he worries that unhelpful variations in doses, durations, patient populations, endpoints and biomarkers could limit what can be learned from pooling data, and biological samples will end up scattered around repositories with no common structure.

Dal Pra would love to see greater collaboration in the collective effort to gather the evidence for the clinical use of metformin in oncology – it’s something he says he discussed with Michael Pollak when the idea of the PROMET trial was conceived, but no one has yet stepped up to take a lead.

As for Pollak, he doubts that many more major metformin trials will be embarked upon until the results of some ongoing robust phase III trials have reported, including the MAST trial, looking at whether metformin can delay progression of low-risk prostate cancer for men who opt for active surveillance, and the MA.32 randomised trial of metformin vs placebo in early stage breast cancer, both of which are expected to report sometime in 2020.

The one exception, he suggests, would be a decision on adding a metformin arm to the Add-Aspirin trial – particularly for colorectal cancer. “That trial would really be looking at a situation where the evidence is a bit better, because of the accumulation of the drug in the colon, the association of colon cancer with metabolic syndrome, and the known adverse effect of weight.”

Pollak remains hopeful that metformin will indeed prove its value in some cancer settings. But he is also interested in efforts to develop analogues that would work in a similar way to metformin, with improved pharmacokinetics that would allow higher doses to reach cancer cells throughout the body. One of the first cancer clinical trials of a metformin analogue – IM-156, from the American Houston-

based biotech Immunomet – is set to start in Korea in the first half of 2018. Other companies, including San Francisco-based Enlilibrium, also have plans to evaluate metformin derivatives for use in oncology.

He worries that efforts to learn about how best to use metformin against cancer may be hampered by lack of co-ordination

Recent research from Japan suggesting a possible immunological mechanism for metformin is now adding new layers of interest to this intriguing drug, with mouse model studies showing that its anti-cancer activity does not work in immune-deficient mice (*PNAS* 2015, 112:1809–14).

Indeed Pollak’s own lab has recently reviewed studies showing the impact of metformin on the gut microbiome, which is itself linked to diabetes and obesity, and also plays a role in immune and inflammatory systems (*Diabetologica* 60:1662–67).

So as happens so often, says Pollak, disappointment that metformin did not turn out to be a panacea that benefits all cancer patients is spawning new areas of research, delving into the subtleties to learn about the specific settings where metformin does have a role to play, or how to adapt the drug to work more effectively. “This is a field that is keeping a lot of people busy.”

To comment on or share this article, go to bit.ly/cw80-metformin