Non-cancer medications for patients with incurable cancer:
time to stop and think?

Patients starting palliative systemic therapy for incurable cancer will often be taking medications on repeat prescription for pre-existing medical disorders. Common examples include antihypertensives, statins, and anticoagulants for the primary or secondary prevention of cardiovascular disorders. Such drugs have uncertain benefits in patients whose life-expectancy is now dominated by advanced cancer, rather than future non-cancer risks. Most landmark studies establishing common preventative medications did not include significant numbers of cancer patients, or excluded them altogether. There is also uncertainty around the risks and side effects of non-cancer medications in patients with cancer. Indeed it appears that, at least within the medical literature, this issue has been almost entirely overlooked by the oncology and wider healthcare communities. Attention is needed as practitioners remain uncertain about how to manage their patient's comorbidities alongside a new diagnosis of cancer. The important role of the GP as an expert in primary and secondary prevention may not be appreciated by patients, oncologists, and the GPs themselves, where the assumption exists that an oncologist will manage, with competence, all aspects of a cancer patient's care.

We shall consider some examples. In the case of statins for the primary prevention of coronary heart disease, the WOSCOPS study was a pivotal randomised controlled trial that justified the use of pravastatin in this setting. With an average follow-up of 5 years, the absolute reduction in all-cause mortality was 0.9% (P = 0.051).[1] Given that the life expectancy of a patient embarking on treatment for advanced cancer may be as little as 6 months (Table 1),[2] it is likely that for many cancer patients continuation of a statin will have negligible benefit. We can also consider the treatment of hypertension. One landmark meta-analysis of antihypertensive clinical trials demonstrated relative reductions in stroke risk of 38% and risk of coronary heart disease by 16%. However, when this is translated into absolute benefit, a cardiac event is prevented in only 0.7% of patients and stroke in 1.3% over a period of 4–5 years.[8] There is no randomised evidence specifically to support or refute the use of antihypertensive drugs in hypertensive cancer patients and the value of such a small incremental benefit in patients with a short life expectancy must be questioned.

As well as the relative efficacy of treatments in patients with cancer compared to the original trial populations, we should also bear in mind that concomitant medications can interact with cancer therapies. For instance the potentiation or inhibition of the p450 cytochrome enzyme family is a consequence of a number of common chemotherapeutic agents, such as the oral drug capecitabine or intravenous irinotecan. These may alter the metabolism of many common drugs such as calcium channel blockers used for the treatment of hypertension. The degree to which such adverse events truly have an impact on clinical outcome remains unknown. Similarly the side effects of concomitant medications can be more serious in patients with cancer who may require a more complex assessment of risks and benefits. For example, there is the potential for a reduced capacity to mount a haemodynamic response in a septic, neutropaenic patient taking a vasoactive antihypertensive agents.[9] The indication for prophylactic anticoagulation in cancer patients, who have an increased risk of both haemorrhage from vascular tumours and thrombosis, is also difficult to define.[10]

We do not advocate automatically stopping all concomitant medications at commencement of systemic cancer therapy. Careful re-evaluation of the risk:benefit ratio is required for each individual patient. Where we have no direct data to define the survival benefit from continuing a concomitant medication in the context of advanced cancer, we should base our decision on more pragmatic reasoning. Patients at particularly high risk of morbidity from non-cancer disease (for example, patients with type 1 diabetes) should be maintained on all medications deemed necessary, but this necessity should be heavily scrutinised: does a patient with type 2 diabetes really need to stay on metformin when they are likely to suffer cachexia in the near future?

The time of diagnosis and treatment initiation for terminal malignancy provides a key opportunity for medication review. A cancer patient's clinical condition is liable to change on a rapid and often unpredictable basis necessitating re-

Table 1. Life expectancy and age of patients with the four most common cancers in the UK.[3–7]

	Primary site, %			
	Breast	Lung	Colorectal	Prostate
Aged >60 years at diagnosis	58	85	83	89
Survival at 1 year for metastatic disease	49	33	49	82
Survival at 5 years for metastatic disease	12	<5	3	30

review or prioritisation of medications. As life expectancy shortens and relative gains from a medication diminish, the trigger threshold for discontinuation will fall. There may be a risk that a patient may interpret medication withdrawal as a negative step, symbolising a lack of hope. In some cases it may have been necessary to emphasise the benefit of a preventative medication to encourage compliance; to then say that the benefit is not so great after all is not easy. Professional barriers may also exist when an oncology specialist feels unqualified to alter medications without agreement from the original prescriber. We should be able to overcome these problems by careful and transparent communication with patients and other professionals. While it is the responsibility of the oncologist to clearly communicate estimated prognosis (which is notoriously difficult to accurately predict) and objectives of palliative treatment, GPs must also be clear about the rationale and expected benefit from treatment aimed at primary and secondary prevention. We also need to be clear whether responsibility for drug rationalisation should lie with GPs or cancer specialists.

Most importantly we require evidence to inform practice, but it is difficult to generate evidence of this type. There is no doubt that robust qualitative research can define patient preferences, helping us to find the correct balance between optimistic intervention and pragmatic treatment withdrawal. Strong evidence for mortality effects requires quantitative methods; for example, clinical trials of new cancer therapies could actively record the use of concomitant medications and associated outcomes alongside investigational cancer therapies. But this would require extra data collection in an area already significantly burdened by regulatory requirements.

In the future, incurable cancer is likely to behave as a chronic disease controllable with modern therapies. Cancer patients, therefore, need to be included in the key clinical trials of medications aimed at the primary and secondary prevention of common medical diseases. For this to be achieved, it is likely that incentives would need to be provided for the pharmaceutical industry, which funds such trials, to make their population samples more representative of the patient populations ultimately treated.

Practice can only be guided by defining the risk:benefit ratio for concomitant medications prescribed in primary care and continued at initiation of cancer therapies. As a first step, awareness of this issue will aid GPs and hospital specialists to collaborate in making considered decisions on drug rationalisation in cancer patients.

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