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Whatever happened to the minimum effective dose?

Traditional assumptions about the benefits of higher doses are being challenged as patients demand more emphasis on quality of life and new knowledge emerges about the development of resistance. So why are drug developers still failing to explore dosing adequately, asks **Simon Crompton**.



Five years ago, at a major ASCO event, the head of haematology and oncology products at the US regulator, the FDA, called out the “terrible job” drug developers were doing in exploring dosing. “The emphasis in clinical trials is primarily on efficacy,” said Richard Pazdur, “and drug companies don’t want to do phase II dosing studies to determine whether the maximum tolerated dose is the optimal dose.”

ASCO’s Chief Medical Officer, Richard Schilsky, backed him. “We need to do a better job of balancing the benefits and risks,” he said, “identifying the drug dose at which efficacy is maximised and toxicity minimised.”

With two such major figures telling it like it is, one might have expected this to mark a turning point – a wake-up call that too many oncology drug approvals are on the basis of the high doses trialled, which then simply get absorbed into practice. But it wasn’t. Speaking recently to *Cancer World*, Schilsky sees no movement. “I fully stand by the comments I made and note that not much has changed since they were made,” he says.

The fizz of excitement about designer drugs heralding an end to blunderbuss toxic approaches appears to have fallen flat. The ‘hit it hard, hit it often’ paradigm seems to have become so firmly ingrained into developing cancer drugs for approval that finding the minimum effective dose – above which there is added toxicity but no added benefit – is still an ill-funded, dimly lit corner of the research agenda.

The failure of drug developers to do the work needed to understand how their products can be used to greatest effect is being challenged by major figures in Europe as well

as the US. Writing recently in *Cancer World*, Denis Lacombe, director of the European Organisation for Research and Treatment of Cancer, commented that current models are “heavily driven by commercial interests” using “a chaotic approach” that fails to provide answers to critical questions asked by treating physicians and patients (*Cancer World* 80, October 2017). He called for research to be re-engineered around the needs of the patient.

“Very few trials, sadly, are asking major strategic questions beyond drug approval”

Patient groups too are voicing concerns. Hans Scheurer, President of Myeloma Patients Europe, says that too few phase II studies examine the lowest effective dose. “The approach is a bad one, especially when you look at patients with an incurable disease like multiple myeloma, because having a good quality of life for the remaining months and years is so important for many people.”

The consequences of high toxicity doses can be far-reaching on patients’ quality of life, particularly when the disease is incurable and many lines of treatment are tried as resistance continually develops. But severe side effects can lead to another life-threatening problem: non-adherence. A survey by the CML Advocates Network, which connects 118 chronic myeloid leukaemia patient organisations across Europe, found that only one third of

patients are highly adherent. One of the most significant factors behind non-adherence was side effects: 41% of patients with well-controlled side effects were highly adherent, while those having considerable difficulty with side effects were only 25% adherent.

Evidence on dosing

The tantalising irony is that there is a developing body of evidence – gained more from academia than commercial trials – that less aggressive, low dose or intermittent dose approaches hold exciting potential, particularly for controlling cancers that cannot be cured.

At a time when awareness of cancer overtreatment is burgeoning, and watchful approaches to prevent unnecessary surgery in prostate, breast and other cancers are gaining ground, traditional ‘cure at any cost’ drug development paradigms are also beginning to be questioned.

For example, a recent article in the journal *Leukemia* said that current dosing of the drug pomalidomide for myeloma was based on very little comparative data, and there was a significant scientific rationale for using it on alternate days rather than daily. “Very few trials, sadly, are asking major strategic questions beyond drug approval,” said lead author Thilo J Zander, head of Lymphoma and Myeloma Services at the Lucerne Cancer Centre in Switzerland. “Pomalidomide might be one good example of how substantial amounts of money may be saved, probably without affecting patient outcome, by using a different dose or schedule than in the registration trial.”

Similarly, studies have indicated

the effectiveness of lower doses of pembrolizumab for non-small cell lung cancer, and shorter treatment with trastuzumab for HER2+ breast cancer. The problem, as Zander points out, is that once a drug has been approved at a particular dose and schedule, then it becomes very hard to conduct trials exploring lower doses and durations. And even if such studies follow after initial approval, the timescales involved can make them redundant as science moves on.

A UK government-funded trial comparing six months of adjuvant trastuzumab against a year for HER2+ positive breast cancer, shows the risks of de-escalation studies being overtaken by events. The Persephone trial started recruiting in 2007, but – being an adjuvant trial – it took more than ten years to complete.

The results, presented at ASCO in 2018, showed that six months is as effective as a year, and is associated with lower cardiac risk. By that time, however, Roche, the developers of trastuzumab, had already got EMA and FDA approval for a new combination treatment involving the addition of pertuzumab to trastuzumab, with the latter being given for one year.

If the new combination treatment is adopted as the standard of care (currently the UK's NICE is recommending against this), then efforts to show that trastuzumab is as effective using half the duration specified in the approved combination protocol would have to start all over again.

Among patient advocacy groups and many clinicians, the fear is that there are few incentives to investigate the potential of lower dosing, drug holidays or stopping treatment – particularly for drug companies. Lower doses means reduced rev-

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enue, so why fund the trials? That leaves researchers having to cover the increasingly onerous cost of drugs. The issue is getting high on the patient advocate agenda, says Jan Geissler, co-founder of the CML Advocates Network.

“There’s probably no commercial interest in measuring the impact of low dosing on disease and quality of life. There’s little academic funding, it’s hard to recruit patients and little probability of academics and clinicians getting into high tier publications on the subject. Where’s the incentive to run this? This is quite bad news for us.”

Pioneering blood cancers

Despite the disincentives and difficulties, less aggressive approaches to treating cancer as a chronic disease are being pioneered in some blood cancers. Chronic myeloid leukaemia is the classic example of a disease where modern drugs (notably TKIs) have led to a dramatic improvement of survival since their introduction in the early 21st century. There is no evidence as yet to show that CML can ever be cured by these drugs, but most people living with CML can now

expect a near normal lifespan if they adhere to treatment, and those with the lowest levels of residual disease have a chance of discontinuing treatment, with 50% remaining free from relapse over the long term.

There are now good data showing the effectiveness of lower dosages of TKIs. Andreas Hochhaus, head of the Haematology and Medical Oncology Department at the University Medical Centre Jena in Germany, and one of CML’s leading drug researchers, is emphatic that the data has to be there to confirm the right drug level and schedule to control disease. Simply reducing or stopping treatment without supporting research runs the risk of encouraging resistance. “All the discussion on lower doses for better tolerability is very dangerous as long as you don’t have data for it,” he says.

The data on dosing in CML has been hard-won. Hochhaus observes that four of the five inhibitors available – nilotinib, dasatinib, bosutinib and ponatinib – were originally approved at too high doses, and severe side effects in trial subjects resulted in new studies at lower doses. The FDA suspended sales of ponatinib in 2013, a year after original approval, because of an increased number of blood clots in patients taking the drug, and gave

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the drug new approval at lower doses in 2016.

For Hochhaus, discontinuation of treatment is as important to investigate as lower dosing. “In CML, I’m now quite happy at the doses currently in clinical use. I think it’s better to discontinue treatment.”

Recent trials demonstrating that some CML patients who have achieved a stable deep molecular response on TKIs can safely stop taking the drug have given rise to the concept of treatment free remission (TFR). Around one third of patients successfully discontinue treatment, with the option of returning to treatment if relapse occurs.

Similar strategies have been found to work in follicular lymphoma. And where blood cancers lead, others can follow, says Hochhaus. “It’s about not aiming to eradicate the disease, but silencing the disease,” he says.

“We’re also seeing TFR in ongoing palliative treatment of inoperable colorectal cancer where there is a very good response to chemotherapy. You can’t continue it for ever, but studies have shown that you can quite successfully stop and restart as needed.

“There are more and more diseases in haematology and oncology where a good response to stopping and restarting is possible, and the applications are quite broad. It’s clear we can learn from CML.”

Re-thinking resistance

The need to pay more attention to quality of life issues, as people live longer with cancer, is a compelling incentive to increase efforts to better define the minimum effective dose and duration. But this is



about more than maximising quality of life. One of the main lessons learnt from 20 years of personalised cancer medicine is that resistance kills, and dose and duration are now taking centre stage in new strategies aimed at slowing the emergence of resistant clones, particularly in solid tumours.

Advances in our understanding of resistance, backed by early clinical evidence, suggest that stopping and starting treatment, in a calibrated response to treatment-affected changes in the tumour, can encourage competition between cells and prevent or delay resistant clones from gaining free-rein.

Recent studies by Robert Gatenby and his team from the Cancer Biology and Evolution Program at the Moffitt Cancer Center, in Florida, challenge current treatment protocols in metastatic prostate cancer, where normally the same drug is given at the maximum possible dose

over and over again until progression. The Moffitt work opens up the possibility of another option.

In a pilot clinical trial reported last year, the Moffitt researchers treated 11 patients with metastatic castrate-resistant prostate cancer with abiraterone until their

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PSA level dropped to half the pre-treatment level. At that point, they stopped treatment until PSA reached pre-treatment levels, and then treated again. The tumours grew but remained treatable because treatment-sensitive cells could keep competing with treatment-resistant cells.

The trial found that time to progression was increased compared to standard treatment, and this was achieved with a lower cumulative dose. Some patients received treatment less than once a year. The Moffitt researchers now plan further clinical trials of this 'adaptive therapy' approach for melanoma, ovarian, thyroid, breast and lung cancer as well as prostate cancer.

Hitting tumours as hard as possible for as long as possible with the maximum tolerated dose becomes the norm to achieve these endpoints

Charles Swanton, Leader of the Cancer Evolution and Genome Instability Laboratory at the Francis Crick Institute in London and Cancer Research UK's Chief Clinician, says that such work makes a "very compelling case" that traditional ways of researching new drug treatments need a major re-think.

"The mainstay approach is generally that you hit your maximum tolerated dose in phase I, and you

move into phase II with that, and then you explore response, so that hasn't changed for decades," he says. "But if we accept that resistance to targeted therapies is inevitable in over 90% of patients, if not more, one has to work out how to prevent that resistant sub-clone from evolving."

A problem with current models of regulatory approvals, he says, is that they are based on clinical trials revolving around reporting minimum progression free survival, response rates and occasionally overall survival outcomes. Hitting tumours as hard as possible for as long as possible with the maximum tolerated dose becomes the norm to achieve these endpoints.

"The difficulty with this model is that inevitably you select out resistant sub-clones that can't be treated as effectively or at all, and then you've lost the battle."

In other words, approvals have not kept up with scientific progress, and there's little appetite for commercial trials using innovative approaches using low doses and breaks in treatment.

It is not a problem of lack of financial incentive for drug companies, according to Swanton. The main reason is a lack of validated approaches to measure the relative proportion of different clones in a tumour – measurements that are crucial for benchmarking drug doses and cycles of administration.

"I think drug companies and researchers are reluctant to go this way because understanding what the doses might be, or the schedules that you might apply to patients in a clinical trial, is currently very hard to establish. This is partly due to the lack of reliable markers of evolving resistant sub-clones."

There are, however, indications that some drug companies are responding to the new evidence about the possibilities of stopping and restarting. Andreas Hochhaus was involved in research leading to the 2017 approval of Novartis' TKI Tasigna (nilotinib) as the first and only CML therapy to include information about attempting treatment discontinuation on its prescribing information. The FDA approval was based on safety and efficacy analysis of two open label trials evaluating the potential to maintain major molecular response after stopping Tasigna therapy among patients with Philadelphia chromosome-positive CML. The trials demonstrated that almost half of the patients who discontinued Tasigna remained in treatment free remission approximately two years after stopping treatment.

"It has long been our ambition at Novartis to make it possible for some people with CML to discontinue therapy," said Bruno Strigini, Novartis Oncology's CEO.

Hans Scheurer says there are signs of growing openness to this approach from some companies working in the field of myeloma. Myeloma Patients Europe, as part of an umbrella of haematology patient organisations, invited nine pharmaceutical companies to a recent community advisory board meeting – 'Hem-CAB' (see Patient Voice, p 53) – and found that some were more stuck in their own agenda of development than others. The more established companies were, the more likely they were to listen and to take patient perspectives into account when designing a clinical trial.

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pean Medicines Agency sends it back saying it’s based on too high a dose,” he says. “Some companies are better at this than others.” At future advisory board meetings, he wants drug companies to address directly engaging with patients’ organisations on dosing.

In the absence of data

Given the general lack of strong data, what are the implications for clinicians who, after discussions with patients, want to take a ‘gentler’ course of treatment, with the emphasis on avoiding unpleasant drug side effects? There are few hard and fast guidelines.

According to Scheurer, haematologists have very different takes on balancing quality and length of life when it comes to incurable but treatable conditions such as myeloma. Some haematologists tend to focus on hitting the disease as hard as possible, based on findings that the disease could stay away longer. But Scheurer says there needs to be awareness that this is a statistical approach, and not suitable for every patient.

“There’s a balance you need to keep advocating, because these kind of approaches tend to look at treatment isolated from the rest of life,” he says. “The reality is that there are a lot of new treatments being introduced, and they are often used one after another as one starts not to work.

“We know that the fitter you are when you start treatment, the better the treatments work. So there’s a case that, although hitting the disease hard at the start may make it stay away longer, it may also make you more frail, and successive treatments may be less effective. So I believe very strongly that there should always be consideration given to how hitting it hard affects the fitness of the patient.”

Scheurer himself, who has had the disease for 13 years, knows about this balancing act. As he contemplates next steps now his cancer is growing again, he’s expecting to have conversations with his doctor that will embrace his daily routines, family life and aspirations – and the effects the drugs will have on him. But not all physicians feel able to personalise care, he says.

“The treatments improve and guidelines change so fast in myeloma at the moment, and most doctors and haematologists become a bit insecure and stick to the guidelines or latest journal articles. The picture of the individual patient fades.”

Jacob Hygen, Vice Chairman of the Norwegian Blood Cancer patient advocacy group, has had multiple myeloma for 19 years, and after initial high-dose therapy his treatment has generally avoided high doses of new drugs, or drugs in combination. This is partly because there weren’t so many options avail-

able when he started drug treatment in 2010, and he and his doctor stayed with the same approach because it seemed to work.

“There is debate in Norway among haematologists about how aggressive you should be in treatment,” he says. “On doses and the use of multiple drugs, the reality is that knowledge of myeloma is still behind other blood cancers, so it is a trial and error approach: they just have to see what works for the individual patient.”

His doctor is Anders Waage, from the Department of Haematology at the Norwegian University of Science and Technology, and one of Norway’s leading multiple myeloma experts. He says the ‘less is more’ debate partly reflects how complicated it can be to find dosages and approaches that suit individual needs. Some patients will need high doses, others will prioritise fewer side effects, and finding effective ways to discriminate is important.

But generally in cancer there is a bias towards overtreatment, says Waage. “Certainly in multiple myeloma, there’s a very marked tendency to start at high doses and continue to relapse, and I’m not sure that’s the right thing to do for all patients.” If there are signs

“Most doctors become a bit insecure and stick to the guidelines... The picture of the individual patient fades”

of the disease coming back after treatment, there's a real tendency to treat again early if the patient is not on maintenance treatment," he says.

"And the clear tendency in myeloma is that all patients should be on maintenance treatment, which is wrong."

Why is this happening? "I think there's the intuitive thought that if it works well for one dose it might work twice as well if you double the dose," he says. "And of course, there's a lot of pressure from the drug companies. They want to sell more drugs. I think that's a very simple explanation."

He admits that charting a gentler approach with patients, often with the emphasis on quality of life, is not always easy. With studies hard to fund and organise, and in the absence of clear guidelines, physicians like himself effectively go out on a limb if they don't take the 'standard' approach – taking an overview of evidence, drawing on personal experience. In patients whose disease is taking a more indolent, benign course, rather than continuing maintenance treatment he will consider lowering doses or pausing treatment and waiting for relapse – which might take several years.

It doesn't put him in a difficult position, he says – maintenance treatment was not considered standard until recently. "But I think many people are now considering doing as I do, particularly in Europe as opposed to the United States," he says. "We can never let the treatment be worse than the disease."

What doctors like Waage would like to see is a greater balance in drug research: always acknowledg-

ing that, for some patients, high or continuous doses will be the right option, but that for many others an approach that maximises quality of life is required – even if it reduces length of life. The problem is that, currently, the evidence base to validate these approaches is badly lacking. The balance is tilted to toxicity.

Ways forward

What needs to happen for drug developers to heed the call of Pazdur and others to do a better job of exploring dosing and duration?

A good first step would be to follow the advice of the EORTC's Denis Lacombe, to "re-engineer" the drug development process around finding solutions for patients rather than approval for new products – a problem hardwired into the whole regulatory system.

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Closer consultation and involvement of patients in setting the research would inevitably bring the issue of toxicity and minimum effective dosing to the fore. The Hem-CAB meeting convened in June 2018 by Myeloma Patients

Europe, where advocacy groups from a spectrum of haematology diseases were able to discuss their needs and concerns with nine companies active in that field, could make a big difference here.

Other mechanisms that have been floated include a proposal to oblige companies to commit to giving adequate attention to dosing issues as a 'quid pro quo' for getting patients to sign informed consent to participating in first-in-human trials. As Lisa Hutchinson, founding Chief Editor of *Nature Reviews Clinical Oncology*, wrote recently in *Cancer World*, this would not only minimise the risk for patients in trials, but it would also encourage a greater sense of trust in the trial process generally (issue 82, May 2018).

"If sponsors had to sign a commitment to perform optimisation work, it may give patients on the trial the best chance of benefit, and maximise the improvements for future patients by ensuring that when new drugs reach the market, we would have a good idea about optimum dosing and cost-effectiveness," she wrote.

Growing scientific knowledge about the way cancers develop is likely to add to pressure for change: trials and approvals that ignore the emerging evidence about the heterogeneity of tumours, the evolutionary causes of resistance and related dosing issues will be increasingly open to criticism.

Charles Swanton points to a future of approvals based on new types of trials that address emerging resistance in tumours, and pinpoint individualised dosing approaches rather than perpetuating the full frontal attack formula. Finding technologies to benchmark



doses and schedules according to cancer activity will be key.

“I think there is some promise here,” he says. “I think one of the ways of dealing with this might be through sensitive measuring of circulating free DNA from mutant clones in the blood.” Swanton’s team has already published research in *Nature* showing the feasibility of profiling circulating tumour DNA for non-small-cell lung cancer, and there’s also evidence that it will work for other metastatic cancers, including breast cancer.

“One attractive model to begin addressing the drug resistance problem is a bespoke sequencing approach where we know what the mutations are in the tumour – we

know the trunk and branch mutations from analysis after surgery – and then we can use sensitive targeted sequencing approaches to see the evolution of one or two branches, which is the hallmark of metastatic recurrence, from blood tests. This means we can begin to see the evolution of therapy-resistant sub-clones before we see disease progress on a CT scan – so-called minimal residual disease.

“Through sensitive resistance sub-clone monitoring in blood, we may be able to think about ways in due course of toggling drug dosing on and off, proportionate to the evolution of resistant markers that come up in blood. I think if the biomarkers improve, these studies

will become more feasible.”

There are understandable fears among some clinicians and researchers that publicity about the prospect of treatment free remission in some cancers with reduced, intermittent or discontinued treatment has its dangers. Improvised do-it-yourself approaches to dosing do not work. Dosing and treatment interval issues are complex and we need data. But that is the point. We need to know more, and those involved in drug development, as well as academia, need to be playing their full part in building understanding.

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