

When is it OK to randomise cancer patients to placebo?

→ Anna Wagstaff

No-one wants to see progress in cancer research more than the patients themselves. But how do we deal with potential conflicts of interest when testing new drugs involves giving placebos to people dying of cancer?

Karen has incurable GIST. She has been kept alive for four years thanks largely to Glivec (imatinib), but eventually developed resistance and was put on Sutent (sunitinib), which kept the tumour in check for a further year. Her latest CT scan, however, reveals that the disease is progressing and she is pinning her hopes on a new drug being trialled for people like her who have run out of options.

The new generation of targeted drugs has certainly transformed the outlook for GIST patients – and she is keen to give it a go. But her only option is the lottery of a phase III randomised trial, where she stands a 33% chance of being given a substance designed to have no deterrent effect at all on the tumour that is killing her.

This will be a crossover trial, and Karen has been assured that if she is in the placebo arm, she will be allowed to change to the active drug – a treatment that is not available outside a clinical trial – if her disease shows signs of progressing. She will be checked every six weeks – twice as often as she is checked outside the trial.

She thinks it very likely that waiting until her cancer has progressed before getting the active treatment means she will die earlier than if she started on the active

treatment straight away. But she also knows that, until the trial is done, it is impossible to say whether this is the case, or how many weeks, months or years she would stand to lose. The phase II trial had shown marked, not dramatic, activity – so it is clearly no wonderdrug. But the fact that the company has decided to invest in a phase III trial indicates some confidence that it will show sufficient benefit to stand a fair chance of approval.

Karen would like to try the drug. She appreciates that the trial at least guarantees her better supportive care and understands that progress in cancer medicine depends on being able to show that experimental treatments show meaningful clinical benefit. But she still does not like the one in three chance that she would be randomised to a placebo.

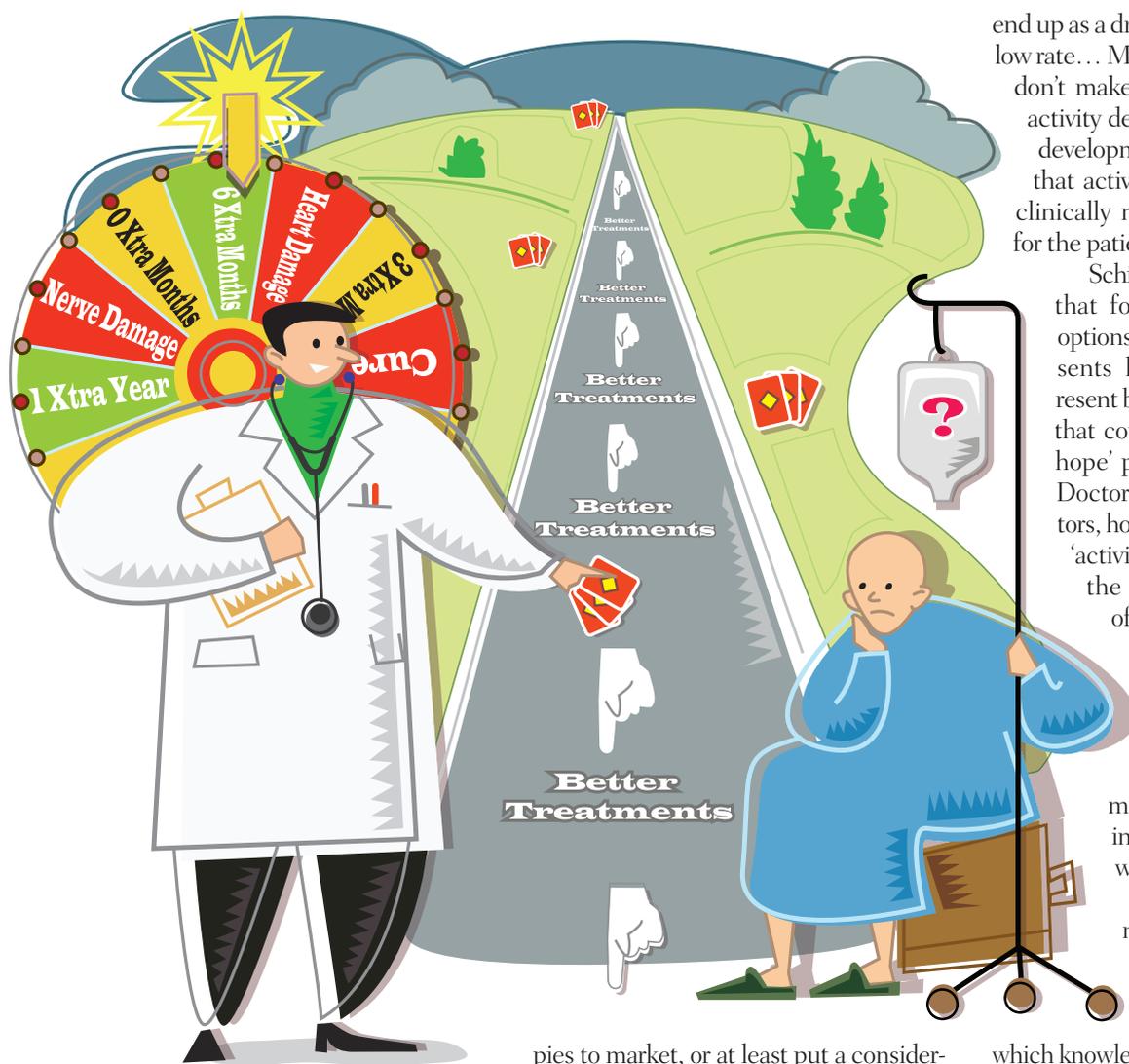
Despite being told that, on the active arm, serious side-effects could outweigh any potential benefit, she remains convinced that her best bet is to get that drug before her disease progresses further. She decides to wait for an expanded access programme somewhere or to apply to join a phase II trial if she can find one. The phase III trial, she thinks, will have to find some other patient to randomise.

PROGRESS DERAILED?

Karen is a hypothetical patient, but her dilemma is real enough. The reluctance of many patients in her position to join randomised placebo-controlled trials is creating concern among many researchers, who argue that this trial design – used rarely in cancer over past decades – is becoming an increasingly vital option for getting the new generation of cytostatic drugs to market. Whereas cytotoxics shrink tumours, cytostatic therapies aim to merely control the disease – and proving a cancer is not progressing can be quite tricky.

For instance, though cancers are rarely known to shrink of their own accord, it is not uncommon to go through periods of remission where growth slows or stops for a while. Without a placebo comparator arm, it can be hard for the researchers – and regulators – to distinguish the effect of the drug from the natural history of the disease.

The assessment of whether a patient's disease has progressed or remained stable is also seen as a problem, being considered to be more susceptible to investigator bias than measurements of tumour shrinkage. Using a double-blind placebo-control design (where neither patients nor clinicians know which patients are in which



end up as a drug approval. It is a dismally low rate... Most of the 95% of drugs that don't make it through phase III had activity demonstrated earlier in their development, but most of the time that activity does not translate into clinically meaningful improvements for the patients."

Schilsky understands completely that for patients with no other options, evidence of activity represents hope, and these patients resent being obliged to join a lottery that could randomise them to 'no hope' plus best supportive care. Doctors, researchers and regulators, however, need proof that such 'activity' could actually improve the quality of life or survival of their patients – and that could require a placebo-controlled randomised clinical trial. Without that, all sorts of compounds could enter the market without anyone having any real idea about what works and what doesn't.

Many patients who have now reached the end of the line, says Schilsky, have benefited earlier in their disease from therapies about which knowledge was gained thanks to an earlier generation of patients who agreed to subject themselves to the lottery of a randomised controlled trial.

FRAMING THE DISCUSSION

Earlier this year, Schilsky teamed up with a group of oncologists, trialists, regulators and ethicists to write a position paper, on behalf of ASCO, on the Ethical, Scientific,

arm) can be important in convincing the regulators that over-enthusiastic clinicians have not read more into the efficacy of their experimental drug than it merits.

The concern is that if patients are unwilling to participate in trials with placebo arms, they could jeopardise the chances of getting promising new thera-

pies to market, or at least put a considerable brake on progress.

Richard Schilsky, professor of medicine at the University of Chicago, is actively highlighting these concerns. "If you look at the success rate over the last 10 years or so of getting new oncology drugs approved, only 5% of new oncology drugs that enter clinical testing actually make it through phase III testing and

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and Regulatory Perspectives Regarding the Use of Placebos in Cancer Clinical Trials (*JCO* 26:1371–78).

The paper argued that there is an ethical case for randomising cancer patients to different treatment arms (either a head-to-head comparison of active treatments or active treatment versus placebo), when there is “genuine uncertainty or disagreement about the relative merits of two or more therapies within the expert medical community” – a situation they refer to as ‘clinical equipoise’. One important corollary of this is that “participants should not receive a treatment inferior to what is otherwise available in clinical practice” – which rules out the use of a placebo arm where an established effective treatment exists for that group of patients.

The issue of whether it is ethically acceptable to randomise some trial patients to placebo then rests on whether a placebo arm is really necessary in order to obtain reliable data – methodological criteria – and whether the patients on the placebo arm would be put at unacceptable risk – ethical criteria.

The ASCO paper argues that placebo controls may be justified when they are necessary to prove that a new treatment has efficacy:

- in a disease with a high placebo response rate, or
 - in a condition that waxes and wanes in severity, or has spontaneous remissions, or has an uncertain and unpredictable course, or
 - when therapies exist that are only minimally effective or have serious adverse effects, or
 - in the absence of any effective therapy.
- It adds that there may be a justification for a placebo arm, “to assure that physicians and patients are blinded to treatment assignment so as to minimize bias in assessment of study end points.”

However, any such trial would have to be designed in such a way that, “a patient randomly assigned to placebo should not be

substantially more likely than those in active treatment group(s) to die; suffer irreversible morbidity, disability, or other substantial harms; suffer reversible but serious harm; or suffer severe discomfort.”

MITIGATING TRIAL DESIGNS

The paper looks at trial design options that could help minimise the risk posed to patients on the placebo arm. Key among these are ‘add on’ designs, where all patients receive an established active therapy, but are then randomised to receive, in addition, either the active experimental drug or placebo. Many new targeted therapies have been tested in this way in combination with an established cytotoxic. Such designs tend to be less controversial because all patients receive something active; however, they introduce an added complexity of drug interaction, and they are not an option where there are no effective therapies available.

Another possibility is the ‘randomised discontinuation design’, as used in the phase II trials of sorafenib (Nexavar) for kidney cancer, in which a placebo arm was used because there was no pre-existing therapy. All trial patients were offered the active therapy to start with, and those who clearly responded were kept on it. Those who progressed or experienced serious toxicity were taken off it. Only those in the middle who tolerated the drug and showed stable disease, so that the benefit/toxicity balance was unclear, were randomised between the active drug and placebo. This allowed the trial to go ahead while guaranteeing access to patients who clearly benefited from the drug and sparing needless suffering to those who clearly did not.

Then there is the crossover design, as used in the phase III trial of sunitinib for

GIST patients who had become resistant to Glivec, when the absence of pre-existing further lines of therapy was seen to justify a placebo arm. Patients were randomised 2:1 between sunitinib and placebo, and were closely monitored. Those showing progressive disease were then unblinded, and if it turned out that they had been on the placebo, were given the option of crossing over to the active treatment.

This ensured that the exposure of patients to the inactive treatment was kept to the minimum necessary to provide data on the primary endpoint of the trial, which was progression-free survival.

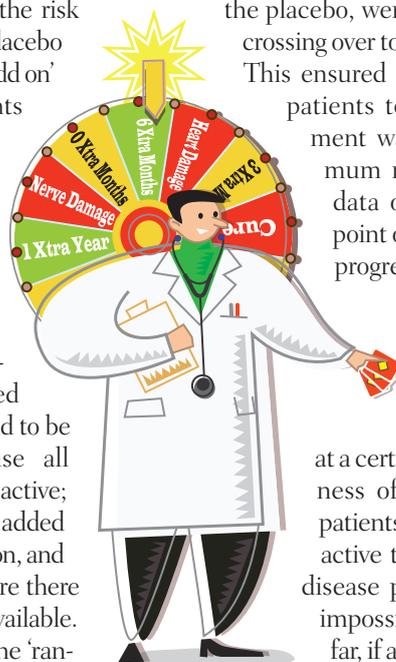
These trial designs go a long way towards making placebo controls more acceptable, although at a certain cost to the robustness of the data. Allowing patients to cross over to the active treatment on signs of disease progression makes it impossible to find out how far, if at all, the experimental drug increases survival. And

while improved progression-free survival (PFS) has been shown to correlate with improved survival in some cases, that does not mean that this can be assumed for all drugs in all disease settings.

The ASCO position paper was intended to add some clarity to the discussion about the use of placebos, to assuage concerns and to contribute to increased enrolment in clinical trials. How far it has fulfilled its aims is difficult to tell as, much to Schilsky’s surprise, the paper seems to have sparked little controversy.

WHO DECIDES?

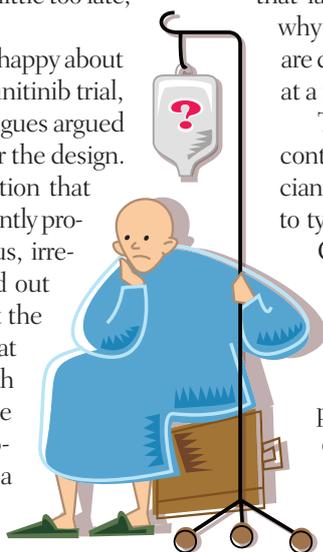
One patient advocate whose concerns have certainly not been assuaged is Norman Scherzer, executive director of the US GIST patient organisation Life Raft. With regard



to the criteria presented in the ASCO paper to justify placebo-controlled trials, he poses this question: who decides? Who decides that such a trial design is necessary on this or that methodological criterion? And who decides that the patients exposed to placebo are not placed at an unacceptable risk?

“If you propose giving a placebo to terminally ill patients to demonstrate that their disease progression or death rate will be greater if they are not given the drug, you must assume the burden of demonstrating that there are no alternatives, and that patients on the placebo arm really won’t suffer serious irreversible harm,” says Scherzer. “Secondly, you must include the recipients of the placebo in the decision-making process. Not in the consent process down the line, which is too little too late, but in the process itself.”

Life Raft was deeply unhappy about the use of placebo in the sunitinib trial, and Scherzer and his colleagues argued hard for the sponsor to alter the design. They challenged the assertion that the crossover design sufficiently protected patients from serious, irreversible harm. “We worked out some theoretical models at the time where we showed that the amount of tumour growth one could experience while on a placebo was pretty substantial. Because you had a combination of the wash-out period [where all trial patients come off their previous medication to clear the system] and then the time that it took before you were unblinded. Also they defined the tumour progression by a standard – RECIST – that much of the clinical community has rejected, which requires a



measurement that allows tumours to grow well over 20% before you are considered actually progressing.”

Life Raft asked the sponsors to consider some alternatives, including the use of an ‘historical’ arm as a comparator in place of a prospective placebo arm. Relevant data could have been gathered from Life Raft’s own data base, in which hundreds of GIST patients voluntarily submit reports of how their disease is progressing, as well as other registries such as that of the US Armed Forces Institute of Pathology, argued Life Raft.

Scherzer feels, however, that they were never taken very seriously. No surprise, perhaps, considering how hard it would have been to change a planned trial design at that late stage – which is exactly why Scherzer and his colleagues are calling for patients to get a say at a much earlier stage.

The sunitinib trial was also controversial among many clinicians, who argued that resistance to tyrosine kinase inhibitors like Glivec tends not to be absolute: some tumour cells still respond. They argued that, in the absence of anything better, trial patients should be randomised between sunitinib and remaining on Glivec, but it turned out to be impossible to have a meaningful dialogue with the sponsor.

Peter Reichardt, a GIST specialist from the Helios Kliniken in Bad Saarow, Germany, found the experience very frustrating. “The sponsor will say that the regulators require this design, and if we don’t use this design they will not accept the

results. You either accept it or you don’t participate in the trial. So the clinicians then have to go to their patients and say: we have no room to argue, so you either join the trial with a 33% chance of getting a placebo, or you don’t.”

Scherzer doubts that the regulators really did insist on a placebo design. “On occasions when we went back to the FDA, it turned out not to be the case. The FDA expects the industry to meet certain scientific standards of proof. In no trial does the FDA tell a company in advance what they need to build into their protocol.

“A placebo is certainly a very viable standard of proof. It clearly helps to demonstrate something, and might help to do so more efficiently in terms of time and cost than not using a placebo. But that wasn’t the question. The question was: was there an alternative?”

Had Glivec been used instead of placebo, he adds, one might have expected to see a smaller difference between the two arms, and it might have taken more patients, more time and more money to reach the standard of proof required by the regulator. “Is that an acceptable reason for exposing a certain number of patients to a placebo? We would say no.

“We would also argue that using the current standard of treatment – in this case Glivec – in place of a placebo is better science, for what we are interested in is not whether a new drug is better than nothing, but whether it is better than the current standard of treatment.”

NO ROOM FOR MANOEUVRE

Thierry Le Chevalier, who heads GSK’s Oncology Clinical Development in Europe, says that the major problem is the complexity involved in getting a drug to

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market under different regulatory regimes, which leaves very little room for manoeuvre. “In big companies you don’t work only with Europe, you have to work with the US, Japan, Korea etc... and they all have different standards of proof and registration. For instance, when you speak to EMEA you cannot make any decision that interferes with what is required by the FDA.”

As well as meeting different standards for measuring efficacy, companies have to meet different safety standards and manufacturing requirements for consistency and shelf-life. All this has to be dealt with in parallel, so that the company can manufacture the drug as soon as approval is given. Upsetting one part of the equation could derail a process that has taken years.

Le Chevalier came to GSK from a career spent largely at France’s Institut Gustave Roussy. He shares the French enthusiasm for giving cancer patients access to experimental drugs as early as possible, and feels uncomfortable about offering placebos to any patient in a phase III trial in his clinics.

“In a phase II one is looking for activity, so it generally easy to obtain consent from a patient to participate. But in phase III studies you know there is the potential for a substantial response. Everyone knows going to phase III sends out strong signals of confidence in the drug. And if the patient knows he has only a 50% chance to get that drug – that is just frustrating.” It is doubly frustrating, he says, for patients who have run out of options – one good reason, he adds, for trialling drugs in earlier disease settings where possible.

“What I would say is that, if the placebo is acceptable and unavoidable, it is mandatory to have very strong early

stopping rules... Sometimes you see differences that are extremely significant from a statistical point of view, and you can imagine that the same results might have been visible with fewer patients.”

Whether the difference is big or small, Le Chevalier accepts that the control arm of any randomised trial is in some sense ‘supposed’ to perform worse in order to prove the activity of the investigational product, and when that trial design involves giving a placebo to a cancer patient with no other options, this is not a comfortable thing to do, even if you are convinced it is the only way to get a potentially important new drug on to the market. “For me it is an unresolved problem. If I had the solution to this, I would tell you.”

A CONFLICT OF INTERESTS

Scherzer puts it this way: “We find ourselves comparing the needs of those who are exposed to a placebo against those who might benefit in the future. We agree with ethicists who state that you’ve got to look at it in the present tense. Good outcomes, no matter how noble, cannot justify research that fails to protect the health and safety of those who participate, particularly terminally ill patients who may have no access to other treatments. When the pathway to a new drug is to run a gauntlet of placebos, that cannot be taken to be consent freely and fairly given. It is coercion by any other name.”

Reichardt puts it this way: “If patients argue ‘we don’t want a placebo trial,’ this could result in the trial not happening... Patients have to understand that no trial means no further improvements, no new treatments, no future achievement.”

Given the element of conflict of interests in this situation, it might be argued

that the only ethical way to proceed would be to allow the patients some say in the way that phase III trials are designed.

This is something Reichardt strongly advocates. “Once a new treatment has shown activity in an early trial, then we can sit down and discuss how can we bring this drug further. Then we start by asking: What kind of trial would be needed to prove efficacy? What would be the target population? What would be acceptable to the regulators? What would be practical with respect to numbers? What would be acceptable to sponsors in terms of money? What would be acceptable to patients as potential candidates for the trial? At that moment the voice of the patient groups could be necessary.

“They can bring their arguments, and learn what it means if they say ‘we cannot accept this’, and we will say, ‘OK then we cannot do the trial’, and then they would say ‘we want the trial’. And then we can start discussing how to go about this.”

The suggestion provokes a certain nervousness among many sponsors, who fear that patient groups could end up holding a gun to their heads. Yet far more damage is already being done by some patient communities who effectively sabotage trials they don’t like, by refusing to enrol.

There has to be a better way. “Nobody has a greater interest in fast-tracking testing and approval of new drugs than a cancer patient has,” says Scherzer. “The whole process would ultimately be a better process if patients like us were seriously engaged in the decision-making process from the very beginning. We might help come up with a protocol that everybody could live with. When you leave out the guinea-pig – in this case the patient – I do think that is by its nature somewhat unfair.”