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Lower risk of serious side-effects in trials of new targeted drugs

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Patients in early clinical trials of new-style targeted cancer therapies appear to have a much lower risk of the most serious side-effects than with traditional chemotherapy, according to a new analysis.

Researchers at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust analysed data from 36 Phase I trials run by the organisations' joint Drug Development Unit.

The study, published today in August's *Annals of Oncology*, found the overall risk to patients of suffering a life-threatening side-effect was around seven times less than for traditional cytotoxic agents*.

Most new cancer drugs developed over recent years are targeted agents, which attack the specific genetic or molecular faults driving cancer growth, rather than one-size-fits-all chemotherapeutics, which kill all rapidly dividing cells.

Recent studies have shown that patient response rates in Phase I trials of new-generation targeted drugs are approximately two-fold higher than for old-style drugs. But until now, the risk of side-effects to patients taking part in early stage trials of new-style drugs has been unclear.

Senior author Dr Rhoda Molife, a medical oncologist and senior investigator in Phase I clinical trials in the Drug Development Unit of The Institute of Cancer Research and The Royal Marsden, said: "Our study found that the risk of developing a serious side-effect in a Phase I

trial of a targeted drug was relatively low, compared with previous analyses of similar trials of old-style chemotherapies.

"The theory behind targeted drugs is that they should affect only cancer cells that have a specific fault and spare healthy cells, which we hoped would lead to higher rates of efficacy and lower rates of side-effects. It's very pleasing that our study seems to back this up, at least in the context of Phase I trials."

"Importantly, we also identified characteristics that put patients at higher risk of these toxicities, including if they were sicker when joining the trial. This will help doctors make the right choices about who should be given new drugs in early stage clinical trials."

Scientists retrospectively analysed data from 687 patients treated at the Drug Development Unit of The Institute of Cancer Research and The Royal Marsden between January 2005 and December 2009. They had a range of cancer types, with gastrointestinal, gynaecological and sarcoma the most common.

The Drug Development Unit of The Institute of Cancer Research and The Royal Marsden is supported by the National Institute for Health Research Biomedical Research Centre for Cancer, and also receives funding from Cancer Research UK and the Experimental Cancer Medicine Centre network.

For targeted drugs, the most common toxicities were gastrointestinal – such as loss of appetite, diarrhoea and vomiting – and fatigue, while side-effects for cytotoxic drugs are generally haematological or cardiovascular in nature

Patients were more likely to suffer side-effects if they were given a higher dose than that which the trial later found to be optimal, or if they

were sicker when they joined the trial. The findings should help guide researchers in selecting patients for trials and improving trial design.

Professor Alan Ashworth, Chief Executive of The Institute of Cancer Research, said: "The discovery of targeted therapies is revolutionising the way we treat cancer, and is a key focus of our research here at The Institute of Cancer Research. Many of these drugs have individually transformed the care of certain cancers, but the strength of this study is that it helps confirm the validity of the overall approach."

More information: "Defining the risk of toxicity in phase I oncology trials of novel molecularly targeted agents: a single centre experience" with corresponding author L. R. Molife publishes in the August issue of the *Annals of Oncology*.

* The overall risk to patients of suffering a Grade 4, life-threatening, side-effect in this study was 1.9 per cent, compared with 14 per cent found in an analysis of trials from 1991 to 2002. The risk of a Grade 3, severe, side-effect in this study was 14.1 per cent, compared to 10-36 per cent found across two previous analyses of Phase I trials of cytotoxic agents.

Phase I trials are designed to evaluate the drug's safety and also the optimal dose to give to patients. As these small trials represent the first time a drug has been tested in people, its effectiveness and side-effects are not yet known and so patients who are considering taking part face many uncertainties.

Although the specific side-effects of each drug will differ, understanding average responses is important so doctors can help patients evaluate whether to participate. Some side-effects are unavoidable as doctors try to establish the most appropriate dose for patients.