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Making sense of off-label drug use

Healthcare professionals should inform patients of the benefits and risks of off-label drug use and involve them in the decision-making process.

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Last year, the Ministry of Health (MOH) came up with a list of clinically proven and cost-effective cancer drug treatments that can be covered by MediShield Life insurance from September this year. The list will apply to coverage by all Integrated Shield Plans (IPs) sold or renewed by private insurers from April next year.

The MOH wants to limit the use of MediShield and IPs for cancer drugs to those that have been clinically proven to work and are cost-effective.

A decision to pursue off-label drug use may be sub-optimal in many clinical scenarios. There are some risks and costs that patients should be aware of.

Sometimes, physicians come across patients with conditions where no approved drug is available. These patients may have exhausted all lines of approved treatment options, or they may have drug intolerance to approved medications.

For specific diseases such as rare tumours, there may be a lack of approved drugs with strong clinical evidence. Regulatory approvals may be pending for clinical use.

Pharmaceutical companies may also be unwilling to pursue additional evidence needed for some indications due to limited additional financial incentive for doing so. Under such circumstances, physicians may adopt off-label use of available drugs, or use non-registered drugs obtained through each country's special access routes.

WHAT IS OFF-LABEL USE?

Regulatory authorities evaluate a drug for registration based on a defined set of licensing criteria. They generally require evidence of drug efficacy and safety obtained from clinical trials to demonstrate improvement in survival or a surrogate outcome.

The use of a registered drug is guided by an approved drug labelling, which provides key prescribing information that includes the specific medical conditions that the drug is approved to treat, how to use the drug to treat those conditions, information on known side effects, and information that prescribers should discuss with patients before they take the drug.

The term "off-label use" means that a drug is used for a medical condition or age group that it is not approved to treat, or administered in a different route or dose not specified in the approved label.

PRACTICE AND IMPLICATION

Off-label prescribing is prevalent across different diseases and healthcare settings, but is however more frequently reported in paediatrics, psychiatry and oncology where there is a considerable unmet medical need.

In oncology, off-label uses mainly occur when the drug is used to treat unapproved clinical indications and line of treatment, or when the drug continues to be used even though the cancer has progressed.

Prescribers of off-label use often rely on their familiarity with the drug, dosing, safety and clinical trials for additional uses beyond what was approved by regulatory authorities. They may perceive it as an indispensable practice to provide patients with what is necessary for their medical care based on the premise of available scientific evidence.

However, as reported in the US medical journal, Jama Internal Medicine, there is a 44 per cent increase in the risk of adverse events with off-label use compared with on-label prescribing, and this risk is higher when a drug is used off-label with no strong scientific evidence to back it up.

The most frequently reported adverse drug events are related to the gastrointestinal tract, nervous, respiratory and musculoskeletal system organ classes.

Coupled with uncertain clinical, humanistic and economic outcomes, a decision to pursue off-label prescription may be sub-optimal in many clinical scenarios.

An evaluation of 150 million off-label prescriptions revealed that 73 per cent of off-label drug use was without strong scientific evidence. Patients may be exposed to the risk of toxicities without any meaningful clinical benefit.

The annual expenditure on off-label drug use is sizeable, especially in areas like oncology where there are many new and expensive cancer treatments. In an analysis of the 10 most commonly used cancer drugs, 30 per cent of use was off-label, accounting for US$4.5 billion (S$6.3 billion) in the United States in 2010, and this figure is expected to grow. Many countries do not subsidise or reimburse off-label uses given the uncertainty over the clinical benefit.

In selected cases, off-label use of well-established drugs that have been on the market for a long time and for which there is some evidence supporting their safety and clinical effectiveness may be appropriate.

In the setting of palliative care, delirium and dyspnea were the most common indications for off-label use. Central nervous system drugs (for example, haloperidol, chlorpromazine), steroids (dexamethasone), and autonomic drugs (glycopyrrolate) were the most commonly prescribed off-label medications. In paediatric oncology, a combination of ifosfamide and etoposide for Ewing's sarcoma for primitive neuroectodermal tumour of the bone and paediatric cancers is standard of care.

Apart from these cases, prescribers are increasingly put under considerable ethical and professional pressures and responsibilities to warrant appropriate and safe medication use, while ensuring availability of treatment options for patients who have exhausted all approved treatment options. It would not be practical or feasible to do clinical trials for every intended drug use and obtain regulatory approvals for it.

CONSIDERATION FOR SAFER USE

More should be done to ensure the safety of patients. Off-label drug use should be monitored, and the effectiveness and outcomes documented. Electronic medical records should capture off-label prescribing data to monitor prescribing patterns and safety.

Pharmaceutical companies should, as part of the signal detection process, play a key role in evaluating off-label indications by searching for patterns of use and safety concerns. Where possible, off-label drug safety information should be incorporated into the organisation's risk evaluation and mitigation plan, as well as risk management plan.

The off-label use of a drug should be an informed decision made between a patient and his physician bearing in mind issues such as effectiveness, quality of scientific evidence, safety and side effects, as well as cost and financing matters.

In conclusion, healthcare professionals should provide more information for patients on the benefits or risks of off-label drug use. The need for patient involvement in the decision-making process, consideration for clinical guidance and educational strategies at institution level to facilitate judicious practice in off-label drug use are positive steps to deliver safer drug use.

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