Access to cancer medicines in India

An editorial in *The Lancet Oncology* stated "It could be argued that since access to—and resources for—cancer treatment are so limited in developing countries, the answer lies in a greater reliance on generic drugs."[1] We agree, but the real question is how best can such generic drug production be stimulated? India provides one model to answer this question.

India encouraged generic production first by updating, in 2011, its national essential medicines list (EML), a formulary that guides both supply and demand of key medicines, to include modern antineoplastics, such as imatinib. Second, India pledged financing for the procurement of EML medicines for public-sector clinics and hospitals. Three states in India—Tamil Nadu, Kerala, and now Rajasthan—are supplying all medicines on the EML in public health facilities at no cost to patients. Third, India's Government has planned to issue compulsory licenses for on-patent drugs for which no substitute medicines exist in the country and importation is too expensive. The country's first compulsory license was for generic production of the kinase inhibitor sorafenib. Two breast cancer drugs, trastuzumab and ixabepilone, and dasatinib for chronic myeloid leukaemia, might soon become available under similar circumstances. Fourth, governments, civil society, and patient groups must work together to challenge the monopoly power of transnationals. Novartis is fighting a legal battle against India's patent laws.[2] Such steps can hinder access to crucial medicines.

Of note, although domestic generic companies in India produce drugs at low-cost rates, the final price of these drugs is 100–5000% higher than the cost of production. At least for 348 drugs on the EML, prices should be directly controlled by government pricing regulations (eg, original cost-based pricing proposed in 1979[3]). Such actions can be helpful worldwide to reduce costs and increase access with generic drugs for cancer, particularly in the context of universal health coverage.

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1   The Lancet Oncology. Access to cancer medicine in low-resource settings. *Lancet Oncol* 2013; **14:** 1.
2   Hogerzeil HV, Liberman J, Wirtz VJ, et al, on behalf of *The Lancet* NCD Action Group. Promotion of access to essential medicines for non-communicable diseases: practical implications of the UN political declaration. *Lancet* 2013; **381:** 680–89.
3   Selvaraj S, Farooqui HH. Draft drug price policy 2011: legitimising unaffordable medicine prices? *Econ Polit Wkly* 2012; **47:** 13–17.

At the crossroads of targeted treatment and resistance in melanoma

Accumulated evidence suggests that outstanding progress has been made in molecularly targeted treatment, particularly for melanoma. In addition to Sekwong Jang and Michael Atkins' elegant review in *The Lancet Oncology*,[1] in which the state of the art in melanoma treatment was discussed, two recent articles[2,3] published in *Nature* could have a huge effect on translational medicine and serve as a potential breakthrough in melanoma treatment. Although these reports are based on mouse models that used human melanoma cells, if the results are proven in human clinical trials, the evidence of resistance to melanoma treatment could change the initial treatment strategy for patients with BRAF-mutant melanoma.

First, Das Thakur and colleagues[2] showed that intermittent dosing of vemurafenib can successfully prevent drug resistance; paradoxically, since drug-resistant cells were shown to acquire drug dependency, drug withdrawal thereafter would cause a fitness deficit in the cells and lead to tumour regression.[2] Thus, on–off treatment with vemurafenib has shown effectiveness in BRAF-mutant melanoma. Whether this strategy is effective against other cancers treated with other inhibitors is of interest, and the underlying mechanisms should be fully elucidated. From a clinical perspective, both stratification of patients according to prediction of drug responsiveness to on–off treatment and optimisation of the treatment protocol are necessary. For patient stratification, we should assess which people would be suitable for on–off treatment and establish a method to predict eligibility, which would enable us to stratify patients as putative responders or non-responders. To optimise treatment protocols, we should decide on the appropriate timing for both drug initiation (restart) and cessation (which should be personalised for every patient); other parameters, including target rate of tumour regression for drug cessation (ie, when to stop treatment) and target rate of tumour regrowth for drug restart (ie, when to start treatment), should be established to find the appropriate schedule. Further clinical trials are needed to assess the efficacy of this strategy.

Second, Landsberg and colleagues[3] reported that inflammation in the tumour microenvironment induces loss of melanocytic antigens in melanoma, which leads to immune escape in mouse models. The authors showed that TNFα is a crucial factor and causes phenotypic plasticity (ie, reversible loss of melanocytic antigens) in melanoma, which is termed dedifferentiation of melanoma. Investigation of whether anti-TNFα treatment is effective against this immunoediting would be interesting. Although Jang and Atkins do mention