Second, the use of carfilzomib in patients with severe renal impairment should be considered carefully. ENDEAVOR excluded patients with a creatinine clearance of less than 15 mL/min and only 28 (6%) patients in each group had a clearance of less than 30 mL/min. In this very small subgroup, no differences were noted in progression-free survival between treatment groups. Moreover, the occurrence of acute renal failure seemed to be higher in the carfilzomib group than in the bortezomib group (all grades: 38 [8%] of 463 patients vs 22 [5%] of 456 patients; grade 3–5: 19 [4%] vs 12 [3%]). Therefore, until more data are available about the efficacy and safety of carfilzomib in the setting of severe renal impairment, bortezomib might remain a better choice in this particular situation.

Even with these limitations in mind, ENDEAVOR has established a role for carfilzomib plus dexamethasone as a standard treatment for patients with relapsed or refractory multiple myeloma who are candidates for treatment based on a proteasome inhibitor. With a median progression-free survival of 18.7 months, carfilzomib plus dexamethasone sets a new benchmark for two-drug regimens in patients who have received one to three previous lines of therapy.

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I have received honoraria from Amgen, Bristol Myers Squibb, Celgene, Janssen, and Novartis.


Price, value, and the cost of cancer drugs

The reports by Wim van Harten and colleagues1 and Sabine Vogler and colleagues2 in The Lancet Oncology on the costs of cancer drugs in European countries deserve special attention from all oncology and biopharmaceutical stakeholders. van Harten identified that, in 15 European countries, list prices can be up to 92% lower than the highest reported, with actual prices paid up to 58% lower. These findings are backed up by Vogler and colleagues’ study3 in 16 European countries, Australia, and New Zealand, which documented that highest-minus-lowest list price differences ranged from 28% to 38% for cancer drugs. Such variability argues strongly for greater transparency in drug pricing and the circumstances leading to such differences. But most importantly, it underscores the need to establish the true value of
cancer therapies, and those who have championed this cause have been handed unequivocal evidence confirming what they have long suspected: drug prices are typically driven by what the market will bear.\textsuperscript{3}

That prices vary substantially between countries is unsurprising. In April–June, 2015, the average price of a gallon of petrol was US$7·71 in Norway, $2·74 in the USA, and $0·13 in Venezuela.\textsuperscript{4} Equally, prices of anticancer drugs vary around the world. But the fact that they vary so greatly and that no uniformity exists in the variation argues strongly for the need for greater transparency, a burden that falls on the entire biomedical ecosystem: the biopharmaceutical industry, insurance companies, pharmacies, doctors, regulators, and policymakers. Market prices reflect many factors, including supply, demand, competition, risk, reimbursement policies, government subsidies, taxes, and regulatory constraints. Consequently, price differences across countries might be due to differences in several of these factors, and pricing transparency involves understanding the contribution of each of these factors to the market price. For example, imposition of pharmaceutical price caps in Europe implies lower prices for new cancer drugs in Europe than in the USA where prices are unregulated, but this difference also implies higher prices for generics in Europe than in the USA.\textsuperscript{5}

A one size fits all approach is unlikely to work for the pricing of cancer therapies. However, large price differences across countries can yield unintended consequences, some of which might be positive (eg, medical tourism) and others negative (eg, reduced incentives for innovation, unintentional subsidies of one country by another). These unintended consequences must be identified and managed while acknowledging the inevitability and desirability of price differences across economic, social, cultural, and geopolitical borders.

The substantial variation in cancer drug prices underscores the need for each country to establish the value of these therapies for its populace. However, societal value need not be the same as market price. In most developed countries, the market price of potable water is essentially zero, despite the fact that water is essential for survival, whereas diamonds cost exorbitant amounts but are irrelevant for survival. Such valuation exercises are fraught with decisions involving economic tradeoffs with wide-ranging ethical, political, and social implications. These decisions should not be made emotionally, inadvertently, or by default—even though this last approach is often the path of least resistance—but should be made through each country’s political process, ideally in a multidisciplinary and collaborative process that reflects all stakeholders’ perspectives as well as the country’s economic realities and sociopolitical customs.

Working examples of such processes include the UK’s National Institute for Health and Care Excellence (NICE) and Canada’s Canadian Agency for Drugs and Technologies in Health (CADTH). Both institutions have done for their countries what many other countries have avoided (to the detriment of patients): establish the value of therapies to society. For example, NICE has introduced value-based pricing policies in which the incremental fees paid for new therapies are commensurate with the incremental therapeutic value.\textsuperscript{6} Although imperfect,\textsuperscript{7} these organisations serve as a useful starting point for making informed, systematic, and carefully considered decisions about allocation of restricted taxpayer resources among many competing therapeutic options. Some critics have accused these institutions of serving as so-called death panels, but such inflammatory rhetoric ignores the fact that government agencies must, and do, make life and death tradeoffs routinely, such as with automobile speed limits.

Numerous transformative therapies in cancer and other fields are imminent, but will be expensive. Therefore, the difficult decisions involving therapeutic value, price, and resource constraints can no longer be postponed. Oncologists can help improve these decisions by developing and publishing objective metrics that gauge the incremental clinical value of new therapies to guide patients, payers, and policymakers. Importantly these metrics must be relevant to the general populace that will be treated, and not be based on the ideal clinical trial enrollee. By identifying and measuring the key drivers of prices and value, and working collaboratively across countries to develop equitable, ethical, and sustainable economic policies for cancer drug development and reimbursement, more and better therapies can be brought to patients faster and cheaper than is presently possible.
A new standard of care for mantle cell lymphoma?

Mantle cell lymphoma is a rare and aggressive form of non-Hodgkin lymphoma that predominantly affects older individuals. Standard first-line therapy for this disease uses immuno-chemotherapy that in younger patients can be consolidated with an autologous stem cell transplant. Whereas a high proportion of patients have an initial response to these treatments, they invariably relapse, and response to subsequent alternate immuno-chemotherapeutic therapies are poor, with patients often dying from progressive disease. The overall survival is about 3–5 years, which has improved over the last decade, probably as a consequence of the widespread adoption of rituximab, more use of cytarabine-based treatments in younger patients, and better supportive care generally. However, relapse therapies are often inadequate, and because many patients are elderly, toxicity can also limit their use. Novel agents have been investigated to exploit alternative mechanisms of cell killing in this disease. Four drugs have been investigated to exploit alternative mechanisms induced by anti-CD20 antibodies in a variety of in vitro models and in a mouse model the concurrent use of ibrutinib and rituximab significantly antagonised the rituximab anti-lymphoma effect.

Ibrutinib is an oral small molecule that irreversibly blocks the kinase leading to irreversible inactivation of this key component of the B-cell receptor signalling pathway. Additionally, it also inhibits 22 other tyrosine kinases, several with homology to Bruton’s tyrosine kinase, including interleukin-2 inducible tyrosine kinase. Interleukin-2 inducible tyrosine kinase is important in the expression of Fc receptor-stimulated natural killer cells and hence antibody-dependant cell-mediated cytotoxicity. This is one of the mechanisms of action of rituximab, and its inhibition might explain the observed antagonism.

In The Lancet Oncology, Michael Wang and colleagues report the first results of the combination of ibrutinib with rituximab for the treatment of relapsed mantle cell lymphoma. In this single-centre phase 2 trial, the combination was delivered concurrently to 50 patients. In comparison with the original phase 2 single agent data for ibrutinib in mantle cell lymphoma the combination appears more active with 88% (95% CI 75.7–95.5) of patients achieving an objective response compared with 68% and 44% (30.0–58.7) achieving a complete response. By contrast, in the study with ibrutinib alone, 68% of patients achieved an objective response and 21% a complete response. The study populations are broadly comparable although there are fewer participants with high-risk Mantle Cell International Prognostic Index in...