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TARGETED THERAPY: Generic imatinib — impact on frontline and salvage therapy for CML

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Abstract

Imatinib has revolutionized the treatment of chronic myeloid leukaemia (CML). In 2016, generic imatinib will be introduced into the US market. We analyse the potential impact of this new product on patient care and optimal CML therapy, and comment on the effect that distorted cancer drug pricing in the USA will have on treatment for patients with limited therapeutic options.

Imatinib (marketed as Gleevec or Glivec) is a targeted tyrosine kinase Inhibitor (TKI), which was approved in the USA in May 2001 for the treatment of patients with chronic myeloid leukaemia (CML) relapsed or refractory to interferon treatment. A year later, it was approved as a frontline therapy for CML, and has transformed the treatment landscape of this disease. In 2015, the global sales of Gleevec were US$4.66 billion, $2.5 billion of which were US sales[1].

In February 2016, Sun Pharmaceuticals released a generic version of imatinib in the USA. Gleevec is an oral treatment, and the FDA approval of generic imatinib was based on the traditional parameters of matching active ingredients and ensuring bioequivalence. Sun Pharmaceutical has announced that it anticipates pricing generic imatinib at a 30% discount below the price of Gleevec[2], but no specific price was mentioned. Of note, this pricing would put the price of generic imatinib at a considerably higher amount than the price of Gleevec when it was first approved in 2001 (>$100,000 versus $26,000).

Anticipating the introduction of generic imatinib into the USA, Padula and colleagues[3] conducted an analysis to estimate the cost-effectiveness of chronic phase CML therapy over a 5-year timeframe (2016–2021). The investigators compared upfront generic imatinib with

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Competing interest statement

FURTHER INFORMATION

Truven Health Analytics RED BOOK: http://micromedex.com/products/product-suites/clinical-knowledge/redbook

Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch–Waxman Amendments): http://www.fda.gov/newsevents/testimony/ucm115033.htm

'physician choice' of frontline treatment using one of three TKIs, selected randomly: dasatinib (Sprycel), nilotinib (Tasigna), or patented imatinib (Gleevec)[3]. The latter approach captures current frontline clinical practice in the USA. The annual prices of the three patented drugs based on 2011–2012 data, adjusted to 2013 pricing, were $59,000 for patented imatinib, $76,000 for dasatinib, and $75,000 for nilotinib[3]. The authors concluded that generic imatinib, when given as frontline therapy (once available), followed by second-generation TKIs (that is, dasatinib or nilotinib) was the most overwhelming cost-effective strategy[3]. We agree with these conclusions, but wish to highlight several issues pertinent to CML therapy.

Despite the conclusion that frontline therapy with generic imatinib was the more 'cost-effective' strategy, the comparison of generic versus patented imatinib reflects a 'cost-minimization' rather than cost-effectiveness analysis — a cost-minimization analysis refers to a comparison of two products equivalent in dose and therapeutic effect. Because the generic and patented versions of imatinib have the same efficacy, the lower price of generic imatinib will obviously result in cost-minimization. Cost-effectiveness would describe the comparison of generic imatinib with dasatinib or nilotinib, as potential differences in not only prices, but also efficacy and toxicity might exist between the drugs being compared.

A second issue pertains to the 'value' of TKIs used to treat patients with CML and the interpretation of the incremental cost-effectiveness ratio (ICER) when comparing first-line therapy of generic imatinib versus physician-choice treatment. To understand the results, we clarify some of the terminology relevant for cost-effectiveness analyses[4]. Cost-effectiveness analyses assess the added benefits and costs of new treatments compared with old treatments. Cost–utility analyses enable measurement of health benefits (that is, effects) in terms of quality-adjusted life-years (QALYs), determined based on both the quality and duration of life lived. The quality-of-life element is determined somewhat subjectively on a health-state scale, where 1 represents perfect health and 0 represents death. In such an analysis, 5 years lived in perfect health will equate to 5 QALYs (5 years × 1), whereas 5 years lived with a 50% reduction in quality of life will result in 2.5 QALYs (5 years × 0.5). Cost-effectiveness of a new intervention compared with an existing one is typically expressed as ICER, the ratio of the change in costs to the change in effects (for example, QALYs). If drug A costs $50,000 (and this includes the costs of managing adverse events) and results in a total of 5.0 QALYs, and a new drug B costs $100,000 and improves survival by 2.0 QALYs, to a total of 7.0 QALYs, the ICER of drug B is calculated as the ratio of $50,000 (that is, $100,000 – $50,000) to 2.0 (that is, 7.0 – 5.0), which equals $25,000 per QALY.

Padula *et al.*[3] indicate that, in their analysis, the primary end point is 5-year survival from 2016 until 2021. In the analysis, frontline generic imatinib QALY scores were 3.82–3.87, while frontline patented drugs QALY scores were 3.97–3.98[3]. The QALY scores are very close, with the difference perhaps reflecting assumed differences in quality of life, favouring the novel TKIs.

Because of the large difference in prices compared with minimal difference in QALY scores (about 0.1 – 0.15), the resulting ICER value is very high, $883,000/QALY. Most developed

countries consider a willingness-to-pay threshold of $50,000 per QALY. In the UK, a threshold of £30,000 per QALY is used (~US$45,000), and in Canada, US$50,000 per QALY in the cutoff. No such threshold exists in the USA; however, the majority of the published studies use $50,000 per QALY. The $100,000 per QALY proposed by Padula and co-workers[3] is unacceptably high, particularly when the 'new' drug offers neither an improvement in efficacy and/or safety, nor an expanded range of patients who might benefit. The $100,000 per QALY criterion is being publicized more frequently in recent analyses, and particularly in industry-supported publications, perhaps as a drug-company-driven strategy to convince investigators about the validity of the higher value. In reality, simplifying the concept, and accounting for the current 25–30% out-of-pocket patient expenses, a price of $50,000 or less for each additional year of life (ignoring quality of the year lived) is the most we can and should pay for an anticancer drug in the USA[5].

A third concern is the variation in ICER values resulting from operative-dependent subjective assumptions (for example, assigning a health-state number, or a drug price). Indeed, ICER values can easily be manipulated based on the investigator's interests. Padula *et al.*[3] determined that the associated ICER for a strategy based on initial use of randomly chosen patented TKI treatment versus generic imatinib was $883,730 per QALY. In simple terms, if we use patented drugs frontline instead of generic imatinib, we would pay $883,730 per additional QALY — an oxymoronic ICER, nearly 18 times higher than the acceptable $50,000 per QALY. Interestingly, the same authors had reported a similar analysis 2 years earlier that focused on the two treatment strategies for first-line therapy (patented versus generic)[6]. The main differences were: first, the price data was from an earlier time period (2001–2007) in the earlier publication, and second, the prices were higher. In both studies, Gleevec ($76,800) was less costly than branded dasatinib or nilotinib ($102,000 each). The conclusion was both similar and different, simultaneously: cost-effectiveness favoured generic imatinib as frontline therapy, but the ICER value was substantially more cost-effective (although still very high), $227,136 per QALY. This represents about a fourfold difference in the ICER value compared with the recent study, which reflects the subjectivity of the assumptions about pricing. Moreover, the prices used in the two analyses have no relation to the current 'reality check' regarding drug prices (TABLE 1). The average wholesale prices of the four TKIs are vastly different from the prices reported by Padula *et al.*[3], upon which their conclusions were based.

Currently, 18 generic versions of imatinib are available worldwide, including three in Canada. In the USA, the Sun Pharmaceutical generic version of imatinib is priced at a near-patented drug price (not 30% lower as publicized; TABLE 1) because of the US market forces and distortions of the Drug Price Competition and Patent Term Restoration (Hatch–Waxman) Act[7], which grants 180-day marketing exclusivity for first-generic drugs — owing to the US market 'duopoly' experienced by the companies who make the branded and first-generic drugs, prices can be inflated during the exclusivity period. Health care is now globalized (medical tourism), however, and generic imatinib is sold at US$8,500 per year in Canada[8], and at US$400 per year in India; the cost of manufacturing a 400 mg imatinib tablet is less than $1[9]. In 2 years, the price of generic imatinib in the USA (or purchased from abroad) will be significantly lower than the authors' assumptions, hopefully less than $1,000 per year.

The results of the study by Padula *et al.*[3] also highlight the exponential rise in prices of the TKIs over the years, as well as in anticipation of the launch of a generic imatinib. Patented imatinib was priced at $26,000 per year in the launch year of 2001, a price that considered the population at risk, cost of research, and profits needed for the company's success. The price of imatinib has increased by 10–20% annually, purely because the drug company could do so with impunity. This behaviour is, in fact, prevalent among all drug companies[10]. The price of patented imatinib was $132,000 per year in 2014 and is $146,000 per year today. Generic imatinib is marketed today at a price very close to that of the patented drug, and higher than the 2014 patented drug price — a clear reflection of the distorted cancer drug pricing in the USA. This situation will hopefully change by July 2016, once the 6-month first-generic exclusivity period granted to Sun Pharmaceuticals expires, and several generic imatinib versions enter the US market. Then, generic imatinib should become a cost-justified frontline therapy for all newly diagnosed patients with CML.

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Biographies

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Table 1

Variations in prices of tyrosine kinase inhibitors in the USA

Drug	Dose/day	2013 prices quoted in the Padula *et al.*[3] paper (US$)	2016 (RED BOOK™)*	
			WAC (US$)	AWP (US$)
Generic imatinib	400 mg	60–80% of brand imatinib in second 6 months; 10–30% thereafter	113,650	142,000
Gleevec	400 mg	59,000	121,450	145,750
Dasatinib	100 mg	76,000	130,350	156,500
Nilotinib	600 mg	75,000	124,000	148,850

*Refer to Truven Health Analytics RED BOOK™ online: http://micromedex.com/products/product-suites/clinical-knowledge/redbook (accessed 15th March, 2016).

AWP, average wholesale price; NA, not applicable; WAC, wholesale acquisition cost.