

# Chronic myeloid leukemia in Asia

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**Abstract** Chronic myeloid leukemia (CML) in Asia has an incidence rather lower than in Western countries yet tends to afflict a younger population. As in the West, imatinib mesylate (IM, Glivec) has supplanted busulphan, hydroxyurea and interferon- $\alpha$  as first-line treatment. Its use has resulted in a dramatic decline in the number of hematopoietic stem cell transplantations (HSCT) performed. Although it is expensive, IM induces a complete cytogenetic response in 60–90% of newly diagnosed patients, and up to 10% for those in blastic phase. The standard dose of 400 mg is well tolerated by most patients, although adverse events have been observed, including drug-induced cytopenia. Through the Glivec International Patient Assistance Program, the majority of CML patients has access to IM and can expect prolonged survival, even

in the absence of HSCT. However, just as in Western countries, resistance to imatinib has emerged in Asian countries. They will require the novel tyrosine kinase inhibitors (dasatinib, nilotinib) becoming available through either clinical trials or market approval. This review examines the available data on CML in China, Hong Kong, India, the Philippines, Singapore, South Korea, Taiwan and Thailand.

**Keywords** Epidemiology · Treatment · Chronic myeloid leukemia (CML) · Asia

## 1 Introduction

Chronic myeloid leukemia (CML) is a clonal stem cell disorder characterized by increased proliferation of

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myeloid lineage. Its diagnosis is made cytogenetically, with the presence of the Philadelphia (Ph) chromosome, a shortened chromosome 22 associated with a fusion gene that codes for an oncoprotein with deregulated protein tyrosine kinase functionality and that conveys a proliferative advantage to affected leukocytes. It is a commonly diagnosed hematological malignancy in Asia but, according to available data (Table 1) its incidence and median age of onset appear to be lower than the respective 1.5 per 100,000 and 65 years seen in the US [1]. This review covers treatment patterns and key clinical issues facing patients and clinicians in China, Hong Kong, India, the Philippines, Singapore, South Korea, Taiwan and Thailand.

As in Western countries, the disease affects men more commonly than women, but perhaps less so (Table 1: M/F ratio in US and Thailand 1.7:1 versus between 1.3 and 1.6:1 elsewhere in Asia). Indian incidence, although based on very sparse data, is closest to that seen in the US while Chinese figures, again not comprehensive, suggest a much lower incidence (0.4–0.6 per 100,000). Most patients tend to be diagnosed in the chronic phase; in the West, where diagnosis often occurs on the basis of routine blood testing, 85% of patients are diagnosed in the chronic phase and half are asymptomatic at first presentation [2].

The countries studied range from economically developed states (Hong Kong, Singapore and South Korea) to enormous, economically diverse nations (India, China). The healthcare systems and insurance coverage also varies widely, which has an important impact on how CML is diagnosed, treated and monitored. Published data from the region being limited, a review of the topic is called for to stimulate discussion and identify data gaps.

## 2 Treatment patterns

Before the introduction of imatinib mesylate (IM, Glivec) through various expanded access programs in the early 2000 s, busulphan and hydroxyurea (HU), which can normalize the number of peripheral blood granulocytes but without affecting the expression of the Ph chromosome phenotype, were the treatments available for patients who were not eligible for hematopoietic stem cell transplantation (HSCT). Interferon- $\alpha$  (IFN) followed as a useful treatment for a subset of patients. IM has since become standard, first-line treatment in most of the countries studied, particularly among patients ineligible for HSCT or for whom suitable donors are unavailable. This practice is consistent with guidelines published by Western expert bodies, which recommend IM as first-line treatment even for patients with sibling-matched donors eligible for HSCT [2–4].

Treatment guidelines have been published for CML by the Thai Society of Hematology and an Indian guideline is under discussion by the Indian Council of Medical Research. The Thai guidelines are essentially similar to what is published in Europe (European Leukemia Net, ELN) and the US (National Comprehensive Cancer Network, NCCN). Most Asian practitioners follow either the ELN or NCCN guidelines.

Access to IM treatment is not universal however; many patients cannot afford it. National health insurance programs in South Korea (since '03), Taiwan (since '04) and Hong Kong (partial coverage since '05) allay all or most of the drug's costs. In Singapore (since '02), the government-run Medisave and Medishield programs partially cover IM

**Table 1** Characteristics of the CML populations in the studied countries compared with US data

Country/region	Source	Annual incidence of CML (100,000 <sup>-1</sup> )	Median age at diagnosis	Male to female ratio
China	Local surveys [49–52]	0.39–0.55	45–50	1.5:1
Hong Kong	Cancer Registry (1983–2003)	0.9	49	1.5:1
India	Cancer registries (covering < 0.3% of the total population) [53]	0.8–2.2 (M) 0.6–1.6 (F)	38–40	NR
The Philippines	From IARC data <sup>a</sup>	0.7–0.9	45–55	1.3:1
Singapore	Singapore Cancer Registry (1998–2002) [54]	0.7	43	1.3:1
South Korea	Government Registries	0.8	37	1.6:1
Taiwan	Cancer Registry (1995–2002)	0.60 (M) 0.39 (F)	50 (M) 46 (F)	1.5:1
Thailand	Nine leading university hospitals [55, 56]	0.50	36–38	1.7:1
US	North American Association of Central Cancer Registries [1]	1.48 1.94 (M) 1.13 (F)	65	1.7:1

CML chronic myeloid leukemia, IARC International Agency for Research on Cancer, NR not reported

<sup>a</sup> IARC incidence of all leukemias in Manila [57] multiplied by 15–20% [58]

therapy. The Glivec International Patient Assistance Program (GIPAP), implemented in 2002 by Novartis, provides IM at no cost to qualified patients in many countries. For example, in India, IM is available almost exclusively (95%) through GIPAP as it is otherwise unaffordable. In China, patients unable to afford IM (or HSCT) rely on IFN with or without HU or meisoindigo. HU still serves as initial therapy in parts of India and the Philippines, particularly in those outlying areas where definitive diagnosis, i.e., confirmation of the Ph chromosome, is beyond the capacity of local facilities. In contrast, the use of HU in Western countries is limited to palliation—for example, in cases where IM and newer treatments have failed and IFN treatment is inappropriate [2].

In general, Asian patients respond to IM therapy as well as those in the West. Table 2 provides some hematological and cytogenetic response rates seen among chronic phase patients from the region, together with some Western data. There were insufficient published data available to perform any statistical analyses (e.g., meta-analysis) and bias cannot be ruled out. Pending further investigation the observed responses are tabulated. Complete hematological response rates above 95% are typical [5–7], as they are in the West [8, 9]. Reported major cytogenetic response rates in Thailand, China and Singapore (60–70%) compare favorably with those in the West (61–85%) as do rates for complete cytogenetic response (49–54% versus 49–77%). Reports from South Korea and Hong Kong have over 84% of patients in early chronic phase achieving complete cytogenetic response (Table 2). In India, where a high

proportion of patients are diagnosed in late chronic phase [5], and the Philippines, where cytogenetic monitoring is often inadequate, cytogenetic response rates are more modest (30–52% major cytogenetic response, Table 2).

Severe but manageable neutropenia and thrombocytopenia are common in Asian patients, similar to what is experienced in Western countries (42–46%: all phases) [10–12]. For example, 18–28% of Chinese CP patients (71–75% of those in AP/BC) suffered severe hematological side effects (Peking hospital). In Hong Kong, 48% of CML patients (all phases) participating in imatinib trials (December 2000 to January 2002) had grade 3 to 4 neutropenia. Among South Korean CML patients (all phases, St Mary's Hospital, Seoul) the rate was 35–45%. Discontinuation of IM therapy due to side effects varies with the region (e.g., < 5% in India, < 2% in Hong Kong and South Korea; as high as 17% in one Thai hospital). The discontinuation rate in the IRIS trial was 4% [9].

In accelerated phase (AP) and blast crisis, the success rate of IM is considerably lower than for chronic phase patients; again, similar to the West. Data from Thai and Indian centers indicate hematological responses to IM among AP patients approaching 60%, similar to some Western reports [8, 13] (Table 3). According to Western reports, complete hematological response is achieved in 60–80% of AP patients treated with IM while cytogenetic response is half that (major response 30–50%, complete response 20–40%) [8, 14, 15]. Cytogenetic response among Asian patients in AP range from 15 to 49% (major) and 6–43% (complete) (Table 3).

**Table 2** Study response to imatinib among chronic phase patients

Country, reference	Patients (n)	Complete HR (%)	Major CR <sup>f</sup> (%)	Complete CR <sup>f</sup> (%)
IRIS Trial; O'Brien et al. [9]	553	95	85	74
Europe; Lahaye [8]	139	97	61	49
US; Cortes et al. [14]	488	98	83	77
China; Jiang et al. [6]	54	98	70	51
Hong Kong <sup>a</sup>	49	100	NR	88
India; Arora et al. [5]	79	96	30	24
The Philippines <sup>b</sup>	NR	91	45–52	NR
Singapore <sup>c</sup>	48	NR	61	49
South Korea <sup>d</sup>	171	100	90	84
Thailand <sup>e</sup>	96	90	70	55

CR cytogenetic response, HR hematological response, IRIS International Randomized Study of Interferon and STI571, NR not reported

<sup>a</sup> Queen Mary Hospital, University of Hong Kong

<sup>b</sup> Data from two tertiary institutions

<sup>c</sup> Data from Singapore General Hospital, response at 1 year

<sup>d</sup> Data from St Mary's Hospital, Seoul

<sup>e</sup> Data from Ramathibodi Hospital, Bangkok

<sup>f</sup> Cytogenetic response is defined in terms of the level of Ph-positive cells or Bcr/Abl protein. The detection of no Ph-positive cells constitutes a complete response; a 2–3 log reduction in Bcr/Abl transcripts is termed a major response

**Table 3** Study response to imatinib in accelerated phase patients

Country, reference	Patients ( <i>n</i> )	Complete HR (%)	Major CR <sup>d</sup> (%)	Complete CR <sup>d</sup> (%)
Europe; Lahaye, [8]	80	61	31	21
US; Kantarjian et al. [15]	176	82	49	43
US; Cortes et al. [14]	226	83	46	39
India; Arora et al. [5]	23	35 <sup>c</sup>	13 <sup>c</sup>	7 <sup>c</sup>
India; Deshmukh et al. [13]	47	56	15	6
China <sup>a</sup>	114	85	NR	28
Thailand <sup>b</sup>	15	80	47	40

CR cytogenetic response, HR hematological response, NR not reported

<sup>a</sup> Data from the Institute of Hematology and Blood Disease, Tianjin

<sup>b</sup> Data from Ramathibodi Hospital, Bangkok

<sup>c</sup> Response results for accelerated phase and blast crisis patients combined

<sup>d</sup> Cytogenetic response is defined in terms of the level of Ph-positive cells or Bcr/Abl protein. The detection of no Ph-positive cells constitutes a complete response; a 2–3 log reduction in Bcr/Abl transcripts is termed a major response

The poorer performance of advanced phase patients has resulted in considerable attention being paid to patient prognostic scores, for example, their Sokal score. A study of 104 patients receiving IM at Singapore General Hospital showed a significant difference in both hematological and cytogenetic response between patients with a low or intermediate Sokal score and those with a high score. Clinical and laboratory parameters of new CML patients have been analyzed and a prognostic scoring system adapted to Chinese CML patients has been proposed that would allow patients to be assigned to different treatment regimes [16]. Although the Sokal score was validated for use with patients treated with HU and busulphan, it remains the most common method of assigning prognostic factors worldwide [2, 17].

A pattern that is becoming clear is that IM-resistant strains of CML are more common among advanced phase patients. As there is no availability of mutational analysis, clonal evolution is the most common cause given for failure to achieve hematological response in the Philippines. Chinese researchers found that the primary resistance rate in AP patients was 16% while in blast crisis patients, the rate increased to 45% [18]. In Singapore, since sequencing for Abl kinase mutations in IM-resistant patients began in 2005, mutations have been detected in 29 out of 60 patients screened [19]. These findings are all consistent with the Western experience, where more than 40 point mutations, mostly interfering with IM binding, have been catalogued. Typically, they lead to resistance and relapse and are correlated with stage of disease [20].

Despite its potential curative outcome, the frequency of HSCT has declined markedly throughout Asia (and the West) since the introduction of IM. This illustrates how IM has changed the natural history of the disease. However, the prognosis of IM-treated patients over the long term is

unknown. Treatment options for those in whom resistant strains emerge would be limited to HSCT, applicable to only a minority of patients, typically due to lack of available donors but also often for financial reasons. Furthermore, complications such as graft versus host disease (GVHD) and opportunistic infections affecting immune suppressed recipients remain significant barriers to successful outcomes of HSCT [21]. Additionally, HSCT may not provide enhanced survival compared to standard doses of IM except among patients younger than 30 years who undergo the procedure within a year following initial diagnosis in chronic phase [21]. In recent years the role of HSCT as frontline CML therapy has come under challenge for patients of all ages except juveniles.

Newly developed tyrosine kinase inhibitors (TKIs), nilotinib, dasatinib and bosutinib, currently available in ongoing research trials in many Asian centers, are showing promise against IM intolerant and resistant CML. In Singapore, the Philippines, South Korea, India and Hong Kong, dasatinib (Sprycel, Bristol Myers Squibb) has received regulatory approval as has nilotinib (Tasigna, Novartis) in South Korea.

### 3 Key clinical issues

#### 3.1 The West

With the 5-year follow up of the International Randomized Study of Interferon and STI571 (IRIS study) reporting that 83% of patients have enjoyed event-free survival (EFS) at 60 months, imatinib is the first-line treatment for CML in all phases [22]. There remains a minority of patients however (17%), who either relapse or progress to the advanced phases while taking imatinib as first line

treatment for the early chronic phase. Dasatinib and nilotinib have recently been approved for use in the many regions, including the US and some parts of Europe and Asia, for patients who are resistant to imatinib. The key clinical issues for CML patients in the West therefore largely involve monitoring of patient response so as to identify those most likely to enjoy continued success with imatinib versus those showing signs of relapse or resistance and exploring the optimal way to manage these patients.

### 3.2 China

In China, IFN has been broadly used to treat CML since the 1980 s, and was found to be the most effective drug prior to the IM era. IFN is still the first choice for CML patients who either cannot receive HSCT or afford IM. Wan et al. [23] used three types of IFN in clinical trials for CML patients in chronic and AP: IFN-1b, 2a and 2b. Considering the effect with respect to hematological and cytogenetic response, there was no difference among the three subtypes. IFN-1b was more effective in reducing thrombocytosis and splenomegaly; thus it may be the better choice for CML patients with high platelet counts or enlarged spleens on diagnosis [24–26].

Some patients cannot receive long-term IFN therapy either because of poor tolerance or their economic situation. Clinics have tried to reduce the dosage of IFN without lowering the effect. A cytogenetic response greater than that observed with high-dose IFN was obtained with a combination of low-dose IFN and other agents such as homoharringtonine, HU and low-dose cytarabine [24, 27–30]. These results indicate that combination treatment may be a better regimen for CML patients in developing countries.

Although many drugs are used to treat CML in China, only IM yields results equivalent to a cure for many patients. However, IM has proven to be less effective when administered to patients in advanced phases of disease, particularly due to increased drug resistance [18]. Increased doses of IM or combination with other chemotherapy agents induced remission in some patients but this was temporary [18, 31]. Of note, Yao and Liu [32] treated AP CML patients with IM before performing allogeneic HSCT, and patients achieved continual hematological remission after transplantation.

Allogeneic sibling donor HSCT is an optimal treatment for CML patients. He et al. [33] examined the results from 51 CML patients in their first chronic phase that received HLA-matched sibling HSCT and found that the engraftment rate was 98% and the 5-year EFS rate 79.2%. In China, approximately 30% of patients have HLA-matched sibling donors [34, 35]. For those without sibling donors, HLA-haploidentical or matched unrelated donor

transplantation may be an alternative choice. CML patients, both in chronic and AP, treated with HLA-haploidentical HSCT achieved long-term EFS with grades I–II GVHD reactions if donors received granulocyte colony-stimulating factor (G-CSF) stimulation before bone marrow harvesting and patients were followed up with T-cell undepleted and combined GVHD prophylaxis [36, 37]. Nowadays, more volunteers are available for bone marrow donation, increasing the chances of obtaining HLA-matched donors. However, the incidence of GVHD is higher in unrelated donor transplantation than in that of sibling donors, partly due to the incompatibility of minor HLA [38].

### 3.3 Hong Kong

The key issue for present day CML treatment in Hong Kong is the snowballing cost of drug dependent survival. All patients in Hong Kong are covered by government health services, with nominal charges for most treatments, including HSCT. With world record longevity in Hong Kong, the health budget is hard to contain. The public health sector handles 93% of all major ailments [39], and private insurance coverage is low. As such, the government has to prioritize the competing needs of targeted anti-cancer therapies. For CML, the risk-benefit ratio of IM justifies universal coverage by a safety net scheme after patient income assessment.

The second issue for treatment is the low tolerance of Chinese patients to IM treatment due to drug-induced pancytopenia, and other side effects [40]. Data from Queen Mary Hospital indicate that 54% of patients could only tolerate doses of 300 mg or less. On the other hand, it is also possible that different pharmacokinetics among Chinese may allow comparable Ph-positive clonal suppression even at lower administered doses. Indeed, efficacy of low IM doses despite low IM blood levels has been observed in our hospital (unpublished). Pharmacogenomic differences from Caucasians are not unheard of [41, 42] and as an emerging topic, this merits further investigation.

Finally, as with CML treatment worldwide, IM resistance and post-HSCT relapses are emerging problems. Better characterization of mutations and clonal kinetics may help tailor treatment with new TKIs. However, it is possible that the demand for HSCT for IM-resistant cases will re-emerge, and since birth rates in Hong Kong are among the lowest in Asia, sibling donors will be less available [43]. Fortunately, due to genetic homogeneity, 55% of cases will have local related donors. With easier communication between Hong Kong and the rest of China, sibling and unrelated donors from mainland China and Taiwan are an increasing source of stem cells. Only 12% of patients will have to search further overseas for donors.

### 3.4 India

In a large country like India with its massive population, relatively poorly organized healthcare system, less than optimal continuing medical education, and lack of advanced teaching in undergraduate curricula, somewhat erratic dosing of IM by physicians is not uncommon. However, it is unusual to notice such practice among hematology/oncology specialists. Indian reports reveal that late chronic phase patients respond relatively poorly to the drug whilst newly diagnosed patients respond in a manner similar to that reported in the Western literature. Almost all (95%) of the approximately 5,700 patients in India receiving IM obtain it through the GIPAP. Additionally, although officially unrecorded, approximately 1,000 patients receive generic IM.

In spite of the significant, immediate and sustained effect of IM in chronic phase CML, as shown in the IRIS study [22], at least 30% of patients on IM need another modality of treatment within 5 years of initial treatment while others require alternative treatment even earlier. In India, IM-resistant cases usually revert to HU therapy.

In major academic institutes and most private sector healthcare settings in India, periodic cytogenetic response monitoring is being done. However, due to the lack of strategic locations of specialty laboratories, it has been difficult to monitor cases treated in remote areas. Private sector laboratories are attempting to meet the need but much more needs to be accomplished. Quantitative molecular monitoring is not widely available yet. Moreover, available facilities are being underutilized due to its high cost, difficulties in transporting samples to the central laboratory, physicians' lack of trust in the reports and inability to offer next line therapy such as allogeneic HSCT or newer medications targeted to IM-resistant cases.

Allogeneic HSCT for CML has been performed in India for the last two decades. Unfortunately, even before IM became the principal drug, only a few centers could carry out HSCT on a regular basis. In the earlier era of transplantation, the early mortality rate was as high as 30%. However, with experience, molecular typing and careful case selection, it is currently < 10%. Incidence of both acute and chronic GVHD is somewhat higher than that; however, with the increasing use of peripheral blood stem cells, the incidence of chronic GVHD has risen to over 60%. This has created difficulties in diagnosing and managing patients from remote areas. Attempts are ongoing to develop relationships among local internists, oncologists and the treating centers for optimal management of those cases. Currently, with the advent of IM, very few patients agree to accept an HSCT in the first year after diagnosis.

### 3.5 The Philippines

In the Philippines, CML patients are usually referred to hematology specialists. There are about 130 adult and pediatric hematologists in a country of 85 million population. Three quarters of these specialists are based in metropolitan Manila and big cities like Baguio, north of Manila and Cebu and Davao in the Southern Philippines. Cytogenetic studies can only be performed in three medical centers situated in metropolitan Manila. Most CML patients are diagnosed based on clinical presentation and hematological and bone marrow findings without cytogenetic confirmation.

Patients usually pay for healthcare in the Philippines; there is no national insurance to pay for medicine and hospitalization. A minority can afford private insurance; unfortunately leukemias are considered "dreaded diseases" and most Health Maintenance Organizations will not pay for the entire course of treatment. IM costs about \$US25.67 per 100-mg tablet, beyond the means of 95% of the population and 99% cannot afford treatment with IM in the long-term. Through GIPAP, the majority of CML patients in the Philippines are able to receive IM treatment. Regular monitoring with cytogenetic and molecular studies to evaluate response poses a challenge because there are too few centers that perform the procedure and the out-of-pocket expenses are too great for most patients. Allogeneic HSCT can be performed at only three centers and the cost is prohibitive for the majority of patients.

### 3.6 Singapore

In Singapore, a total of 107 HSCT have been performed for CML to date (1985–2006), but in keeping with the global trend, there has been a marked decrease in numbers of transplants done since 2000. An evaluation of 53 patients who received an HLA-identical sibling HSCT from 1985 to 2002 revealed a survival at 10 years of 54 and 31% for patients with first chronic phase and more advanced phase disease, respectively. Acute GVHD of grade II to IV severity was observed in 63% of patients. The incidence of chronic GVHD was 57%, of which 22% was extensive [21].

Before the introduction of IM in 2000, busulphan, HU and IFN were the treatments available for patients who were not eligible for HSCT in Singapore. IFN was generally poorly tolerated, especially at high doses and complete cytogenetic responses were achieved in only a few patients. IM was first introduced in Singapore in September 2000 as part of the IM Expanded Access Program study for patients in the chronic phase who relapsed after HSCT or who were resistant or intolerant to IFN, or for patients in the AP or blast crisis.

Imatinib mesylate became commercially available in Singapore in 2002. The cost of IM is high but there are a number of options available to assist Singapore residents. Apart from private health insurance schemes, there are also government-run savings and medical insurance programs. Medisave is a compulsory savings plan introduced in April 1984. It helps Singapore residents build up sufficient savings for their hospitalization expenses. Every employee contributes 6–8% of their monthly salary to a personal Medisave account, which can then be drawn upon to pay the hospital bills of the account holder and his immediate family members. Savings in a Medisave account can also be used to pay for out-patient chemotherapy. Medishield is a medical insurance scheme introduced in July 1990 to complement Medisave in situations where Medisave alone would not be sufficient. The GIPAP was also launched in Singapore in 2002; TOUCH Community Services (TCS) has been assisting in the administration of GIPAP by conducting financial assessments, making recommendations for subsidies and ensuring that requirements are met for patients to continue in this program. In 2007, GIPAP was changed to the Glivec Patient Assistance Program in which TCS now assists Novartis directly in conducting financial assessments.

Apart from hematological and conventional cytogenetic response monitoring, molecular monitoring in IM treated patients has now become an integral part in the management of these patients. Real-time quantitative polymerase chain reaction (RQ-PCR) for BCR-ABL transcripts to determine the level of minimal residual disease has been performed routinely at the Singapore General Hospital (SGH) since 2004. Efforts are currently underway to standardize the laboratory's RQ-PCR results with a reference laboratory [44]. Sequencing for Bcr-Abl kinase mutations in IM-resistant CML patients started in 2005. Mutations have been detected in 29 of 60 imatinib-resistant patients and were located in the ATP-binding site ( $n = 14$ ), imatinib-binding site ( $n = 4$ ), catalytic domain ( $n = 3$ ), activation loop ( $n = 2$ ) and other sites ( $n = 9$ ) [19].

Phase II/III clinical trials with dasatinib were initiated at the SGH in March 2005 for IM-resistant or intolerant patients. A total of 33 patients from Singapore, India, Malaysia and China were recruited into dasatinib trials at SGH, with 9 patients in the chronic phase and 24 in the advanced phases. Dasatinib is now registered for use in Singapore. A phase II clinical trial with nilotinib for IM-resistant or intolerant advanced phase patients was initiated in December 2005. Eight patients were enrolled into this trial. An expanded access study for nilotinib was also started at the SGH in 2005 and twenty patients were enrolled.

### 3.7 South Korea

In Korea, CML patients may choose to be treated in either university or private health facilities. There are 41 university hospitals which manage about 90% of CML patients. In CML management, there is little difference between physicians' choices for first-line therapy, but some differences for optimization of IM treatment, such as optimal dose, response assessment and toxicity management. Now, the Korean government reimburses 90% of the cost of IM for CP patients (400 mg), advanced phase patients (600 mg) and suboptimal responders and IM failed patients (800 mg). Currently, > 1,200 patients are being treated with IM monotherapy, and < 5% of all CML patients receive HSCT annually.

As many physicians have a concern about increased toxicity during IM treatment, some patients are treated with < 300 mg daily. However, little difference has been documented between Korean and Western patients for all parameters of non-hematological and hematological toxicities (data from St Mary's Hospital) [10–12].

Real-time quantitative polymerase chain reaction to determine the level of Bcr-Abl transcripts has been performed routinely at St Mary's Hospital, The Catholic University of Korea since 2000. Although standardization of molecular assays including RQ-PCR and mutational assays has recently been started in other university hospitals, they are not yet fully concordant with international standards. Recently, the Catholic University's international referral laboratory for RQ-PCR and mutational assays became involved in several international cooperative projects and serves as an Asia-Pacific central referral laboratory for Novartis. Since 2007, the University has run a training program for Asian hematologists [44].

Allele specific oligonucleotide-polymerase chain reaction (ASO-PCR) assay was compared with conventional direct sequencing for screening mutations in patients with IM-resistant CML at the Catholic University of Korea. Among the 68 IM resistant CML patients studied, 44 patients (65%) had 53 mutations involving 18 amino acid substitutions as detected by the two assays. The changes of three amino acids, Y253, E255 and T315, accounted for 71% of the total mutations identified by ASO-PCR and 59% by direct sequencing. The sensitivity of ASO-PCR was superior to that of direct sequencing and now both assays are used simultaneously for the detection of mutation in the hospital [45].

Currently, about 200 Korean CML patients from five university hospitals are in global phase II clinical trials for the second generation TKIs, dasatinib, nilotinib and bosutinib. The costs of leukemia diagnosis and IM treatment are now mostly (~ 90%) covered by national insurance. Recently national insurance coverage has been extended to

dasatinib, however, it is unclear whether national insurance will reimburse all second generation TKIs in the near future or the costs of various mutation assays such as direct sequencing, HPLC, and ASO-PCR.

### 3.8 Taiwan

In Taiwan, the National Health Insurance (NHI) provides IM as first-line treatment, and most patients receive IM soon after a CML diagnosis. Therefore, hematologists are able to give the same quality of care enjoyed in most developed countries. As the IRIS trial indicated, the earlier IM is used, the less severe are its side effects [22, 46, 47]. Most newly diagnosed CML patients tolerate IM well. However, among some patients, especially those in late chronic phase or with more advanced disease, cytopenia associated with IM use does occur. These patients require more frequent visits to outpatient clinics and component therapy comprising G-CSF treatment. If IM treatment must be halted to allow for management of cytopenia, an increased risk of mutation development is incurred. In Taiwan, a supportive system including patient consultation, patient groups and physician reassurance helps these patients overcome their discomfort.

Another clinical issue is salvage therapy after failing TKI therapy (including second generation therapies). In the current situation, the only effective salvage treatment is allogeneic HSCT. However, for more patients to receive such treatment, progress in HSCT technology will be required. In addition, the role of conventional immune therapy and chemotherapy in such patients should be reconsidered.

An increasingly important issue in medical care is the burden imposed on Taiwan's national health insurance (NHI) system which tries to provide high quality care at low cost. Nearly every hospital in Taiwan has signed a contract with the NHI to provide care for more than half of the citizens of Taiwan. CML is classified as a serious disease by the NHI and, as such, patients are not required to pay any additional medical costs and receive IM without increases in their insurance fee. However, despite this funding and the expansion of medical expenses in general, the budget has not increased. The government has been warning the public that the collapse of the NHI system is imminent. The standard IM treatment of 400 mg/day costs US\$35,000 per patient per year in Taiwan. If the NHI system were to collapse, few patients could afford this treatment. To avoid collapse of the system, the NHI has restricted the expansion of medical costs by introducing a global budget payment system in which all medical care costs are pooled within each group of medical care units (e.g., hospitals, clinics) in the form of points, and fixed budgets are assigned for each group. The hospitals share

the budgets according to the points allotted to them. However, the number of points for every hospital has expanded far beyond what the budget can support. Therefore, nearly every hospital endeavors to cut costs, and some patients do not receive CML management as supported by the literature.

### 3.9 Thailand

The majority of patients with CML in Thailand are covered by basic universal insurance that does not pay for HSCT or IM. Through GIPAP, these patients are now able to receive IM treatment and HSCT activity has dropped dramatically. Both dasatinib and nilotinib are available in clinical trials; their commercial availability is expected this year. Thus, current common practice for treating CML patients in Thailand depends on the type of health coverage that they have.

For patients covered by the Social Security Department (about 10% of the population), most will seek approval for HSCT then proceed pending suitable donor availability and patient preference. If a suitable donor is unavailable or they prefer medication, IM therapy is considered. Usually GIPAP does not cover patients who receive treatment reimbursed by Social Service but patients may be approved on an individual basis. For government officials (about 40% of patients), they are informed of all treatment options and often receive HSCT pending suitable donor availability and patient preference. If the patient prefers medication, IM treatment is started. In the case of patients under universal coverage (HSCT is not covered and most of the time these patients, about 30% of the population, cannot afford HSCT), patients are registered in GIPAP and IM treatment is started.

## 4 Conclusion

In terms of prevalence, CML is the most common hematological malignancy in Asia, but its incidence and median age of onset may be lower than that observed in the US [48]. Treatment options for CML in Asia have changed dramatically over the past decade, and patients can expect prolonged median survival, even without HSCT. This change has been spurred by the introduction of IM, beginning in 2001. Although it is extremely efficacious and well-tolerated in most patients, IM-resistance has become a significant hurdle for some patients. The development of second-generation TKIs such as dasatinib, nilotinib and bosutinib may prove to be an important alternative for such patients in Asian countries.

Throughout the region however, the economic burden of the disease is growing as new treatment options introduce

not only new drug costs but may require ever more sophisticated monitoring.

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