Horizon Scanning in Oncology

Dasatinib (Sprycel®) for the 1st-line treatment of Philadelphia chromosome positive chronic myeloid leukaemia in the chronic phase

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AGENCJA OCENY TECHNOLOGII MEDYCZNYCH
HTA

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Ludwig Boltzmann Gesellschaft (LBI-HTA)

in collaboration with

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Author(s):	Katharina Hintringer, BA (LBI-HTA)
Internal review:	Jadwiga Czeczot, MSc Pharm (AHTAPol)
	Tomasz Garbaty, MSc Eng (AHTAPol)
External review:	Prof. Dr. Dominik Wolf
	Innsbruck, University Hospital
	Department of Haematology and Oncology

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CONTACT INFORMATION

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Responsible for Contents:

Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

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1 Drug description

Generic/Brand name/ATC code:

Dasatinib/Sprycel®/ L01XE06

dasatinib/Sprycel®

Developer/Company:

Bristol-Myers Squibb

Description:

Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) targeting the BCR-ABL tyrosine kinase protein. [1]. BCR-ABL is the oncogenic product of the Philadelphia chromosome, which is present in >90% of cancer cells of all adult patients suffering from chronic myeloid leukaemia (CML). The BCR-ABL fusion protein acts as a tyrosine kinase inhibitor (TKI) mediating the development and maintenance of CML through interaction with multiple downstream signalling partners, resulting in altered cellular adhesion, activation of mitogenic signalling and inhibition of apoptosis. This leads to the transformation of hematopoietic stem cells. Briefly, TKIs have the ability to significantly reduce the proliferation of BCR-ABL positive CML cells by inhibiting the BCR-ABL pathway [2]. Further, dasatinib also inhibits other tyrosine kinases, including Src family kinases, c-Kit, EPH receptor A2, and platelet-derived growth factor receptor (PDGFR)-β [3-4].

second-generation TKI targeting BCR-ABL

TKI significantly reduce proliferation of BCR-ABL positive CML cells

The current standard of care in patients with CML is imatinib therapy. Despite high response rates of CML patients to imatinib, many patients require alternative treatment options (e.g. second-generation TKIs like dasatinib or nilotinib) [3].

many patients require alternative treatment options to current standard of care

The recommended dose for the treatment of chronic phase CML patients is dasatinib 100mg administered orally once daily. The treatment of CML patients with dasatinib is continued until disease progression or unacceptable toxicity in clinical trials [5].

recommended daily dose: 100mg once orally

2 Indication

Dasatinib is indicated for the 1st-line treatment of adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) in the chronic phase (CP) (Ph+ CML-CP).

1st-line therapy of Ph+CML-CP

3 Current regulatory status

The European Medicines Agency (EMA) granted orphan drug designation to dasatinib (Sprycel®) for the treatment of CML in December 2005. Since 2006 dasatinib is approved for the treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior

EMA: approved since 2006

therapy including imatinib mesylate and for the treatment of adults with Ph+ acute lymphoblastic leukaemia (Ph+ALL) and lymphoid blast CML with resistance or intolerance to prior therapy [6].

approved for 1st-line therapy of Ph+CML-CP

In October 2010, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion to recommend dasatinib for the treatment of newly diagnosed Ph+ CML-CP patients [7], which was confirmed by the European Commission in December 2010 [8].

FDA: approval 2006 for CML and ALL patients intolerant to prior therapy

The US Food and Drug Administration (US FDA) initially approved dasatinib for the treatment of adults with CML with resistance or intolerance to prior therapy including imatinib and for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy in 2006 [9].

accelerated approval for 1st-line therapy

As EMA, the US FDA granted accelerated approval of dasatinib for the 1st-line treatment of newly diagnosed adults with CML in the chronic phase in October 2010. The US FDA approved dasatinib within this indication under the condition that the Marketing Authorisation Holder will present follow-up data of the current phase III trial NCT00481247 as specified in the study protocol – until 2014 [10].

4 Burden of disease

a clonal haematopoietic stem-cell disorder

CML is a clonal haematopoietic stem-cell disorder resulting in a dysregulated production and uncontrolled proliferation of mature and maturing granulocytes (i.e. white blood cells) [11]. CML is one of the few malignant diseases triggered by a single oncogene – the BCR-ABL fusion protein, which acts as an active kinase. Thus, kinase inhibitors such as imatinib, nilotinib and dasatinib are efficacious in the CML-CP therapy by blocking the activity of BCR-ABL [12]. CML is initially diagnosed by typical findings in the blood and in the bone marrow. Blood tests at diagnosis include a complete blood count with microscopic differential count, assessment of BCR-ABL mRNA transcripts, cytogenetic analysis and HLA-typing [13]. Investigations for the staging of CML include a chest X-ray, electrocardiogram and echocardiogram, if needed (e.g. when a relevant co-existing cardiac disease is suspected). Further, depending on the clinical situation and symptoms, a computed tomography, neurologic tests or a lumbar puncture may be required. Details about diagnosis and staging are described in more detail elsewhere [13-15].

CML is initially diagnosed by typical findings in the blood

3 phases – chronic phase, accelerated phase and blast crisis

CML has basically three different stages – chronic phase, accelerated phase and blast crisis. The initial chronic phase (CP) can be asymptomatic and if left untreated the disease will progress at random to an accelerated phase (AP) and then to fatal blast crisis (BC) within 3 to 5 years [16]. After 2002, with the introduction of imatinib as 1st-line therapy in CML, the 5-year survival rate improved from 53% (1999-2005) to 89% [16].

phase of disease as prognostic factor

Despite different definitions of accelerated phase and blast crisis, the phase of the disease strongly influences the response to therapy, the duration of the response and overall survival (OS) with better results for chronic phase than for accelerated phase and for accelerated phase than for blast crisis [17].

symptoms: fatigue, weight loss, sweating, abdominal discomfort

Typical symptoms of CML are fatigue, weight loss, sweating and abdominal discomfort from an enlarged spleen [15].

CML accounts for approximately 15-20% of all adult leukaemia patients [18-19] with a yearly incidence of 1 in 100,000 of population in Western countries [18]. CML is uncommon in children and accounts for less than 5% of all childhood leukaemia. Men are generally more often affected than women (3:2) and the incidence increases steadily [18] with age. Median age is 55-66 years at time of diagnosis [2, 16].

CML accounts for ~20% of leukaemia

median age at diagnosis: 55-66 years

Approximately 90-95% of patients are diagnosed in the CP of their disease [20] and more than 90% of CML patients are Philadelphia-chromosome positive [2].

90% of CML patients are Ph+

In the treatment management of CML, several prognostic factors have been identified, which can be categorised in baseline factors and response-related factors. Whereas baseline factors such as phase of the disease and risk scores (e.g.: encompassing phase of the disease, blast cell counts, basophils, spleen size and cytopenias [13]) can be identified *prior to* the treatment, response-related factors like cytogenetic, haematologic and molecular response (CyR, HR, MolR) are prognostic factors that can be identified *during* the treatment of CML [17, 21]. As these prognostic factors were established based on efficacy data of the 1st-line treatment of CML patients with imatinib and recombinant interferon-alpha (rIFNα), the European LeukemiaNet [22] points out that these prognostic factors cannot necessarily be applied to dasatinib or nilotinib, two second-generation TKIs targeting the BCR-ABL fusion gene due to several reasons – short follow-up of existing studies and more rapid responses to dasatinib and nilotinib therapy compared to imatinib therapy, saying that if a patient has not achieved a CyR at 3 months or a less than minor CyR at 6 months, the probability of achieving a complete CyR (CCyR) later on is small. Thus, prognostic factors regarding the 1st-line therapy in Ph+ CML-CP with dasatinib or nilotinib are not yet finally established [22].

prognostic factors: differentiation between baseline factors and response-related factors

prognostic scores not finally established for therapy with second-generation TKIs

In Austria, the overall incidence of leukaemia was 894 patients, of which 489 are male and 405 female in 2008 [23]. Applying the above mentioned estimates, the incidence of newly diagnosed Ph+ CML-CP patients is approximately 110 per year in Austria.

~ 110 Ph+ CML-CP patients newly diagnosed per year

5 Current treatment

Since December 2002, imatinib mesylate (IM) at a dose of 400mg once daily is approved as 1st-line therapy for CML and is currently considered to be standard of care in newly diagnosed CML-CP patients [15, 19, 24].

standard of care: imatinib 400mg once daily

The motivation for treatments other than IM are intolerance or excess toxicity, treatment failure, development of BCR-ABL resistant mutations and suboptimal response [17]. Therapy options for those patients are:

other treatment options: rIFNα, hydroxyurea, low-dose arabinosyl cytosine or alloHSCT

- imatinib dose escalation to 600-800mg/kg,
- rIFNα,
- chemotherapeutic drugs such as hydroxyurea, low-dose arabinosyl cytosine
- or allogeneic hematopoietic stem cell transplantation (alloHSCT), for those patients who are eligible [15, 25].

alloHSCT: potential to cure CML

Though, alloHSCT is considered to be the only possible treatment to cure CML, imatinib is still the 1st-line therapy of choice for CML-CP. This is because only highly selected patients are eligible for alloHSCT, because of the fear of transplant-associated morbidity and mortality and also due to the ease of drug administration [12, 26]. An interim safety analysis of the randomized German CML Study IV compared the three-year survival probability of patients eligible for an alloHSCT (n=53) with matched pairs (n=106) not receiving alloHSCT, showing that there was no statistical significant difference - alloHSCT: 91.9% (CI 82.9%-97.8%) vs. imatinib-based drug therapy: 95.9% (CI 91.1% - 98.9%) [26].

intolerance and resistance to imatinib

Despite the positive results of the pivotal imatinib study (IRIS), 18% of patients do not achieve a CCyR, approximately 10% of patients who achieve CCyR eventually lose their response and 4% to 8% are intolerant to imatinib. This results in 30-35% of patients whose outcome with imatinib is not optimal [24]. Some population-based series even describe an higher necessity for 2nd-line treatments of 51% as presented at the 2010 annual meeting of the American Society of Hematology (ASH) [27].

treatment options for imatinib resistant or intolerant patients: second-generation TKIs

Therefore, new strategies for the treatment of imatinib intolerant or resistant patients need to be established. Current options for these patients are:

- Higher doses of imatinib, or combination therapy
- or the use of second-generation TKIs like dasatinib, nilotinib and bosutinib [24].

In vitro and clinical study results show that these newer TKIs are generally more potent inhibitors of BCR-ABL kinase activity and are active against most imatinib-resistant tumours harbouring BCR-ABL kinase domain mutations. Nilotinib and dasatinib have already demonstrated high efficacy with a favourable toxicity profile in CML after failure of imatinib [24].

For both new second-generation TKIs, nilotinib and dasatinib, the CHMP adopted a positive opinion recommending these new agents for the 1st-line treatment of Ph+ CML-CP [7, 28].

NCCN guidelines: category 1 treatment options

Within the latest version of the CML clinical practice guideline of the National Comprehensive Cancer Network (NCCN) all three TKIs, imatinib, nilotinib and dasatinib, are considered to be category 1[1] treatment options for 1st-line therapy of adult patients with Ph+ CML-CP [19].

[1] Category 1 recommendation: based on high-level evidence (i.e., high-powered randomized clinical trials or meta-analyses), and the NCCN Guidelines Panel has reached uniform consensus that the recommendation is indicated. In this context, uniform means near unanimous positive support with some possible neutral positions [29]

6 Evidence

one phase II and one phase III trial identified

In addition to a free text search including the websites of the EMA and the US FDA, a systematic literature search was conducted in PubMed, EMBASE and the Database of the Center for Review Dissemination Database of the National Institute of Health on the 15th of December 2010. Search terms included were "dasatinib", "bms 354825" or "sprycel" for the study drug and "chronic myeloid leukemia", "chronic myelogenous leukemia", "chronic myeloid leukaemia", "chronic myelogenous leukaemia" and CML for the disease.

447 references were identified of which one phase III trial and one phase II trial evaluating the efficacy and safety of dasatinib as 1st-line therapy in Ph+CML-CP patients were included. Both studies together investigated 581 patients.

DASISION trial: confirmed CCyR by 12 months +11%

The phase III, open-label DASISION trial evaluates the efficacy and safety of dasatinib in the 1st-line treatment of adults with Ph+CML-CP. 519 patients were randomly (1:1) assigned to receive either 100mg dasatinib once daily or 400mg imatinib once daily. The confirmed CCyR by 12 months was 11 percentage points higher among the dasatinib treated patients than the imatinib group based on the interim analysis when all patients had a follow-up of at least 12-months.

The aim of the phase II study was to assess the safety and efficacy of dasatinib as initial therapy in patients with CML in the early chronic phase with the primary objective to improve the MMR rate at 12 months from the expected 40% based on historical experience with standard-dose imatinib.

6.1 Efficacy and safety - Phase III study

Table 1: Summary of efficacy

Study title An Open-Label, Randomized, Multicenter Phase III Trial of Dasatinib (SPRYCEL®) vs. Standard Dose Imatinib (400mg) in the Treatment of Subjects With Newly Diagnosed Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia [30-32]		
Study identifier	NCT00481247; ATC Code L01XE06; EUDRACT 2006-005712-27, BMS Code: CA180-056 (DASISION)	
Design	Randomized (1:1), open-label, multicenter (108 centres in 26 countries)	
	Duration	Enrolment: September 2007 - December 2008 Median follow-up: 14 months (=all patients had a minimum follow-up of 12 months) Cut-off date for primary outcome analysis: December 2009 Estimated study completion date: January 2014 Minimum follow-up: 5 years
Hypothesis	Superiority	
Treatment groups	Intervention (I)	Dasatinib 100mg once daily, orally (with or without food); until disease progression or unacceptable toxic effects developed; 259 patients
	Control (C)	Imatinib 400mg once daily, orally (with food); until disease progression or unacceptable toxic effects developed; 260 patients

Endpoints and definitions	Confirmed complete cytogenetic response by 12 months *(primary outcome)*	Confirmed CCyR	A CCyR on two consecutive assessments at least 28 days apart. Patients who had a first assessment of CCyR at 12 months that was confirmed on a second assessment thereafter were considered to have had a confirmed CCyR by 12 months
	Complete cytogenetic response	CCyR	0% Ph+ cells in metaphase in the bone marrow
	Time to confirmed CCyR		Time from randomization to confirmed CCyR
	Rate of CCyR		The proportion of subjects who achieved a CCyR at any time from the date of randomization, provided that it is confirmed later as described above
	Major molecular response	MMR	a BCR-ABL transcript level of 0.1% or lower on the International Scale (conversion factor of 0.81), corresponding to a reduction in the BCR-ABL transcript level by at least 3-log from the standardized baseline level; assessed with the use of a quantitative reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay at a centralized laboratory
	Time to a MMR		Time from randomization date to MMR
	Rate of MMR		The proportion of subjects who achieved a MMR at any time from the date of randomization
	Progression to the accelerated phase or blast crisis		If any of the following occurred: a doubling of the white-cell count to more than $20x10^9$ per litre in the absence of complete haematologic response; a loss of complete haematologic response; an increase in Ph-positive bone marrow metaphases to more than 35%; progression to accelerated phase or blast phase CML (details see study protocol [31]); or death from any cause
	Progression-free survival	PFS	Time from randomization date until the subject progressed or died
	Overall survival	OS	From date of randomization to death

Results and analysis

Analysis description	Primary analysis: Intention-to-treat analysis First interim analysis: all patients had a minimum follow-up of 12 months			
Analysis population	Characteristics: median age I 46 years vs. C 49 years, with I 10% and C 11% of patients being ≥65 years, male I 56% vs. C 63% ECOG PS 0 or 1: I 100% vs. C 99%, Hasford risk score – low I 33% vs. C 33%, intermediate I 48% vs. C 47%, high I 19% vs. C 19% Inclusion: previously untreated patients (≥18 years) with Ph+ CML-CP, ECOG PS 0-2, adequate hepatic function (≤2.0 times the institutional upper limit of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the institutional ULN); adequate organ function (serum creatinine ≤3 times the institutional ULN) Exclusion: women who are pregnant or breastfeeding, pleural effusion at baseline, uncontrolled or significant cardiovascular disease, history of significant bleeding disorder, prior chemotherapy for peripheral stem cell disorder, prior treatment for CML (except anagrelide or hydroxyurea)			
Descriptive statistics and estimate variability	*Treatment group*	*I*	*C*	*p-value*
	Number of subjects	259	260	
	Confirmed CCyR by 12 months %, (n) 95% CI	 77 (199) 71 to 82	 66 (172) 60 to 72	0.007*
	Confirmed CCyR by 18 months %, (n) 95% CI	 78 (n.r.) n.r.	 70 (n.r.) n.r.	0.0366***

	CCyR by 12 months %, (n) 95% CI	83 (216) 78 to 88	72 (186) 66 to 77	0.001*
	MMR at any time %, (n) 95% CI	52 (135) 46 to 58	34 (88) 28 to 40	<0.0001*
	MMR by 12 months %, (n) 95% CI	46 (119) 40 to 52	28 (73) 23 to 34	<0.0001*
	Rates of CCyR by 3 months, % 6 months, % 9 months, %	54 73 78	31 59 67	n.r.*
	Rates of MMR by 3 months, % 6 months, % 9 months, %	8 27 39	0.4 8 18	n.r.*
	Progression to the accelerated phase or blast crisis % (n) 95% CI	1.9 (5) n.r.	3.5 (9) n.r.	n.r.**
	Estimated PFS by 12 months % 95% CI	96 n.r.	97 n.r.	n.r.**
	Estimated OS by 12 months % 95% CI	97 n.r.	99 n.r.	n.r.**
	Estimated PFS by 18 months % 95% CI	94.9 n.r.	93.7 n.r.	n.r.***
	Estimated OS by 18 months % 95% CI	96.0 n.r.	97.9 n.r.	n.r.***

Effect estimate per comparison		*Comparison groups*	*I vs. C (HR for shorter time to response)*
	Time to CCyR was significantly shorter with dasatinib than with imatinib treatment	Hazard ratio (HR)	1.5
		95% CI	n.r.
		P value	<0.0001**
	Time to MMR was significantly shorter with dasatinib than with imatinib treatment	HR	2.0
		95% CI	n.r.
		P value	<0.0001**
	Time to confirmed CCyR was significantly shorter with dasatinib than with imatinib treatment	HR	1.5
		95% CI	n.r.
		P value	<0.0001**
Notes	- The provided data are based on a minimum follow-up of 12 months of all patients. A minimum 5-year follow-up is planned for the study.		

n.r. – not reported; CI – confidence interval; ECOG PS – Eastern Cooperative Oncology Group performance status [33]

**Cochran-Mantel-Haenzel test stratified by Hasford Score*

***performed using the Kaplan-Meier-product limit method; 95% CI*

****18-months follow-up data presented at the 2010 annual meeting of the American Society of Hematology (ASH) [32].*

Table 2: Most frequent adverse events

		Study ID NCT00481247	
Grade (according to CTC version 3.0)	**Outcome**	**Intervention** (n=259)	**Control** (n=260)
All grades	Haematological		
	Neutropenia (%)	65	58
	Thrombocytopenia (%)	70	62
	Anaemia (%)	90	84
	Non-haematological		
	Fluid retention (%) Superficial edema (%) Pleural effusion (%)	19 9 10	42 36 0
	Diarrhoea (%)	17	17
	Nausea (%)	8	20
	Vomiting (%)	5	10
	Myalgia (%)	6	12
	Muscle inflammation (%)	4	17
	Rash (%)	11	17
	Headache (%)	12	10
	Fatigue (%)	8	10
Grade ≥3	Haematological		
	Neutropenia (%)	21	20
	Thrombocytopenia (%)	19	10
	Anaemia (%)	10	7
	Non-haematological		
	Fluid retention (%)	1	1
	Diarrhoea (%)	<1	1
	Rash (%)	0	1
	Hypophosphatemia (%)	4	21
	QTc interval ≥450msec (%)	2.4	4.4
	Discontinuation of treatment, % (n) Drug-related AEs, % (n) Death, % (n) Treatment failure, % (n)	15.5 (40) 5 (13) 1.6 (4) 2.3 (6)	18.6 (48) 4.3 (11) 0.4 (1) 3.9 (10)

first interim results at a minimum follow-up of 12-months of all patients randomized

The first interim results of the phase III DASISIONS trial evaluating the efficacy and safety of dasatinib as 1st-line treatment of newly diagnosed Ph+ CML-CP patients show that the confirmed CCyR by 12 months is statistically significant higher in the dasatinib group compared to the current standard of care imatinib (I 77% vs. C 66%, p=0.007). Also the rate of MMR at 12 months was statistically significant higher in the dasatinib group compared to the imatinib group (I 46% vs. 28%, p<0.0001). Whereas in the dasatinib group 5 patients (1.9%) progressed to accelerated or blast phase, 9 patients (3.5%) in the imatinib group did so. The authors also provide estimated rates for PFS and OS at 12 months – PFS is estimated to be 96% and 97% for the dasatinib and imatinib group, respectively. The estimated rates for OS at 12 months are 97% vs. 99% for the intervention

equal estimated 12-months rates of PFS and OS

and control group, respectively. The safety profile was generally considered to be clinically manageable and tolerable. Whereas haematological AEs (neutropenia, thrombocytopenia and anaemia) were more frequent and more severe (grade ≥3) in the dasatinib group than in the imatinib group, the opposite is true for non-haematological AEs. Fluid retention (all grades) occurred more frequent in the imatinib group than in the dasatinib group (I 19% vs. C 42%). The two types of fluid retention reported were superficial edema and pleural effusions. Whereas, superficial edema occurred more frequent in the imatinib group (I 9% vs. C 36%), pleural effusions were only observed in the dasatinib group (I 10% vs. C 0%). 13 patients (5%) in the dasatinib group and 11 patients (4.3%) in the imatinib group discontinued therapy due to drug-related AEs. 4 (1.6%) and 1 (0.4%) patients discontinued therapy due to death in the intervention and control group respectively. This study is still ongoing. A follow-up of 5 years is planned.

haematologic AEs were more frequent in the dasatinib group

Besides, the 18-months follow-up data presentation at the 2010 annual meeting of ASH, a safety and efficacy sub-group analysis of patients with baseline cardiovascular co-morbidity (85 patients (16%) with ≥ 1 baseline cardiovascular condition) was presented. Saglio et al. concluded that though, fluid retention and cardiac AEs were more common in patients with baseline cardiovascular condition, these data show no substantial impact of baseline cardiovascular condition on general safety and efficacy of dasatinib or imatinib in the initial treatment of CML-CP [34].

6.2 Efficacy and safety - further studies

Cortes et al. (2010) [35] conducted a phase II study to investigate the safety and efficacy of dasatinib as 1st-line therapy in patients with chronic-phase CML. The primary objective was to improve the MMR rate at 12 months to ≥ 40%. 62 patients were randomly allocated to either receive dasatinib 100mg once daily or 50mg twice daily. 50 patients have been observed for at least 3 months and thus the efficacy analysis is based on these fifty patients. After a median follow-up of 24 months (range 1 to 39) 41 patients (82%) achieved a MMR and 49 patients (98%) achieved a CCyR at any time. There was no significant difference in response observed between the two treatment arms. The toxicity profile can be divided in haematological and non-haematological AEs. Haematological AEs of grade ≥3 are neutropenia (21%), thrombocytopenia (10%) and anaemia (6%). The most frequent non-haematological AEs of grade ≥3 are fatigue (6%), joint and muscle pain (6%), peripheral neuropathy (5%), dyspnoea (5%) and memory impairment (5%). Again no statistical significant differences between the two study arms could be observed regarding frequency and severity of AEs. During the study 30 of the 62 patients had treatment interruptions. 5 patients discontinued therapy – three because of treatment intolerance, one because of patient choice and the other one due to noncompliance.

50 pts were evaluable for efficacy analysis

at 24 months 98% of pts achieved a CCyR

7 Estimated costs

estimated monthly treatment costs: € 4,457

Currently, no official price estimate is available for dasatinib (Sprycel®) in Austria. However, the price for one package of Sprycel® including 60 pieces of 50mg tablets is € 4,457.- at the Tiroler Landeskrankenanstalten GmbH [36]. As stated in chapter 1, the recommended daily dose of dasatinib is 100mg once daily. Thus, the estimated monthly treatment costs are € 4,457. For the current standard of care, imatinib mesylate, the estimated monthly treatment costs in Austria are € 2,700.- [37]. Due to expiring patents, these costs are expected to drop sharply in the near future.

life-long therapy?

Up to date, no data on the median duration of 1st-line dasatinib therapy in Ph+CML-CP patients are available yet. As imatinib is able to suppress leukemic cell growth for prolonged time periods but cannot eradicate the disease, life-long imatinib therapy appears to be required in patients responding to the therapy [12]. Considering that dasatinib is able to reduce the proliferation of BCR-ABL positive CML cells, but does not cure CML, these considerations might also hold true for dasatinib therapy [2].

8 Ongoing research

9 phase III trials of dasatinib in different indications registered

By searching www.clinicaltrial.gov [2] (search restrictions: dasatinib + phase III) 9 phase III trials assessing the efficacy and safety of dasatinib in different indications were identified.

1st-line CML therapy:

- NCT00481247 (DASISION): an open-label, randomized, multicenter, phase III trial investigating the efficacy and safety of dasatinib compared to imatinib in patients newly diagnosed with Ph+ CML-CP. Interim results of this study are presented in chapter 6.1. The estimated completion date for the DASISION trial is January 2014.

2nd-line CML therapy:

- NCT00123474: a phase III, randomized two-by-two, multicenter, open-label study of dasatinib in patients with Ph+CML-CP or BCR-ABL positive CML who are resistant or intolerant to imatinib. Dasatinib is studied in four different dosing regimens. The estimated study completion date is May 2013.
- NCT00320190: an open-label, randomized phase II/III study of dasatinib vs. high-dose imatinib (800mg) in patients suffering from CML-CP who have had a suboptimal response after at least 3 months of therapy with 400mg imatinib.
- NCT00362466: a study comparing the rate of CCyR of dasatinib versus high-dose imatinib (600mg) in Ph+CML-CP patients who have failed imatinib therapy or who had a suboptimal response

[2] ClinicalTrial.gov is a trial registry run by the U.S. National Institutes of Health

after 18-months of therapy with 400mg imatinib. This study was terminated in 2009 due to insufficient enrolment.

Further, 5 phase III trials assessing the safety and efficacy of dasatinib for the treatment of acute lymphoblastic leukaemia and castration-resistant prostate cancer are registered at www.clinicaltrial.gov. One phase III trial investigating the safety and efficacy of dasatinib in gastrointestinal stromal tumours has been terminated in 2009 based on the recommendation of the independent data monitoring committee (IDMC).

162 studies registered

All in all, 162 studies assessing the safety and/or efficacy of dasatinib in different indications are registered at ClinicalTrials.gov. Besides different types of leukaemia, the effect of dasatinib is investigated in treating patients with prostate cancer, breast cancer, glioblastoma, melanoma, pancreatic cancer, multiple myeloma, ovarian, peritoneal and tubal cancer, bladder cancer myeloproliferative disorders and colorectal cancer [38].

9 Commentary

October 2010: approval of dasatinib for initial therapy of Ph+CML-CP

In October 2010, both regulatory agencies the EMA and the US FDA adopted a positive opinion to approve dasatinib for the 1st-line treatment of adult patients with Ph+CML-CP. As the results of the pivotal DASISION trial submitted for the approval process are first interim results, the Marketing Authorisation holder committed to the post-marketing requirement to submit long-term follow-up data (at least 60 months of follow-up) from the DASISION trial [10].

interim results of the DASISION trial

The first interim results of the DASISION study – phase III trial to investigate the safety and efficacy as an initial therapy in adults with Ph+CML-CP – are presented in chapter 6.1. With a median age of 46 years, the study population (n=519) is slightly younger than patients usually are at diagnosis. The primary endpoint of this analysis was confirmed CCyR by 12 months, which was 11 percentage points higher among dasatinib treated patients compared to the imatinib group (I 77% vs. C 66%, p=0.007; 18-months follow-up: difference of 8 percentage points between dasatinib and imatinib, p=0.0366). The effect estimate comparisons show that the time to confirmed CCyR is shorter for the dasatinib group compared to the imatinib treated group (HR 1.5, p<0.0001). Progression to AP or BC was observed in 5 (1.9%) and in 9 (3.5%) patients in the dasatinib and imatinib groups, respectively. The 18-months estimates for PFS are 94.9% vs. 93.7% and for OS 96% vs. 97.9% for the dasatinib vs. imatinib groups, respectively. Generally the safety profile was considered to be acceptable and clinically manageable. Whereas, haematological AEs were more frequent and more severe in the dasatinib treated group than in the imatinib treated group, the opposite was observed for non-haematological AEs, except pleural effusions, which were only observed in dasatinib treated patients [33].

confirmed CCyR: I 77% vs. C 66%
progression to AP or BC: I 1.9% vs. C 3.5%

surrogate endpoint demonstrated superiority

Based on the 12- and 18-months interim results the surrogate and primary endpoint confirmed CCyR demonstrated superiority of dasatinib over imatinib (p=0.007). CCyR was accepted as the primary endpoint by EMA and US FDA as the analysis of the pivotal imatinib trial showed that CCyR at one year is predictive for PFS. Though, further follow-up is essential to show long-term efficacy of dasatinib [6, 10].

dasatinib and nilotinib vs. imatinib: equal survival rates at 18-months

As DASISION trial investigates the safety and efficacy of dasatinib as 1st-line therapy in Ph+CML-CP patients compared to imatinib, the ENESTnd trial compares nilotinib to imatinib. The estimated OS rates at 18-months median follow-up are 98.5% and 99.3% for the nilotinib treated groups and 96.9% for the imatinib treated group. The progression to AP or BC at 12 months was <1% in the nilotinib groups and 4% in the imatinib group [39]. Comparing the interim results of these two studies it cannot be concluded which drug is more effective in treating Ph+CML-CP patients.

main objective: prevent disease progression

The main objective in the treatment of CML patients in the chronic phase is to prevent disease progression to accelerated or blast crisis, to reduce the number of leukemic cells even if the elimination of the disease cannot be achieved [3, 40].

three different 1st-line treatment options available

With the approval of dasatinib and nilotinib, another second-generation TKI targeting the BCR-ABL tyrosine kinase protein, there are now three different treatment options available for the 1st-line therapy of CML-CP. Both drugs are compared to imatinib in clinical trials. As all three drugs are considered to be category 1 (details see chapter 5) treatment options, all targeting the BCR-ABL protein, the question for oncologists remain which patient to treat with which drug and/or in which sequence these drugs should be given [19]. Thus, efficient monitoring is essential to assess the efficacy and identify those patients who are responding well and should continue the therapy unchanged and those who do not respond and may benefit from an alternative treatment option [25].

estimated monthly treatment costs: € 4,500

Another issue that needs to be pointed out is the treatment costs. Estimated monthly treatment costs with dasatinib are around € 4,500 versus € 2,700 for one month treatment with imatinib [37], which is about 1.6 times more costly than imatinib. Further, the costs of imatinib are expected to drop sharply in the near future, due to expiring patents.

head-to-head trial for comparison of nilotinib and dasatinib

Long-term efficacy and safety of dasatinib and nilotinib as initial therapy in Ph+CML-CP patients, the quality of life of the patients, and a head-to-head comparison of these two second-generation TKIs are some questions that have to be addressed in future trials to improve the treatment of patients suffering from CML.

mature data on PFS, OS have to be awaited

Despite encouraging data at the interim analyses at 12- and 18-months follow-up, mature data on PFS and OS, safety profile and quality of life have to be awaited to demonstrate the long-term effectiveness and safety of dasatinib as initial therapy in Ph+CML-CP patients.

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