

*Living with CML:
Practical management and long-term treatment
effects*

*Luigia Luciano, MD
Hematology
Federico II University
Naples*

Living with Imatinib

Side effects

- Common
 - Fluid retention
 - Muscle cramps
- Delayed and Uncommon
 - Dermatological
 - Ocular
 - Cardiotoxicity
 - Renal
- Drug interactions
- Cost effectiveness
- Pregnancy
- Long term treatment
 - Late side effects?
 - Compliance
 - How long?

Response
Duration of response
CURE?

Summary of "common" side effects Imatinib

AEs ≥30% of pts (N=532)	% All grades	% Grades 3/4
Fluid retention	69	4
- Superficial edema	67	2
- Other fluid retention	7	2
Nausea	63	3
Muscle cramps	62	2
Diarrhea	48	3
Fatigue	48	1
Rash and related terms	47	3
Arthralgia	40	1
Musculoskeletal pain	38	2
Vomiting	36	2
Headache	36	<1
Abdominal pain	32	1
*Weight increase	32	7
Hemorrhages	30	2

Non Hematological SE

Type of AE	Time of onset		
	Early	Intermediate	Late
Myalgia and bone pain	x		
Superficial edema	x	x	X
Nausea/Vomiting	x	x	
Diarrhea	x	x	
Muscle cramps	x	x	X
Rash	x		
Fever	x		
Fatigue		x	X
Gynecomastia		x	
Dermatologic		x	X
Ocular		x	X

Fluid Retention

50-60% F >65 y

- Periorbital edema
– Diuretics

Rare

- Pleural, pericardial fluid retention, cardiac tamponade (Fatal)
- Ascites and Anasarca
- Cerebral edema (2 cases)
- Retinal and papilledema; macular edema
- Joint effusions

Dermatologic side effects

- 1) Maculopapular Exanthem
- 2) Exfoliative dermatitis
- 3) Generalized pustulosis
- 4) Epidermal Necrolysis
- 5) Hypopigmentation
- 6) Erythema nodosum
- 7) Oral lichenoid eruption
- 8) Purpuric vasculitis
. . . and others
- 9) Stevens-Johnson Syndrome

Increased sensitiveness to sun:
High protection suggested

Usually self limited despite
continued treatment

Ocular side effects

Table 1
Ocular side effects, predisposing factors and outcome

	Sex/age	Disease phase	Ocular adverse event	Predisposing factors	Time from starting imatinib (nos.)	Dosage of imatinib (mg/day)	Imatinib interruption	Treatment	Outcome
1	M/45	CP	Abnormal vision, increased intraocular pressure	No	2	800	3 weeks	None	Resolved
2	M/56	CP	Recurrent vitreal haemorrhage, glaucoma	Diabetes	1	800	8 weeks	Acetazolamide	Resolved; imatinib gradually restarted
3	M/47	CP	Recurrent conjunctival haemorrhage, increased intraocular pressure	No	10	800	No	Acetazolamide, topical steroids	Not resolved; continued imatinib
4	F/54	CP	Increased intraocular pressure	Myopia	23	400	No	Diuretic	Resolved
5	F/76	CP	Glaucoma	Hypertension	4	400	1 week	Surgical	Resolved; imatinib gradually restarted
6	F/65	CP	Recurrent retinal haemorrhage	Myopia	1	400	No	None	Not resolved
7	F/67	AP	Recurrent conjunctival haemorrhage	Myopia	13	600	No	Topical steroids	Resolved
8	M/66	CP	Recurrent conjunctival and corneal haemorrhage	Hypertension	23	400	No	Topical steroids	Resolved
9	M/68	CP	Recurrent conjunctival haemorrhage	Myopia	3	400	No	Topical steroids	Resolved
10	F/65	CP	Increased intraocular pressure	Myopia	11	800	No	Topical steroids	Not resolved; imatinib reduced to 400 mg/day
11	F/38	CP	Optical neuritis	No	51	400	6 weeks	Vitaminic therapy and topical steroids	Resolved
12	F/76	CP	Recurrent retinal haemorrhage	Hypertension	2	800	No	None	Resolved; imatinib reduced to 400 mg/day
13	F/62	CP	Recurrent conjunctival and corneal haemorrhage	No	24	800	No	Local	Resolved

Renal Toxicity

Mild chronic renal failure

Acute Tubular Necrosis: rare

Current conclusion

Altered Bone Remodeling (Imatinib directly stimulates bone formation while restraining resorption)

Pathogenesis: Failure due to complicated interrelationship between osteoblastic and osteoclastic activity, suppression of PDGF and cFMS

Hematological SE

- Frequent in Late CP and in elderly
- Mild anemia is the most frequent SE
- Hematological SE in early CP correlate with worse response and worse prognosis
- More frequent with high doses

- Closer Follow-up
- GF rarely needed

Filgrastim and Erythropoietin allow more-sustained administration of imatinib and may lead to improvement in response

Cardiotoxicity of the cancer therapeutic agent Imatinib Mesilate

Kerkela et al, Nature Medicine 2006; 12: 908-916

Here we report ten individuals who developed severe congestive heart failure while on imatinib and we show that imatinib-treated mice develop **left ventricular contractile dysfunction**. Transmission electron micrographs from humans and mice treated with imatinib show mitochondrial abnormalities and accumulation of membrane whorls in both vacuoles and the sarco- (endo-) plasmic reticulum, findings suggestive of **a toxic myopathy**. Retroviral gene transfer of an imatinib-resistant mutant of c-Abl largely rescues cardiomyocytes from imatinib-induced death. **Thus, cardiotoxicity is an unanticipated side effect of inhibition of c-Abl by imatinib.**

**IN REPLY TO "CARDIOTOXICITY OF THE CANCER THERAPEUTIC AGENT IMATINIB MESYLATE"
*NATURE MEDICINE 2007; 13: 13-16***

	NO. OF PTS	YEARS PTS EXPOSURE	NO. CHF	% OF PTS	% OF YEARS PTS EXPOSURE
HATFIELD et al NOVARTIS	2327	5595	12	0.51	0.21
GAMBACORTI et al MILANO MONZA	103	412	0	<0.97	<0.24
ATALLAH et al M.D. ANDERSON	1276	6380	7°	0.55	0.11
ROSTI et al GIMEMA CML WP	833	2383	0*	<0.12	<0.04
TOTAL	4539	14770	19	0.42	0.13

° 22 RECORDED, 7 CONFIRMED

* 3 CASES OF MYOCARDIAL INFARCTUS

Incidence of CHF in patients exposed to imatinib compared with CHF incidence in General Population

Patients Exposed to Imatinib		Data From Framingham Heart Study ¹		
Age, Yrs (n/N)	Incidence of CHF,* %	Age, Yrs	CHF 5-Year Risk,* %	
			Male	Female
< 45 (0/409)	0	40	0.2	0.1
45-55 (1/322)	0.3	50	0.8	0.1
56-65 (6/291)	2.0	60	1.3	0.7
66-75 (5/211)	2.3	70	4.0	2.2
76-85 (4/43)	9.3	80	8.3	7.8

■ Cardiac toxicity:

- ✓ BNP (BRAIN NATRIURETIC PEPTIDE) AS A MARKER OF THE HEART FAILURE IN THE TREATMENT OF IMATINIB MESYLATE

PARK YH et al, CANCER LETTERS 2006; 243: 16-22

useful echocardiographic study before and during treatment ?

Remember: Potential Drug Interactions with Imatinib

<p>May ↓ plasma levels of imatinib</p>	<p>Rifampin Rifabutin Dexamethasone</p>	<p>Phenobarbital Phenytoin Carbamazepine</p>	
<p>May ↑ plasma levels of imatinib</p>	<p>Atazanavir Clarithromycin Indinavir Itraconazole</p>	<p>Ketoconazole Nefazodone Nelfinavir Ritonavir</p>	<p>Saquinavir Telithromycin Voriconazole Grapefruit juice</p>
<p>Plasma levels may be ↑ by imatinib</p>	<p>Acetaminophen Alfentanil Cyclosporine Diergotamine Dihydropyridine- Ca⁺ channel-blockers</p>	<p>Ergotamine Fentanyl Select statins Pimozide Quinidine</p>	<p>Simvastatin Sirolimus Tacrolimus Triazolobenzodiazepines Warfarin</p>

Cost-effectiveness

$$ICER = \frac{(QALY_B - QALY_A)}{(COST_B - COST_A)}$$

ICER is the additional cost per additional QALY gained

Cost-Effectiveness in the Base-Case Analysis

	Imatinib	IFN + LDAC	Difference	ICER (95% CI) ^a
Undiscounted				
Life-years	15.30	9.07	6.23	\$39,100/LYS (34,700–45,400/LYS)
QALYs	12.11	6.26	5.85	\$41,500/QALY (37,300–46,400/QALY)
Lifetime costs	\$424,600	\$182,800	\$241,800	
Discounted				
Life-years	11.42	7.48	3.93	\$43,100/LYS (37,600–51,100/LYS)
QALYs	9.06	5.17	3.89	\$43,300/QALY (38,300–49,100/QALY)
Lifetime costs	\$320,100	\$152,000	\$168,100	

IFN + LDAC: interferon- α plus low-dose cytarabine; ICER: incremental cost-effectiveness ratio; 95% CI: 95% confidence interval; LYS: life-year saved; QALY, quality adjusted life-year.

^a95% confidence intervals were based on the 26th and 975th rankings of the 1000 base-case simulations.

The resulting ICERs of \$43,000 per life-year saved and \$43,300 per QALY compare favorably with the widely cited cost-effectiveness threshold of \$50,000 per QALY.

PREGNANCY

- Effective contraception during treatment is therefore advised in **women** of child bearing age
- No special suggestions for **male** patients who wish to father a child during treatment

Unplanned Pregnancies (In the past, most were unplanned)

- Balancing the risk to the fetus of continuing imatinib vs. the risk to the mother of stopping imatinib remains difficult.
- Fetal perspective: potential risk of serious developmental abnormalities ($\pm 10\%$).
- Pregnancy was often “realized” only at 8-12 weeks (of exposure to imatinib).

Imatinib and Pregnancy (N = 125)

- Of 180 mothers exposed to imatinib during pregnancy, outcomes available for 125 (69%)
- Normal live infants 63 (50%)
- Elective termination 35 (28%)
 - Fetal defects: 3
- Spontaneous abortion 18 (14%)
- Fetal abnormalities 12 (10%)
- Interrupted imatinib 10 (8%)
 - Increase in Ph+: 6
 - 3 of 10 achieved a MCyR at a median of 18 mos. after reinitiating treatment.
- Balancing risk to fetus vs risk of decreased response to therapy remains difficult

Managing a Planned Pregnancy in 2009

Pre-conception	<ul style="list-style-type: none">• At least 24 months MRD• Counselling• Rule-out common causes of male and female infertility
Imatinib wash-out before trying to conceive	<ul style="list-style-type: none">• 7- 10days seems appropriate (1)
Disease monitoring	<ul style="list-style-type: none">• Monthly RQ-PCR• No treatment if CMR / MMR• IFN if molecular relapse (?)• Restart imatinib > 4 months of gestation
After delivery	<ul style="list-style-type: none">• Breast feeding Contraindicated: 1-2 mg daily of imatinib to the newborn (2)• D/C Breast feeding before re-start imatinib (\approx 3-5 days)

1) H.P.Gschwind et al Drug Metabolism and Disposition: 33 (10) 1501-1512, 2005

2) M.A. Russel et al. Journal of Perinatology: 27, 241-243, 2007

Long term treatment

- Compliance:
may I take one less tablet? or May I skip one or two days in a week ?
- How long ?

Imatinib Discontinuation

Reference	N. Pts	Time from discontinuation	Outcome
Cortes J et al, Blood 2004	3	+3 mo +6 mo +6 mo	Cyt. relapse
Merante S et al, Haematologica 2005	4	+7 mo +10 mo +14 mo +15 mo	Mol. Relapse Mol. Relapse Still in CMR Still in CMR
Okabe S et al, Int J Hematol 2007	1	+36 mo	Still in MMR
Verma D et al, Leuk Lymphoma 2008	1	+24 mo	Mol. Relapse
Kiguchi T et al, Rinsho Ketsueki 2009	1	+24 mo	Mol. Relapse

Imatinib Discontinuation

CLINICAL TRIALS AND OBSERVATIONS

Brief report

Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years

Philippe Rousselot,^{1,2} Françoise Huguet,³ Delphine Rea,¹ Laurence Legros,⁴ Jean Michel Cayuela,⁵ Odile Maarek,⁵ Odile Blanchet,⁶ Gerald Marit,⁷ Eliane Gluckman,¹ Josy Reiffers,⁸ Martine Gardembas,⁹ and François-Xavier Mahon,¹⁰ on behalf of the Intergroupe Français des Leucémies Myéloïdes Chronique (IFLMC)

12 patients in late CP

- 10/12 received IFN based regimens before imatinib
- Best responses to IFN: 5 CCyR, 3 minor CyR, 2 no response
- 10/12: no response before imatinib
- 6/12 No relapse after imatinib discontinuation
- **All 6 received IFN** before imatinib for 29 to 152 mos)
- **All 6 sensitive** to IFN (4 CCyR and 2 minor CyR)
- One patient has gone for 4 years with no evidence of recurrent disease

Mean follow up 39 mo (range 30-49 mo)

French STIM study

- Inclusion criteria: IM treatment for at least 3 years and sustained CMR
- 69 pts from 22 centres were included
- 60 pts had a follow up ≥ 1 months
- 31 previously treated with IFN, 29 de novo patients
- 49 patients had more than 6 months FU
- 27 patients relapsed in first 6 months

46% chance of being in CMR at 6 months

All patients relapsed are sensitive after imatinib rechallenge.
IFN may not make the difference

Which one is the future?

Cure CML