Imatinib Long Term Effects (ILTE) Study: An Independent, International Study in CML Patients

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Objectives

Imatinib is an effective first line therapy for chronic myeloid leukemia (CML) and has substantially changed its biological and clinical behavior. Durable complete cytogenetic responses (CCyR) were reported in the majority of patients, with a rather benign side effect profile, despite the 'off target' inhibition of several other kinases, including Kit, PDGFR and Lck. The ILTE study was conceived as an industry-independent, academic, multicenter trial supported by the Italian Drug Safety Agency (AIFA); it enrolled CML patients who were in CCyR two years after starting imatinib.

Study endpoints were **(I)** survival, **(II)** serious adverse events (SAE, including second cancers), **(III)** toxicities not qualifying as SAE (NSAE) but judged by the referring physician as substantially impacting quality of life, **(IV)** loss of CCyR, and **(V)** development of PCR negativity.

Results

Table 1. Patients distribution by center

Center	Imatinib Start minum	Imatinib Start maximum	n	% of eligible
MONZA	17/11/1999	15/11/2004	67	95.5
ORBASSANO	10/02/2000	18/10/2004	46	93.5
NAPOLI	25/01/2000	21/06/2004	86	64.0
VICENZA	18/01/2001	16/11/2004	34	100.0
CATANIA	28/02/2002	14/12/2004	33	93.9
BERGAMO	06/12/2000	21/12/2004	40	100.0
BOLZANO	27/08/2001	29/07/2004	22	77.3
TORINO	16/08/2001	24/11/2004	11	100.0
ALESSANDRIA	05/02/2003	28/07/2004	9	100.0
BERLIN	15/08/2000	30/12/2004	34	91.2
MONTREAL	23/04/2001	31/12/2004	11	81.8
MILANO	24/01/2001	18/11/2004	35	100.0
ROMA	29/11/2000	22/11/2004	34	100.0
FIRENZE	01/11/2001	31/12/2004	29	58.6
POITIERS	03/09/1999	09/12/2004	61	83.6
OREGON	10/09/1999	08/07/2004	49	95.9
KOREA	31/05/2001	31/12/2004	131	100.0
BORDEAUX	13/01/2000	21/12/2004	107	98.1
ISRAEL	24/01/2000	13/11/2004	41	100.0
MEXICO	07/12/2000	30/11/2004	29	96.6
ZARAGOZA	11/04/2002	06/07/2004	10	100.0
NIGERIA	04/08/2003	30/11/2004	10	60.0
REGGIO CALABRIA	09/10/2000	18/08/2004	22	100.0
OLANDA	09/10/2002	14/12/2004	6	83.3
Total	**03/09/1999**	**31/12/2004**	**957**	**91.5**

Table 2. Age and gender distibution of 876 eligibile patients

First line	n (%)	Age at start of Imatinib (years) minimum	maximum	median	Gender %males
YES	381 (43.5%)	15	84	47	56
NO	495 (56.5%)	17	92	52	60
Total	**876**	**15**	**92**	**50**	**59**

Median FUP from enrollment : 2.9 years

Median treatment duration : 4.8 years

Table 5. Rates of SAE and NSAE in which a certain, probable or possible relationship to Imatinib was considered, according to age and gender

Gender	n. of eligible	SAE rate	SAE n	SAE person-years	NSAE rate	NSAE n	NSAE person-years
Male	513	0.9	13	1510	14.1	213	1510
Female	363	0.8	8	1055	18.3	193	1055
Age (years)							
<50	431	0.7	8	1196	16.3	195	1196
>50	445	0.9	13	1369	15.4	211	1369
Total	**876**	**0.8**	**21**	**2565**	**15.8**	**406**	**2565**

Table 3. Occurence of SAE and relationship to imatiminib use.

Relationship to Imatinib use	n	%
Certain	4	4.0
Probable	0	0.0
Possible	17	17.0
Not Likely	32	32.0
Not Related	26	26.0
Not known	17	17.0
Missing	4	4.0
Total	**100**	**100**

Table 4. Occurence of NSAE and relationship to Imatiminib use.

Relationship to Imatinib use	n	%
Certain	126	22.1
Probable	181	31.8
Possible	99	17.4
Not Likely	68	11.9
Not Related	40	7.0
Not known	43	7.5
Missing	13	2.3
Total	**570**	**100**

SAE (where relationship to Imatinib use = certain, probable, possible)	n	%
anasarca	1	4.8
coxarthrosis	1	4.8
diarrea	2	9.5
fever	1	4.8
fracture: tendon shoulder	1	4.8
gastritis	1	4.8
heart failure	2	9.5
herpes zooster	1	4.8
infarction: IMA	1	4.8
otitis	1	4.8
pneumonia	1	4.8
pyomyositis in glutens biceps femoris	1	4.8
skin rash	1	4.8
surgery: fracture	1	4.8
surgery: right cubitus nodule	1	4.8
surgery: uterus	1	4.8
thyroiditis	1	4.8
ulcer: duodenal	1	4.8
Missing	1	4.8
Total	**21**	**100**

NSAE (where relationship to Imatinib use = certain)	n	%
asthenia	3	2.4
CPK increase	1	0.8
cutaneous lesions rash/skin fragility	2	1.6
diarrhea	10	7.9
eye discharge/tearing	2	1.6
hematologic toxicity	3	2.4
muscle cramps	41	32.5
nausea/didspepsia	4	3.2
ocular irrit/scleral hemorr	5	4.0
oedema	39	31.0
ocular pain	1	0.8
gynecomastia	7	5.6
sexual disfunction	1	0.8
abdominal distension	3	2.4
osteoarticular pain	2	1.6
dyspepsia	1	0.8
missing	1	0.8
Total	**126**	**100**

Table 6. Rates of loss of CCyR, second neoplasias and death

Gender	n. of eligible	Loss ccr rate	Loss ccr n	Loss ccr person-years	Neoplasia rate	Neoplasia n	Neoplasia person-years	Death rate	Death n	Death person-years
Male	513	1.3	19	1470	1.2	18	1477	0.4	6	1510
Female	363	1.4	15	1038	0.9	9	1039	0.5	5	1055
Age (years)										
<50	431	1.0	12	1175	0.4	5	1187	0.2	2	1196
>50	445	1.6	22	1334	1.7	22	1330	0.7	9	1369
Total	**876**	**1.4**	**34**	**2509**	**1.1**	**27**	**2517**	**0.4**	**11**	**2565**

Results

Table 7. Rates of loss of CCyR according to the year of follow-up in the study (year one corresponds to year 3 on imatinib). First line patients started Imatinib within 6 months from diagnosis and had previous exposure to HU only.

FIRST LINE

Gender	one year n. of eligible	one year rate	one year n	one year person-years	two years n. of eligible*	two years rate	two years n	two years person-years	three years n. of eligible	three years rate	three years n	three years person-years	four years n. of eligible*	four years rate	four years n	four years person-years
Male	215	1.0	2	209.1	193	0.7	1	139.8	96	1.6	1	63.0	36	4.3	1	23.2
Female	166	0.0	0	162.7	153	1.7	2	120.7	85	1.7	1	58.5	35	0.0	0	25.1
Age (years)																
<50	213	1.0	2	208.2	194	1.4	2	143.7	94	1.6	1	62.8	38	3.6	1	27.7
>50	168	0.0	0	163.7	152	0.9	1	116.8	87	1.7	1	58.7	33	0.0	0	20.6
Total	**381**	**0.5**	**2**	**371.8**	**346**	**1.2**	**3**	**260.6**	**181**	**1.6**	**2**	**121.5**	**71**	**2.1**	**1**	**48.3**

NO FIRST LINE

Gender	one year n. of eligible	one year rate	one year n	one year person-years	two years n. of eligible*	two years rate	two years n	two years person-years	three years n. of eligible	three years rate	three years n	three years person-years	four years n. of eligible*	four years rate	four years n	four years person-years	five years n. of eligible*	five years rate	five years n	five years person-years
Male	298	1.0	3	293	289	1.1	3	275	253	1.7	4	232	187	0.7	1	140	96	2.9	2	70
Female	197	1.5	3	195	192	0.6	1	182	171	1.3	2	153	124	3.4	3	89	61	5.4	2	37
Age (years)																				
<50	218	0.9	2	217	215	0.5	1	201	186	0.6	1	169	133	4.3	4	93	58	5.3	2	38
>50	277	1.5	4	272	266	1.2	3	255	238	2.3	5	217	178	0.0	0	135	99	2.9	2	69
Total	**495**	**1.2**	**6**	**489**	**481**	**0.9**	**4**	**457**	**424**	**1.6**	**6**	**386**	**311**	**1.8**	**4**	**228**	**157**	**3.7**	**4**	**107**

Table 8. Numbers of deaths compared to available rates in the italian population (ISTAT 2004)

gender	O=Observed	E=Expected	O/E	95% CI
M	6	15.83	0.38	0.14 , 0.82
F	5	7.23	0.69	0.22 , 1.61
TOTAL	**11**	**23.06**	0.48	0.24 , 0.85

Only 3 out of 11 observed deaths (27%) were caused by progression of CML

Table 9. Numbers of second cancers compared to IARC cancer rates.

gender	O=Observed	E=Expected	O/E	95% CI
M	18	15.5	1.16	0.69 , 1.75
F	9	6.5	1.38	0.63 , 2.41
TOTAL	**27**	**22.1**	1.22	0.81 , 1.73

Table 11. Occurrence of durable (>1 year) PCR negativity among patients in whom data are available.

PCR negativity>1 year	n	%
NO	326	60.3
YES	215	39.7
Total	**541**	**100**

Table 10. Types of second cancers detected

Type	n	%
Lymphoma	1	3.7
Ph neg. Leukemia	1	3.7
Renal	1	3.7
Prostate	10	37.0
Lung	2	7.4
Breast	2	7.4
Squamous cell	4	14.8
Colon	2	7.4
Adenoc. endom	1	3.7
Adenoc. biliar	1	3.7
CNS	1	3.7
Mucoepidermoid ca	1	3.7
Total	**27**	**100**

Conclusions

These preliminary results from the ILTE study show that CML patients on imatinib die infrequently of CML related causes, do not appear to have substantially higher second cancer rates than the general population, have mortality rates lower than expected in an age/sex matched population and do not show new types of Imatinib-related adverse events. They also experience a low but steady rate of loss of CCyR and develop PCR negativity in approximately 1/3 of cases for which data are available. Further follow-up is planned to assess long term effects.

ILTE - Imatinib Long Term Side Effects Study