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Management of CML in countries with limited access to treatment and diagnostics

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26.05.2017, Frankfurt

Serbia- WHO statistical profiles

Basic statistics

Indicators	Statistics	Year
Population (thousands)	9511	2013
Population aged under 15 (%)	16	2013
Population aged over 60 (%)	21	2013
Median age (years)	39	2013
Population living in urban areas (%)	55	2013
Total fertility rate (per woman)	1.4	2013
Number of live births (thousands)	92.5	2013
Number of deaths (thousands)	113.5	2013
Birth registration coverage (%)	99	2010
Cause-of-death registration coverage (%)	90	2010-2012
Gross national income per capita (PPP int $)	12020	2013
WHO region	European	2013
World Bank income classification	Upper middle	2013

GDP - 14493 $/per capita (2016 IMF)
Health investment
9% GDP (1312$/per capita 2014) through centralized system of Republic Health Insurance Fund

Who are our patients?
How we diagnosed and treated them?

Epidemiology of CML in Serbia

Leukemia (2015) **29**, 1336–1343
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www.nature.com/leu

ORIGINAL ARTICLE

The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries

VS Hoffmann[1,29], M Baccarani[2,29], J Hasford[1], D Lindoerfer[1], S Burgstaller[3], D Sertic[4], P Costeas[5], J Mayer[6], K Indrak[7], H Everaus[8], P Koskenvesa[9], J Guilhot[10], G Schubert-Fritschle[11], F Castagnetti[12], F Di Raimondo[13], S Lejniece[14], L Griskevicius[15], N Thielen[16], T Sacha[17], A Hellmann[18], AG Turkina[19], A Zaritskey[20], A Bogdanovic[21], Z Sninska[22], I Zupan[23], J-L Steegmann[24], B Simonsson[25], RE Clark[26], A Covelli[27], G Guidi[27] and R Hehlmann[28]

Table 1. Countries and country regions of registration, number of inhabitants (≥20 years old), registration time (months) and number of newly diagnosed Ph+ and/or BCR-ABL1+ cases, all phases (chronic, accelerated and blastic)

Country	*Regions*	*No. inhabitants ≥20 years old*	*Registration time (months)*	*No of cases*	*Male %*	*Male, median age (years)*	*Female, median age (years)*	*Total, median age (years)*	*Males, raw incidence*	*Males, standardised incidence*	*Females, raw incidence*	*Females, standardised incidence*	*Males and females, raw incidence*	*Males and females, standardised incidence*
Austria	Upper Austria, Salzburg, Tirol, Voralberg, Styria	3 350 069	13–36 (median 25)	55	61.8	57	59	57	0.91	0.91	0.53	0.50	0.71	0.70
Croatia	Whole country	3 493 000	38	126	55.6	54.5	57	57	1.34	1.30	0.96	0.89	1.14	1.10
Cyprus	Whole country	660 000	18	9	66.7	52	55	53	1.27	1.33	0.58	0.63	0.91	0.98
Czech Republic	Olomouc, Prague region, Brno region, Moravian-Silesian, Hradec Kralove, Pardubice, Plzen, Karlovy Vary, Usti nad Labem, South Boemia	7 563 278	24-42 (median 41)	308	55.2	55	58	56	1.38	1.36	1.06	1.01	1.22	1.19
Estonia	Whole country	1 055 000	35	31	74.2	59	65.5	64	1.67	1.74	0.47	0.45	1.01	1.10
Finland	Helsinki region	1 225 661	39	38	47.4	54	56	55.5	0.95	0.94	0.96	0.88	0.95	0.91
France	Poitou-Charentes	1 356 836	43	49	38.8	59	58.5	59	0.82	0.76	1.18	1.11	1.01	0.93
Germany	Oberbayern	3 710 064	36	139	49.6	63	60	61	1.28	1.12	1.22	1.09	1.25	1.11
Italy	Emilia-Romagna, Sicily	7 294 154	17–60 (median 46)	356	52.5	56	60	57	1.53	1.40	1.27	1.16	1.39	1.28
Latvia	Whole country	1 797 000	36	42	52.4	50	62.5	52.5	0.91	0.93	0.67	0.61	0.78	0.77
Lithuania	Whole country	2 550 000	36	81	48.2	56	52	54	1.12	1.15	1.01	1.04	1.06	1.10
Netherlands	Amsterdam region, Rotterdam region. South region	4 819 282	45	179	57.0	50	56	54	1.14	1.10	0.82	0.79	0.98	0.94
Poland	Kujawsko-Pomorskie, Pomorskie, Warmińskie, Małopolskie, Podkarpackie, Świętokrzyskie	9 494 215	41	225	49.3	56	54.5	55	0.71	0.74	0.67	0.66	0.69	0.70
Russia	St. Petersburg, Leningrad region, Mordovia, [illegible]	13 097 675	28–39 [illegible]	337	48.4	44	54	50	0.89	0.90	0.75	0.73	0.81	0.82
Serbia	Belgrade city and district, East Serbia, West Serbia, South Banat	3 059 053	41	96	56.3	58	52.5	57	1.06	1.01	0.78	0.76	0.92	0.89
Slovakia	Whole country	4 263 268	39	147	53.6	57	56.5	57	1.18	1.22	0.94	0.94	1.06	1.08
Slovenia	Whole country	1 639 000	35	44	52.3	64	59	59.5	1.00	0.94	0.85	0.81	0.92	0.87
Spain	Comunidad de Madrid, Castilla-La Mancha, Aragon	7 942 014	32–36 (median 35)	249	58.2	51	56.5	54	1.30	1.31	0.88	0.81	1.08	1.06
Sweden	Whole country	7 136 000	41	264	58.7	62	62	62	1.29	1.17	0.88	0.75	1.08	0.96
United Kingdom	North Wales, Lancashire and South Cumbria, Merseyside and Cheshire, Yorkshire	5 592 562	31–40 (median 35)	112	49.1	58	58	58	0.76	0.71	0.73	0.69	0.75	0.70
Total	20 Countries 49 regions	92 526 127	39	2887	53.7	55	57	56	1.12	1.10	0.88	0.82	0.99	0.96

Distribution by sex and age. Raw incidence and standardized (old European standard population) incidence of newly diagnosed chronic myeloid leukemia patients (≥20 years), per 100 000/year.

Techniques used to diagnose/monitor CML

- Complete Blood Counts
- Cytogenetic analysis
- More sensitive testing PCR

  RQ-PCR from 2008 at Clinical Centre of Serbia (EUTOS lab certifications)

  Three centers have GeneXpert from 2012

CML treatment in Serbia

4 University centers covering all country

300 patients – Imatinib
100 patients- Nilotinib as second line

Two level for approval of TKI

1. First level- hospital Board

2. Second level central Board of Health Insurance Fund

What is the situation like in Serbia?

- The TKI drugs on the active list in NHIF until may 2017:

  - Imatinib (Glivec®, Anzovip®, Imatinib Pharma Swiss®, Alvotinib®, Meaxin®, Plivatinib®) as a 1st line therapy

  - Nilotinib (Tasigna®) as a 2nd line therapy

Branded Imatinib- Glivec®

- 2001 Glivek® was registrated in 2001
- 2006 Glivek® available regularly by Insurance as the first line treatment of CML in chronic phase
- 2006-2012. – The patients treated with Glivec in all institutions in Serbia

Who are our patients treated with Glivec® (N-55)?

Parameters	Mediana	Min	Max
Gender (M/F) 28/27			
Age (years)	49	21	77
WBC (10^9/l)	107	12	411
Hgb (g/l)	112	64	139
Platelets (10^9/l)	429,5	131	3795
Blasts %	2,5	1	8
Promyelocyte %	4	2	9
Eo %	3	1	6
Basophils %	2	1	8
Sokal score Low 23,1% Intermediate 30,7% High 46,2%			
EUTOS Low 61,5% High 38,5%			

Median duration of treatment- 23,5 m (3-100 months)

25% loss of CCgR after switch to generic Imatinib

Distribution of patients according to Sokal and Eutos score

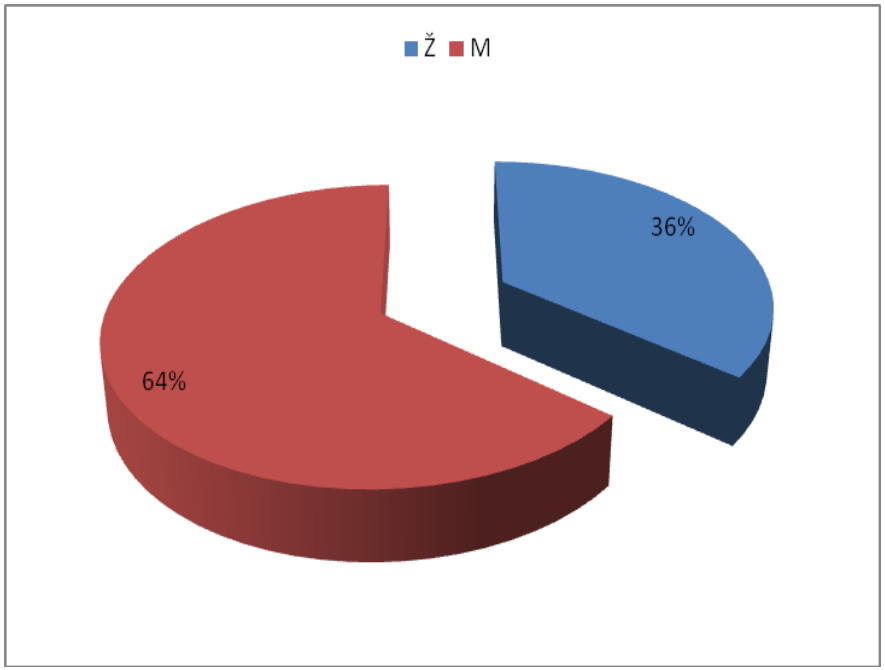
Group	Sokal score	Eutos score
Low	23,1%	53,8%
Intermediate	23,1%	
High	53,8%	46,2%

Generic Imatinib as first line of treatment

- During August and September 2012 all patients were switched from Glivec to Anzovip and all newly diagnosed patients started with Anzovip therapy.

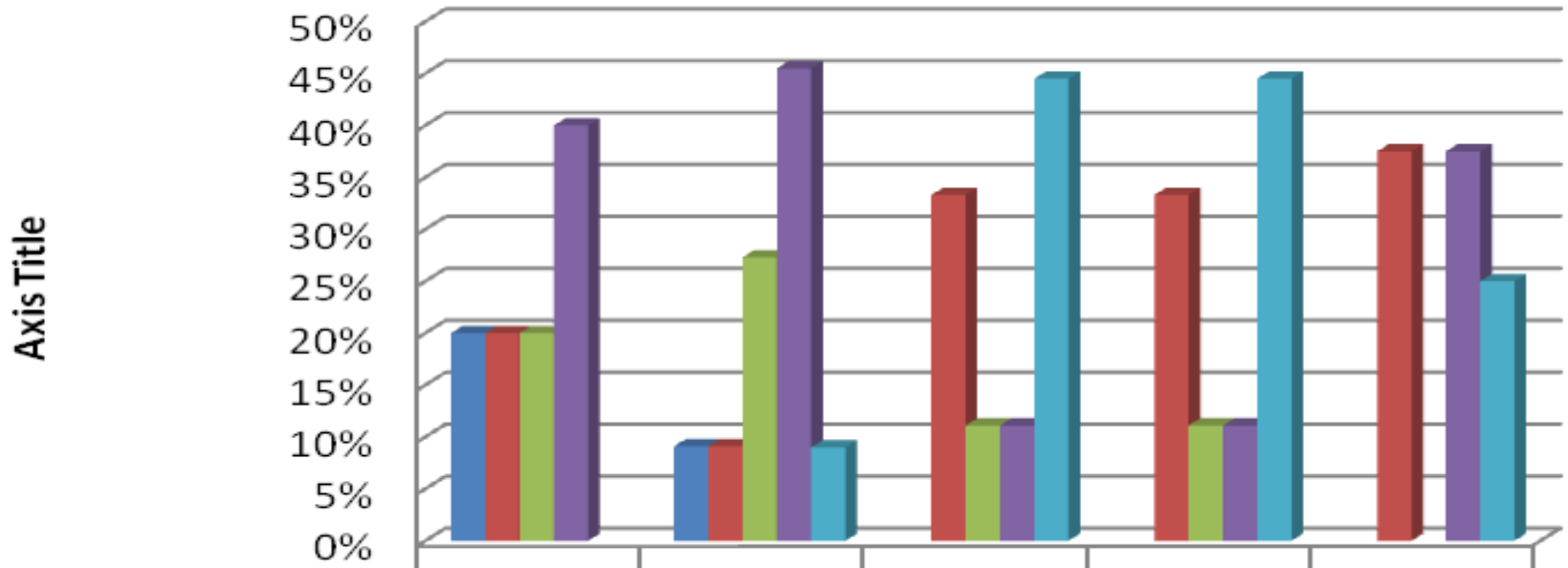
- **55 CML patients on Glivec → Anzovip (2012)**
- **57 newly diagnosed CML patients (2012-2017)**

Nilotinib as second line of treatment (N- 28 patients)



- Age 47,5 y
- WBC (mean) 215,88x109/L
- Basophils (mean) 3,8%
- Eosinophils (3,5%)
- Spleen 17,35cm

Molecular responce at 3,6,12,18,24 months



	3 meseca	6 meseca	12 meseci	18 meseci	24 meseca
>1%	20%	9,10%			
1-0.1%	20%	9,10%	33,30%	33,30%	37,50%
0.1-0.01%	20%	27,30%	11,10%	11,10%	
0.01-0.0032%	40%	45,50%	11,10%	11,10%	37,50%
0.0032%-0.001%		9%	44,50%	44,50%	25%

First guidelines 2008

ELN (2006) based national guidelines 2008

Imatinib for all CML patients in chronic phase

Cytogenetics evaluation 6,12,18, and thereafter yearly

ELN suboptimal or failure criteria for treatment change (escalation dose of Imatinib or Nilotinib switched from 2011)

2014 recommendation

ELN (2013) based national recommendation released 2014

Imatinib as the first line (generic Imatinib)

Cytogenetics evaluation 6,12,24 and thereafter on second year

RQ-PCR at 3,6, and 12 monts and thaen a twice a year for all patients

ELN failure criteria for treatment change

Can we do better?

- What can we do with the patient on Nilotinib failure?
- The third line of therapy? Dasatinib.....
- Can we treat the select group of patient with Nilotinib as the first line? Younger patients, intermediate or high risk?
- Careful follow- up of a selected patients treated with generic Imatinib.

Can we do beter in the region?

- How can we improve epidemiological data in the region?
- Common registar: snapshoot of current epidemiological situation?
- How can we improve therapeuticals options?
- Association beetwen doctors and CML patients groups
- Synergistic cooperation and influence to the NHIF budget spending policies (best treatment options with limited money resource)

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