RARE HAEMATOLOGICAL DISEASES

74%
OF HAEMATOLOGICAL DISEASES ARE RARE

INCIDENCE

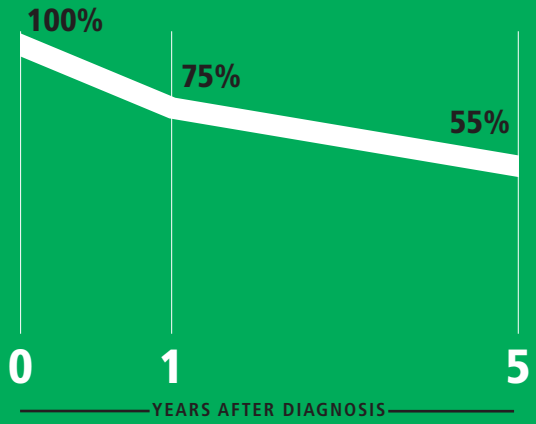
27 084
ESTIMATED NEW CASES
ITALY, 2015

17 464	RARE LYMPHOID DISEASES	48	% OF RARE HAEMATOLOGICAL DISEASES OUT OF ALL HAEMATOLOGICAL DISEASE
3 572	ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS	10	
3 610	MYELOPROLIFERATIVE NEOPLASMS	10	
2 371	MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/ MYELOPROLIFERATIVE DISEASES	6	
68	HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	0.2	

PREVALENCE

225 872
ESTIMATED PREVALENT CASES
ITALY, 2010

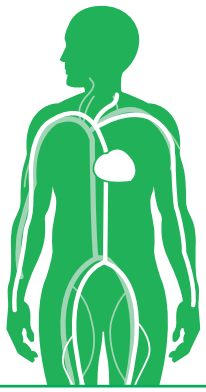
SURVIVAL



SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

RARE HAEMATOLOGICAL DISEASES

INCIDENCE



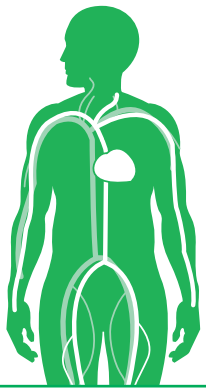
RARE HAEMATOLOGICAL DISEASES. Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

	AIRTUM POOL (period of diagnosis 2000-2010)														ITALY
					SEX				AGE						
					MALE		FEMALE		0-54 yrs		55-64 yrs		65+ yrs		
	RATE	95% CI	OBSERVED CASES (No.)	RARE CANCERS BY SITE (%)	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	ESTIMATED NEW CASES 2015 No.
RARE HAEMATOLOGICAL DISEASES	**41.08**	**40.81-41.35**	**91 094**	**74%**	**45.43**	**45.03-45.84**	**37.00**	**36.65-37.36**	**16.17**	**15.97-16.38**	**53.07**	**52.21-53.94**	**118.92**	**117.9-119.94**	**27 084**
RARE LYMPHOID DISEASES	**26.78**	**26.56-27.00**	**59 384**	**48%**	**29.33**	**29.00-29.65**	**24.39**	**24.11-24.68**	**11.96**	**11.78-12.13**	**36.78**	**36.06-37.50**	**71.32**	**70.54-72.12**	**17 464**
Hodgkin lymphoma, classical	3.50	3.43-3.58	7 769		3.84	3.73-3.96	3.18	3.08-3.29	3.73	3.64-3.83	2.59	2.40-2.78	3.29	3.12-3.46	2 101
Hodgkin lymphoma nodular lymphocyte predominance	0.14	0.12-0.16	309		0.18	0.16-0.21	0.10	0.08-0.12	0.14	0.12-0.16	0.18	0.13-0.24	0.12	0.09-0.16	85
Precursor B/T lymphoblastic leukaemia/lymphoma (and Burkitt leukaemia/lymphoma)	1.86	1.80-1.92	4 127		2.23	2.14-2.32	1.52	1.45-1.59	1.91	1.84-1.98	1.31	1.17-1.45	2.05	1.92-2.19	1 168
T cutaneous lymphoma (Sezary syndrome, Mycosis fungoides)	1.07	1.02-1.11	2 363		1.40	1.33-1.47	0.76	0.71-0.81	0.38	0.35-0.41	1.92	1.76-2.09	2.88	2.73-3.04	700
Other T cell lymphomas and NK cell neoplasms	0.87	0.83-0.91	1 922		1.09	1.03-1.16	0.66	0.61-0.70	0.41	0.38-0.44	1.25	1.13-1.40	2.19	2.05-2.33	563
Diffuse large B-cell lymphoma	6.94	6.83-7.05	15 393		7.24	7.08-7.40	6.67	6.52-6.82	2.44	2.37-2.52	9.31	8.95-9.68	20.87	20.45-21.31	4 568
Follicular lymphoma	2.85	2.78-2.92	6 320		2.80	2.70-2.90	2.90	2.80-3.00	1.28	1.23-1.34	5.90	5.61-6.20	6.32	6.09-6.56	1 849
Hairy cell leukaemia	0.44	0.42-0.47	985		0.72	0.67-0.77	0.19	0.16-0.21	0.24	0.21-0.26	0.86	0.76-0.98	0.89	0.80-0.98	292
Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	8.36	8.24-8.48	18 545		8.75	8.58-8.93	8.00	7.83-8.16	1.27	1.22-1.33	12.11	11.70-12.53	30.31	29.80-30.83	5 643
Mantle cell lymphoma	0.72	0.68-0.75	1 588		1.04	0.98-1.10	0.42	0.38-0.46	0.15	0.13-0.17	1.32	1.19-1.46	2.29	2.15-2.44	476
Prolymphocytic leukaemia, B cell	0.03	0.02-0.04	63		0.04	0.03-0.05	0.02	0.01-0.03	<0.01	0.00-0.01	0.03	0.01-0.05	0.11	0.08-0.15	20
ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS	**5.34**	**5.24-5.44**	**11 837**	**10%**	**5.80**	**5.66-5.95**	**4.90**	**4.78-5.03**	**1.73**	**1.67-1.80**	**6.12**	**5.83-6.42**	**17.19**	**16.81-17.58**	**3 572**
Acute promyelocytic leukaemia (AML) with t(15;17) and variants	0.23	0.21-0.25	513		0.23	0.20-0.26	0.23	0.21-0.26	0.19	0.17-0.22	0.26	0.20-0.33	0.35	0.30-0.41	145
Acute myeloid leukaemia	4.79	4.70-4.88	10 620		5.22	5.09-5.36	4.38	4.26-4.51	1.49	1.43-1.55	5.60	5.32-5.88	15.58	15.21-15.95	3 204
MYELOPROLIFERATIVE NEOPLASMS	**5.47**	**5.37-5.56**	**12 119**	**10%**	**6.27**	**6.12-6.42**	**4.71**	**4.58-4.84**	**2.02**	**1.95-2.09**	**7.67**	**7.34-8.00**	**15.90**	**15.53-16.28**	**3 610**
Chronic myeloid leukaemia	1.61	1.56-1.66	3 566		1.87	1.79-1.95	1.36	1.30-1.43	0.65	0.61-0.69	2.09	1.92-2.27	4.59	4.39-4.79	1 075
Other myeloproliferative neoplasms	3.80	3.72-3.88	8 425		4.34	4.21-4.47	3.29	3.19-3.40	1.32	1.27-1.38	5.50	5.22-5.79	11.22	10.91-11.53	2 499
Mast cell tumours	0.06	0.05-0.07	128		0.06	0.05-0.08	0.05	0.04-0.07	0.04	0.03-0.06	0.08	0.05-0.12	0.10	0.07-0.13	36
MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES	**3.39**	**3.31-3.46**	**7 511**	**6%**	**3.90**	**3.78-4.02**	**2.91**	**2.81-3.01**	**0.35**	**0.32-0.39**	**2.44**	**2.26-2.63**	**14.36**	**14.01-14.72**	**2 371**
Myelodysplastic syndrome with 5q syndrome	0.02	0.01-0.03	41		0.01	0.01-0.02	0.02	0.02-0.03	<0.01	0.00-0.01	0.02	0.01-0.04	0.08	0.05-0.11	12
Other myelodysplastic syndrome	3.04	2.96-3.11	6 733		3.45	3.34-3.57	2.64	2.55-2.74	0.32	0.29-0.35	2.18	2.01-2.36	12.86	12.53-13.20	2 129
Chronic myelomonocytic leukaemia	0.31	0.29-0.34	694		0.41	0.37-0.45	0.22	0.19-0.25	0.03	0.02-0.04	0.22	0.17-0.28	1.35	1.24-1.46	216
Atypical chronic myeloid leukaemia BCR/ABL negative	0.02	0.01-0.02	39		0.02	0.01-0.03	0.01	0.01-0.02	<0.01	0.00-0.01	0.01	0.00-0.04	0.07	0.04-0.09	12
HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	**0.11**	**0.10-0.12**	**243**	**0.2%**	**0.13**	**0.11-0.16**	**0.09**	**0.07-0.11**	**0.11**	**0.09-0.13**	**0.07**	**0.04-0.10**	**0.14**	**0.11-0.18**	**68**
Histiocytic malignancies	0.08	0.07-0.09	181		0.10	0.08-0.12	0.06	0.05-0.08	0.10	0.08-0.11	0.03	0.02-0.06	0.07	0.04-0.09	50
Lymph node accessory cell tumours	0.03	0.02-0.04	62		0.03	0.02-0.04	0.03	0.02-0.04	0.01	0.01-0.02	0.03	0.02-0.06	0.08	0.05-0.11	18

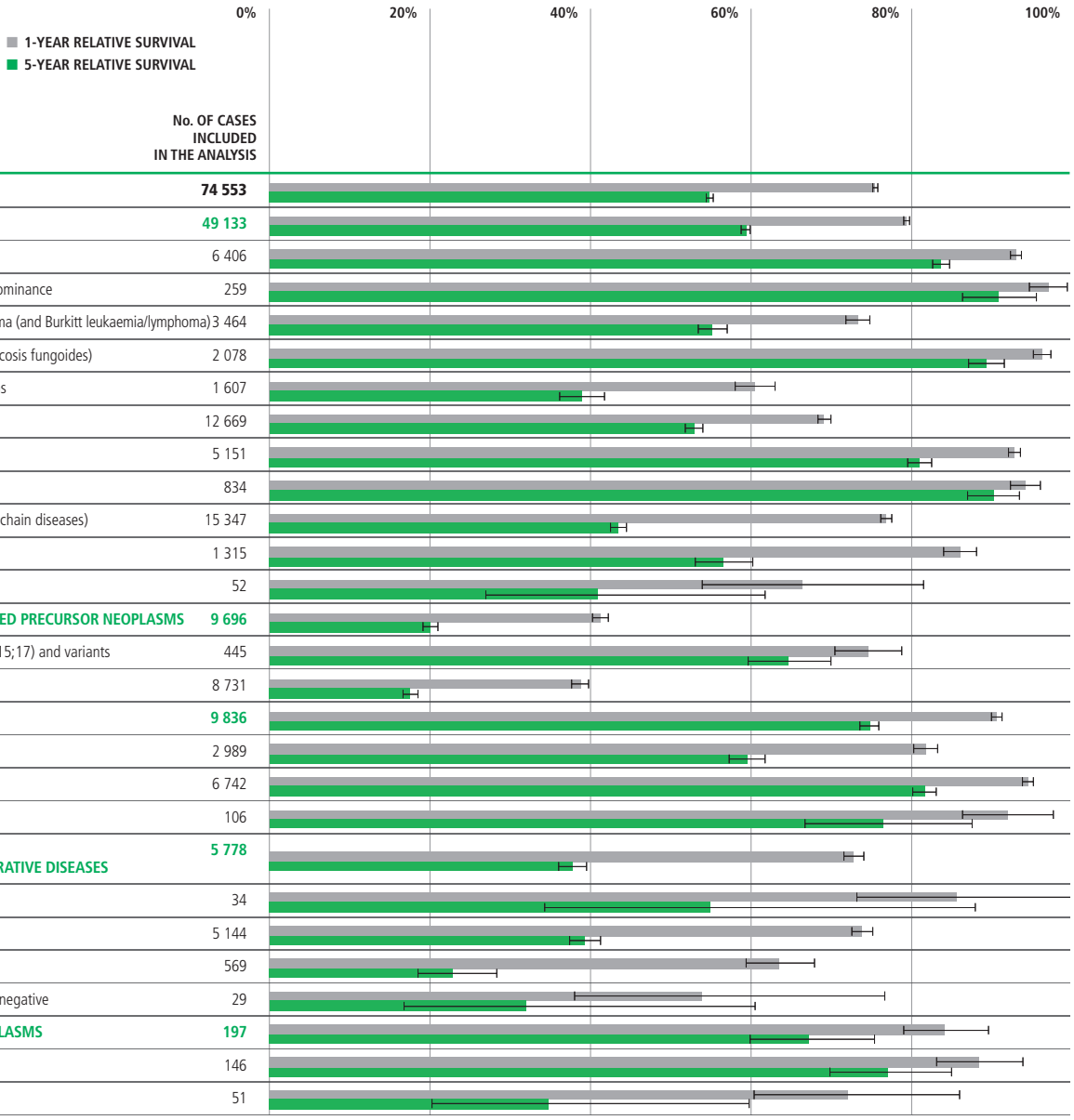
NK: natural killer

RARE HAEMATOLOGICAL DISEASES

SURVIVAL



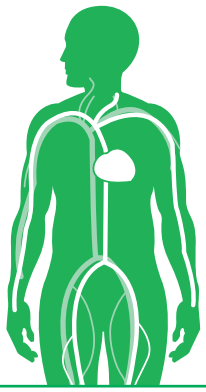
RARE HAEMATOLOGICAL DISEASES. One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.



	No. OF CASES INCLUDED IN THE ANALYSIS
RARE HAEMATOLOGICAL DISEASES	**74 553**
RARE LYMPHOID DISEASES	**49 133**
Hodgkin lymphoma, classical	6 406
Hodgkin lymphoma nodular lymphocyte predominance	259
Precursor B/T lymphoblastic leukaemia/lymphoma (and Burkitt leukaemia/lymphoma)	3 464
T cutaneous lymphoma (Sezary syndrome, Mycosis fungoides)	2 078
Other T cell lymphomas and NK cell neoplasms	1 607
Diffuse large B-cell lymphoma	12 669
Follicular lymphoma	5 151
Hairy cell leukemia	834
Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	15 347
Mantle cell lymphoma	1 315
Prolymphocytic leukaemia, B cell	52
ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS	**9 696**
Acute promyelocytic leukaemia (AML) with t(15;17) and variants	445
Acute myeloid leukaemia	8 731
MYELOPROLIFERATIVE NEOPLASMS	**9 836**
Chronic myeloid leukaemia	2 989
Other myeloproliferative neoplasms	6 742
Mast cell tumours	106
MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES	**5 778**
Myelodysplastic syndrome with 5q syndrome	34
Other myelodysplastic syndrome	5 144
Chronic myelomonocytic leukaemia	569
Atypical chronic myeloid leukaemia BCR/ABL negative	29
HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	**197**
Histiocytic malignancies	146
Lymph node accessory cell tumours	51

NK: natural killer

RARE HAEMATOLOGICAL DISEASES



PREVALENCE

RARE HAEMATOLOGICAL DISEASES. Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

	AIRTUM POOL								ITALY
	OBSERVED PREVALENCE BY DURATION						COMPLETE PREVALENCE		
	≤2 YEARS		2-5 YEARS		≤15 YEARS				
	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	ESTIMATED PREVALENT CASES 2010
RARE HAEMATOLOGICAL DISEASES	**71.79**	**70.02-73.59**	**68.28**	**66.56-70.04**	**253.26**	**249.92-256.62**	**277.80**	**271.10-284.50**	**225 872**
RARE LYMPHOID DISEASES	**47.76**	**46.31-49.23**	**49.20**	**47.73-50.69**	**187.44**	**184.58-190.34**	**298.94**	**290.05-307.84**	**178 237**
Hodgkin lymphoma, classical	6.83	6.29-7.40	8.99	8.37-9.64	37.95	36.66-39.26	78.56	75.58-81.54	45 356
Hodgkin lymphoma nodular lymphocyte predominance	0.26	0.17-0.40	0.33	0.22-0.48	1.25	1.03-1.51	3.32	2.35-4.30	1 974
Precursor B/T lymphoblastic leukaemia/lymphoma (and Burkitt leukaemia/lymphoma)	2.66	2.33-3.03	2.71	2.38-3.08	12.19	11.46-12.94	56.49	48.73-64.26	33 843
T cutaneous lymphoma (Sezary syndrome, Mycosis fungoides)	2.62	2.29-2.98	3.44	3.06-3.86	13.35	12.6-14.15	18.57	17.43-19.70	11 173
Other T cell lymphomas and NK cell neoplasms	1.01	0.81-1.25	1.02	0.82-1.25	3.64	3.25-4.07	4.61	4.10-5.13	2 817
Diffuse large B-cell lymphoma	10.61	9.94-11.32	10.78	10.10-11.49	41.36	40.02-42.73	48.29	46.71-49.88	29 550
Follicular lymphoma	6.54	6.02-7.10	6.01	5.51-6.55	23.61	22.6-24.65	27.28	26.06-28.51	16 815
Hairy cell leukaemia	0.98	0.78-1.21	1.33	1.10-1.60	5.05	4.59-5.54	7.59	6.73-8.46	4 637
Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	14.70	13.91-15.53	13.20	12.45-13.98	43.70	42.32-45.11	47.76	46.23-49.30	28 229
Mantle cell lymphoma	1.51	1.26-1.79	1.36	1.12-1.62	5.46	4.98-5.97	6.25	5.68-6.81	3 731
Prolymphocytic leukaemia, B cell	0.05	0.01-0.12	0.08	0.03-0.17	0.16	0.09-0.27	0.19	0.09-0.29	112
ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS	**4.47**	**4.03-4.93**	**2.73**	**2.40-3.10**	**12.48**	**11.75-13.25**	**18.94**	**17.79-20.09**	**11 146**
Acute promyelocytic leukaemia (AML) with t(15;17) and variants	0.37	0.25-0.52	0.43	0.30-0.59	1.62	1.36-1.91	1.79	1.49-2.09	1 039
Acute myeloid leukaemia	3.82	3.42-4.26	2.15	1.85-2.48	10.05	9.39-10.74	16.53	15.40-17.67	10 481
MYELOPROLIFERATIVE NEOPLASMS	**12.21**	**11.49-12.97**	**12.06**	**11.34-12.81**	**38.95**	**37.65-40.28**	**45.30**	**43.64-46.96**	**26 243**
Chronic myeloid leukaemia	2.42	2.10-2.77	3.00	2.65-3.39	9.98	9.33-10.67	10.76	10.04-11.49	6 221
Other myeloproliferative neoplasms	9.68	9.04-10.35	8.86	8.24-9.50	28.49	27.38-29.63	33.88	32.45-35.32	19 620
Mast cell tumours	0.11	0.06-0.21	0.21	0.12-0.33	0.48	0.35-0.65	0.97	0.64-1.29	579
MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES	**7.17**	**6.62-7.76**	**4.17**	**3.76-4.63**	**13.90**	**13.12-14.70**	**15.87**	**14.96-16.78**	**9 213**
Myelodysplastic syndrome with 5q syndrome	0.09	0.04-0.18	0.05	0.01-0.12	0.15	0.08-0.26	0.17	0.08-0.27	102
Other myelodysplastic syndrome	6.52	5.99-7.08	3.83	3.43-4.26	12.67	11.93-13.44	13.52	12.72-14.32	7 965
Chronic myelomonocytic leukaemia	0.54	0.40-0.72	0.30	0.20-0.44	1.03	0.83-1.27	1.37	1.07-1.67	803
Atypical chronic myeloid leukaemia BCR/ABL negative	0.02	0.00-0.08	0.00	0.00-0.04	0.05	0.01-0.12	0.05	0.00-0.10	28
HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	**0.22**	**0.13-0.34**	**0.13**	**0.06-0.23**	**0.77**	**0.60-0.98**	**1.68**	**1.19-2.17**	**1 033**
Histiocytic malignancies	0.11	0.06-0.21	0.11	0.06-0.21	0.64	0.49-0.84	1.45	0.99-1.92	895
Lymph node accessory cell tumours	0.10	0.05-0.20	0.01	0.00-0.06	0.13	0.06-0.23	0.23	0.09-0.37	138

NK: natural killer

The classification of lymphoproliferative disorders includes various entities divided according to cytohistological features, immunephenotype, molecular characteristics, and clinical relevance. Overall, about 74% of haematological cancers are rare (incidence table, p. 102). This group includes:

- **rare lymphoid diseases** (classic Hodgkin lymphoma, Hodgkin lymphoma with nodular lymphocyte predominance, precursor B/T lymphoblastic leukaemia/lymphoma, Burkitt's leukaemia/lymphoma, T cutaneous lymphoma – Sezary syndrome, Mycosis fungoides, other T-cell lymphomas and NK-cell neoplasms, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukaemia, plasmacytoma/multiple myeloma and heavy chain diseases, mantle cell lymphoma, B-cell prolymphocytic leukaemia);
- **acute myeloid leukaemia** (acute promyelocytic leukaemia with t(15;17) translocation and variants, acute myeloid leukaemia);
- **myeloproliferative neoplasms** (chronic myeloid leukaemia, other myeloproliferative neoplasms, mast cell tumours);
- **myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases** (myelodysplastic syndrome with 5q syndrome, other myelodysplastic syndrome, chronic myelomonocytic leukaemia, atypical chronic myeloid leukaemia BCR/ABL negative);
- **histiocytic and dendritic cell neoplasms** (histiocytic malignancies, accessory cell tumours).

It is worth mentioning that variations in classification between ICD-O-2 and ICD-O-3 mainly concern these diseases and especially the group of myeloproliferative neoplasms (MPNs) and the group of myelodysplastic/myeloproliferative diseases (MDS/MPDs). Many of the tumours included in these 2 groups changed behaviour (becoming malignant invasive) with the ICD-O-3, which was introduced in the year 2000. Thus, cancer registries (CRs) started to register these entities only from 2000 on and at different paces. In addition, information sources used by CRs to identify cancer cases do not properly capture all cases of haematological diseases. All this translates into an underestimation in our data of these diseases.

However, the proportion of haematological diseases with «not otherwise specified» (NOS) morphology across Italian CRs was below 30%, which is the cut-off used by international studies to exclude CRs from analyses because of low quality.[1]

In addition to the proportion of NOS morphologies, we also looked at the incidence trends of MPNs and MDS/MPD across the different Italian CRs. In this exploratory analysis of the incidence trend, two groups of CRs were identified: the first included CRs with lower than average (4 per 100,000) age-standardised incidence rates for MPN during the 2000-2010 period, whereas the second included CRs with higher than average rates. The first group had a very low incidence rate, which increased after 2000 without reaching, in 2010, the incidence rate of the other AIRTUM CRs, for both MPN and MDS/MPD. The incidence rate in the second group of CRs increased up to 2010 to almost double the rate of the CRs of the first group for both MPNs and MDS/MPDs. It is very likely that in the first group there are CRs which tend to not properly record all cases of MPNs and/or MDS/MPDs. Nevertheless, the incidence rate obtained considering only the second group of CRs is substantially comparable to the one obtained combining together the two groups of CRs. Thus, all CRs were considered in order to include the largest possible number of cases in the analysis of these tumours, which, for the first time, are described in Italy in such morphological detail. This is an opportunity to provide estimates to discuss with clinicians and CRs how to improve registration.

RARE LYMPHOID DISEASES

WHAT DO WE KNOW ABOUT THESE CANCERS?

Lymphoid diseases comprise a heterogeneous group of disorders originating from clonal proliferation of B or T lymphocytes and covering both Hodgkin and non-Hodgkin disease. These are considered in this group, clinical management is rapidly evolved and various treatments (in terms of drugs employed and intensity of approaches) are now applied according to different entities and characteristics of patients: the new targeted therapy inhibits the proto-oncogenes which signal cells to proliferate, differentiate, and survive, and whose overactivity results in malignancy.[2]

About one-third of non-Hodgkin lymphomas (NHL) arise from sites other than lymph nodes, spleen, or bone marrow, and even from sites which normally contain no native lymphoid tissue. In principle, as for primary nodal disease, treatment strategies depend on the patient's clinical conditions, the extent and/or location of the disease, and the histological type.[3] However, in the list of rare haematological diseases proposed by RARECARE,[4] extranodal lymphomas are not separated from the others.

THE EPIDEMIOLOGICAL DATA IN ITALY

Incidence

Rare lymphoid diseases account for 65% of all rare haematological diseases (see table p. 102). About a third of rare lymphoid diseases (31%) are plasma cell tumours, followed by diffuse large B-cell lymphoma (26%), classic Hodgkin lymphoma (13%), and follicular lymphoma (11%). The other lymphoid diseases represent a minority of cases ranging from 1% to 7% of all rare lymphoid diseases. The rarest is prolymphocytic leukaemia, B-cell (see table p. 102). Most rare lymphoid diseases are diagnosed in people aged 50 years and older, with a few exceptions. Classic Hodgkin lymphoma has the highest incidence in the 15-29 year age group and precursor B/T lymphoblastic leukaemia/lymphoma has the highest incidence in children (0-14 years) (data not shown). The former represent 64% of all rare lymphoid diseases in adolescents and young adults (15-29 years) and the latter account for 77% of all rare lymphoid diseases in children (data not shown).

The highest male to female ratio (M/F ratio) is observed for hairy cell leukaemia and mantle cell lymphoma (M/F ratio: 3.8 and 2.5, respectively). About 17,000 new cases of rare lymphoid diseases are expected in Italy in 2015 (see table p. 102). Among young adults, about 600 cases of rare lymphoid diseases are expected, of which 500 are classic Hodgkin lymphoma. Among children, about 330 cases of rare lymphoid diseases are expected in 2015, of which 250 are precursor B/T lymphoblastic leukaemias/lymphomas (data not shown).

The incidence rate (IR) of rare lymphoid diseases in Italy is much higher than the IR observed in the European RARECAREnet database (www.rarecarenet.eu) (IR 26.8 per 100,000 in Italy vs.

18.1 per 100,000 in Europe), because in Italy the IR of diffuse large B-cell lymphoma and multiple myeloma is higher than in Europe. Thus, these two diseases are rare in Europe but not in Italy (see «The burden of rare cancers in Italy», pp. 22-27).

Survival

Rare lymphoid diseases have a good survival rate 1 year after diagnosis (79%), which decreases after 5 years from diagnosis (59%) (survival figure, p. 103). However, 5-year relative survival (RS) differs across diseases, and is 80%-90% for classic Hodgkin lymphoma, follicular lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, T cutaneous lymphoma, and hairy cell leukaemia (HCL) (see figure p. 103) and around 40% for other T-cell lymphomas and NK-cell neoplasms, plasmacytoma/multiple myeloma and prolymphocytic leukaemia, B cell. The lower survival observed in the latter diseases could be due to the fact that they mainly arise in the elderly (>70 years), thus in people who are likely to have comorbidities and are more difficult to treat.

These results are similar to those observed in Europe, where a significant increase of survival over time (from 1997 to 2008) for all lymphoid malignancies, with the greatest increases for follicular lymphoma and diffuse large B-cell lymphoma was also reported.[5] The survival increase for follicular lymphoma and diffuse large B-cell leukaemia are probably a result of the adoption of RITUXIMAB, which is safe and effective in older as well as younger patients.[1,2] Improved supportive care with better control of comorbidities, especially for older patients, might also have contributed to improve survival for lymphoid malignancies in general.[5]

Five-year RS for rare lymphoid diseases is 86% and 85% among children and young adults, respectively (data not shown). In children, 5-year RS is 89% for precursor B/T lymphoblastic leukaemias/lymphomas; among young adults, 5-year RS is 94% for classic Hodgkin lymphoma (data not shown).

Prevalence

Around 178,000 persons were estimated to be living with a previous diagnosis of rare lymphoid diseases in Italy in 2010; 37% of these cases had survived more than 15 years from diagnosis. Most prevalent cases are represented by patients with a previous diagnosis of classic Hodgkin lymphoma (25%) and precursor B/T lymphoblastic leukaemia/lymphoma (19%), diffuse large B-cell lymphoma (17%), and plasmacytoma/multiple myeloma (16%). This is due to the high survival for classic Hodgkin lymphoma and relatively high IR for the other entities, which have a 5-year RS rate ranging from 50% to 40%.

ACUTE MYELOID LEUKAEMIA

WHAT DO WE KNOW ABOUT THESE CANCERS?

Acute myeloid leukaemia (AML) is a heterogeneous clonal disorder (differentiation arrest or malignant proliferation) of haemopoietic progenitor cells, in particular myeloid precursors in the bone marrow and blood.[6] The new 2008 WHO classification[7] divides them, according to their cellular and molecular characteristics, into myelocytic, myelogenous, or non-lymphocytic disorders. Furthermore, they are classified as primary (or de novo) or secondary, if they arise after an MDS or MDS/MPN, or a blast transformation in a previously diagnosed MPN, or as consequence of exposure to toxic substances and/or chemotherapy.

However, AML has long been recognised as a nosological entity, thus the criteria for disease definition are stable over time. In the past twenty years, there has been little improvement in chemotherapeutic regimens with the exception of the treatment of acute promyelocytic leukaemia (APL), in which all trans-retinoic acid (ATRA) is used.[8] Thus, within the RARECARE[4] project it was decided to identify two major groups of AML on the basis of the different way in which they are treated.

THE EPIDEMIOLOGICAL DATA IN ITALY

Incidence

AML and related precursor neoplasms account for 13% of rare haematological diseases. AML mainly occurs in the over 65 population (see table p. 102), the IR is 5 per 100,000 per year in those aged 50-55 and 7 per 100,000 per year in those aged 60-64 (data not shown). The IR is very low <1 per 100,000 in children (0-14 years) and increases slightly from 1 per 100,000 (in those aged 20-24 years) to 2 per 100,000 (in those aged 40-44 years) confirming that AML is typical of the elderly (data not shown).

APL with t(15;17) translocation and variants accounts for 4% of all AML. Its IR increases with age, and is very low in children (IR 0.1 per 100,000; data not shown) and highest in the elderly (see table p. 102). However, APL is typical of children and young adults, representing in the 0-29 year age class 14% of all AML, compared to only 2% of all AML in those aged >65 years (data not shown).

The M/F ratio is 1.2, and approximately 3,600 cases of AML and related precursor neoplasms are estimated in Italy in 2015 (see table p. 102).

The IR of AML in Italy is slightly higher than that observed in the European RARECAREnet database (IR 5.3 per 100,000 in Italy vs. 3.8 per 100,000 in Europe).

Survival

Survival is different for the two observed entities. APL has a better prognosis at 1 year and 5 years after diagnosis (74% and 64%, respectively) compared to AML (39% and 18%, respectively) (see figure p. 103). The relatively good prognosis of APL is mainly attributable to the use of trans retinoic acid (ATRA) and is consistent with previous findings[8] and the new results observed in Europe.[5]

Unfortunately, in the past twenty years, there has been little improvement in chemotherapeutic regimens and hence in the overall survival for patients with AML (other than APL). The major improvements in AML treatment during the last two decades have not come from the introduction of new therapeutic agents, but rather from improved use of well-known drugs. However, the limit of acceptable toxicity for standard chemotherapeutic drugs used in AML therapy has been reached and new therapeutic strategies are therefore needed.[8]

Prevalence

Around 11,000 persons were estimated to be living with a previous diagnosis of AML and related precursor neoplasms in Italy in 2010; this is due to the relatively high IR of AML rather than to RS, which is low for AML.

MYELOPROLIFERATIVE NEOPLASMS

WHAT DO WE KNOW ABOUT THESE CANCERS?

Myeloproliferative neoplasms (MPNs) comprise clonal blood disorders, such as chronic myeloid leukaemia (CML), polycythaemia vera, essential thrombocythaemia, primary myelofibrosis, and mast cell tumours and are characterised by increased production of terminally differentiated myeloid cells. These disorders are classified according to rearrangements or mutations of genes (i.e. Ph-chromosome-positive, the BCR-ABL1 fusion gene, in CML, and JAK2-, CALR-, MPL-, and KIT-mutation-positive in the other neoplasms).[9,10]

The management of these tumours with targeted treatments is based on clinical, biologic, cytogenetic, and molecular characteristics. The prognosis of CML has dramatically improved since the availability of IMATINIB in current practice.

THE EPIDEMIOLOGICAL DATA IN ITALY

Incidence

MPNs represent 13% of all rare haematological diseases. These pathologies are mainly diagnosed in the over 65 population (see table p. 102). The majority of these diseases is represented by the group of «other myeloproliferative neoplasms», which include primary myelofibrosis, essential thrombocythaemia, polycythaemia vera, which together account for 75% of the «other myeloproliferative neoplasms» group (data not shown).

CML represents the second most common MPN (see table p. 102).

The M/F ratio is 1.3, with no differences among the different diseases. New cases of MPNs are estimated to be around 3,500 in Italy in 2015 (see table p. 102). Selecting only CRs with the higher incidence rates (see definition of group two in the introduction to the present chapter), the number of estimated new cancer cases would be of about 4,500 in Italy in 2015.

The IR of these diseases is, in any case, higher in Italy than in the European RARECAREnet database (IR 5.5 per 100,000 in Italy vs. 3.0 per 100,000 in Europe). Probably, the main reason for the low rates in Europe is the not yet standardised and complete registration in Europe of MPNs other than CML, as they were only recognised as malignant in the ICD-O-3 classification. The discovery of the JAK2-V617F mutation, which is a clue in the diagnosis of primary myelofibrosis essential thrombocythaemia and polycythaemia vera, will make it easier than in the past to diagnose these diseases. This will likely increase the systematic registration of essential thrombocythaemia and polycythaemia vera, and will probably lead to an increase of the reported incidence.

Low incidence rates in Europe for MPNs with a relatively indolent behaviour might also be due to the fact that most CRs use information of pathology labs and hospital discharge records as their main notification source. Information from outpatient departments is not always systematically notified and thus a large proportion of patients with polycythaemia vera and essential thrombocythaemia, which often lack pathological confirmation and are outpatients only, are not registered by those CRs. This can explain also the difference between the IR observed in the two groups of CRs in Italy (see definition of group one and two in «A guide to the cancer-specific data sheets», pp. 28-31).

Survival

MPNs have a good prognosis at 1 and 5 years after diagnosis (90% and 75%, respectively), with differences across the specific disease subtype. The highest 5-year RS was observed for mast cell tumours and other myeloproliferative neoplasms (76% and 81%, respectively) (see figure p. 103). The latter group includes entities with high survival, such as essential thrombocythaemia (5-year RS 94%) and polycythaemia vera (5-year RS 92%), as well as entities with poor survival, such as primary myelofibrosis (5-year RS 54%) (data not shown).

The 5-year RS of patients with CML was 59% (see figure p. 103).The treatment of CML has been significantly modified since the discovery of IMATINIB, a targeted molecule that inhibits the tyrosine kinase activity of the neo protein resulting from the BCR ABL fusion gene. The prognosis of CML has dramatically improved since the availability of IMATINIB in current practice. In Europe, an increase in survival was observed, from 32% in the period 1997-1999 to 54% in the period 2006-2008.[5] Thus, these data confirm, for the first time even in Italy, the great impact that the introduction of IMATINIB has had at the population level.

Prevalence

Around 26,000 persons were estimated to be living with a previous diagnosis of MPNs in Italy in 2010; 14% of these cases had survived more than 15 years from diagnosis.

MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/ MYELOPROLIFERATIVE DISEASES

WHAT DO WE KNOW ABOUT THESE CANCERS?

Myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases (MDS/MPD) comprise a heterogeneous group of disorders originating from clonal hematopoietic stem cells. These are characterised by ineffective haematopoiesis, peripheral cytopoenias, and a variable propensity for leukaemic transformation.[11] The classification is based on genetic mutations: for example, chronic myelomonocytic leukaemia (CMML) is associated with diverse pathways that include mutations of signal transduction, DNA methylation, transcriptional regulation, chromatin modification, and the RNA splicing machinery.[12] Though the general approach for the treatment is tailored to symptoms of patients, some therapeutic approaches, including lenalidomide, azacitidine, erythropoiesis stimulating agents and iron chelation have been demonstrated to alter the natural history of these disease in selected MDS patients.[13]

THE EPIDEMIOLOGICAL DATA IN ITALY

Incidence

MDS/MPDs represent 8% of all rare haematological diseases (see table p. 102). The majority of these tumours are represented by the group of «other myelodysplastic syndromes», which includes, in decreasing order: refractory anaemia (18%), refractory anaemia with excess of blasts (12%), refractory cytopoenia with multilineage dysplasia (4%), refractory anaemia with sideroblasts (3%), myelodysplastic syndrome NOS (64%) (data not shown). The other specific disease subtypes are very rare. This group of diseases has a high IR in the elderly,

however, chronic myelomonocytic leukaemia is much more common in children than in the elderly: it represents 26% of all MDS/MPDs in children compared to 9% in those aged >65 years (data not shown). The highest M/F ratio is observed for CML (1.9) while myelodysplastic syndrome with 5q syndrome is more common among females than males. Around 2,500 cases of MDS/MPD are expected in 2015 in Italy (see table p. 102). Selecting only CRs with higher incidence rates (see definition of group two in the introduction to the present chapter), the number of estimated cancer cases in Italy would be of about 3,000 in 2015. The IRs observed in Italy are slightly higher than those reported by the European RARECAREnet database (IR 3.4 per 100,000 in Italy vs. 2.5 per 100,000 in Europe). As for myeloproliferative neoplasms, even for this group of diseases the lower IR in Europe could be due to heterogeneity in the registration of these entities across European CRs.

Survival

In general, these disorders do not have a good prognosis: 1-year RS is 73%, but 5-year RS decreases to 38%. Five-year RS is highest for myelodysplastic syndrome with 5q syndrome (55%) and lowest for chronic myelomonocytic leukaemia (23%) (see figure p. 103). Major changes in treatment are attributable to the introduction of new drugs such as lenalidomide, azacytidine, and decitabine. However, their effect on survival in the general population has not been observed yet. At the European level, the 5-year RS is higher (48%) than in Italy, but no major changes were observed from 2003-2005 to 2006-2008.[5]

Prevalence

Around 9,000 persons were estimated to be living with a previous diagnosis of MDS/MPD in Italy in 2010; 12% of these cases had survived more than 15 years from diagnosis.

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

WHAT DO WE KNOW ABOUT THESE CANCERS?

These disorders include Langerhans cell histiocytosis, histiocytic sarcoma, follicular dendritic cell sarcoma, interdigitating cell sarcoma, indeterminate cell sarcoma, and fibroblastic reticular cell tumours. Histiocytic and dendritic cell neoplasms are very rare and should be diagnosed with a combination of morphology review and a battery of immunohistochemistry to rule out mimics such as carcinoma, lymphoma, and neuroendocrine tumours, and to better sub-classify these hard-to-diagnose lesions.[14] The treatment for localised disease is surgical resection and the role of adjuvant therapy is unclear. In patients with multiple areas of involvement, multimodality treatment at tertiary care centres is likely needed.[15]

THE EPIDEMIOLOGICAL DATA IN ITALY

Incidence

Histiocytic and dendritic cell neoplasms represent only 0.3% of all rare haematological diseases (see table p. 102). Histiocytic malignancies have the highest IR in children and in particular in those aged <4 years. They represent 99% of histiocytic and dendritic cell neoplasms in children compared to 45% in those aged >65 years. On the contrary, accessory cell tumours have the highest IR in the elderly (>65 years) and are extremely rare in children (IR 0.1 per 100,000) (data not shown). The M/F ratio is 1.6 for histiocytic malignancies, while no differences exist between males and females for accessory cell tumours. About 70 cases of histiocytic and dendritic cell neoplasm cases are estimated in 2015 in Italy (see table p. 102). In the European RARECAREnet database, the IR is lower (IR 0.1 per 100,000 in Italy vs. 0.05 per 100,000 in Europe).

Survival

Overall, histiocytic and dendritic cell neoplasms have a good 1-year RS (84%), which decreases after 5 years from diagnosis (67%). However, differences exist between the specific disease subtype. Five-year RS is highest for histiocytic malignancies (77%) and lowest for lymph node accessory cell tumours (35%) (see figure p. 103). This could be partially due to the fact that the latter are typical of the elderly, and poor survival in elderly patients is generally attributed to the inability to give potentially curative treatments because patients are frail or have comorbidities. Late diagnosis and under-evaluation of disease symptoms could also play a part. Finally, most clinical trials do not include older patients or those with low performance status, so treatment protocols are not optimised for the elderly.

Prevalence

Around 1,000 persons were estimated to be living with a previous diagnosis of histiocytic and dendritic cell neoplasms in Italy in 2010; 54% of these cases had survived more than 15 years from diagnosis and were represented by histiocytic malignancies because of both high incidence and high 5-year RS compared to lymph node accessory cell tumours.

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