Epidemiological aspects of myelodysplastic syndromes and acute myeloid leukaemia in the Netherlands

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SUMMARY

The main aim of this thesis was to progress our understanding on different epidemiologic aspects of myelodysplastic syndromes and acute myeloid leukaemia at the population level in the Netherlands. These aspects include surveillance of the cancer burden, guideline adherence concerning diagnostics and therapy, and comparative effectiveness research. Population-based registries are useful instruments to study all patients within a well-defined area, so as to overcome patient selection which is always at hand in clinical intervention studies. The results described in this thesis provided a benchmark for incidence, diagnosis, treatment, trial participation and survival of myelodysplastic syndromes and acute myeloid leukaemia in the Netherlands. Future studies should provide insight whether clinical practice changed following the results described in this thesis.

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INTRODUCTION

Myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML) are heterogeneous malignancies of myeloid origin that both occur with an age-standardised incidence rate of approximately 3.0/100,000 persons in Western countries.[1,2] The incidence of both malignancies sharply increases after the age of 65, making them diseases that typically affect older people.[3] At present, there is a scarcity of epidemiologic research published on MDS and AML. Most information on these diseases comes from randomised controlled trials (RCTs) that are generally associated with patient selection. Therefore, findings from RCTs may not be generalised to a patient population that is commonly seen in daily practice. Furthermore, RCTs are not designed to study the epidemiology of diseases at population level. In this regard, population-based cancer registries are useful instruments to study cancer patients within a well-defined area, so as to overcome patient selection. In addition, population-based cancer registries can be utilised to complement findings from RCTs and to provide information to support clinical decision-making.

The main aim of this thesis was to progress our understanding of different epidemiologic aspects of MDS and AML at the population level in the Netherlands. These aspects include surveillance and evolution of the cancer burden, guideline adherence concerning diagnostics and therapy, and comparative effectiveness research. The following two population-based registries were utilised to unravel real-world characteristics and management of patients with MDS and AML in the Netherlands, namely 1) the nationwide population-based Netherlands Cancer Registry (NCR) and 2) the Dutch **P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies

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in MDS (PHAROS MDS) registry. The PHAROS MDS registry is an extension of the NCR, as it documents additional and more detailed data on various patient-, disease- and treatment-related characteristics next to the dataset of the NCR. While the NCR entirely covers the Netherlands, the PHAROS MDS registry essentially covers the west part of the Netherlands with around six million inhabitants (approximately 40% of the Dutch population).

DIAGNOSTIC AND PROGNOSTIC PROCEDURES IN MDS

Specific morphological features in the bone marrow (BM) (e.g. type and degree of dysplasia, as well as myeloblasts) constitute a diagnostic hallmark of MDS. Careful assessment and subsequent documentation of these features are necessary to facilitate an accurate classification of MDS according to the World Health Organization (WHO) classification, which was initially published in 2001 and updated in 2008.[4,5] We investigated how the classification of MDS was applied in the Netherlands to classify MDS into a particular subtype. Of note, the 2016 revision of the WHO classification was outside the scope of the thesis.[6] The proportion of patients with an unclassified MDS decreased from 60% in 2001 to 36% in 2010.[7] This finding might support the notion that haematologists, cytomorphologists and pathologists became increasingly aware of the WHO classification of MDS, which was initially introduced in 2001.[4] Although our finding is very encouraging, the degree of BM dysplasia in erythroid, myeloid and megakaryocytic lineages was only reported in one third of patients.[8] Therefore, diagnostic practices in MDS can be further improved in the Netherlands.

Next, we investigated the utilisation of cytogenetics in the diagnostic and prognostic work-up of MDS. MDS with an isolated del(5q) is a specific MDS subtype that can only be classified as such through cytogenetic assessment.[4-6] Further, specific cytogenetic aberrancies, in combination with the percentage of blasts and the number of cytopaenias, are incorporated in the International Prognostic Scoring System (IPSS) to predict clinical outcome and plan risk-adapted therapy in MDS.[9,10] Despite the importance of cytogenetic analysis, it was not performed in 46% of patients with MDS diagnosed between 2008-2011.[8] As a result of incomplete diagnostic work-up, mainly due to lack of cytogenetic information, accurate prognostication as per IPSS was not possible in almost half of all patients, which, in turn, might have led to inappropriate risk-adapted management. In addition, multivariable logistic regression analysis showed that older patients, patients with two or more comorbidities, patients diagnosed in non-university hospitals and patients who did not receive prior cytotoxic therapy for an antecedent malignancy had lower odds to undergo cytogenetic assessments.[8]

AZACITIDINE FOR THE TREATMENT OF HIGHER-RISK MDS

Azacitidine is indicated for the treatment of patients with higher-risk MDS who are not suitable for an allogeneic hematopoietic stem cell transplantation (alloHSCT), which is the only modality with a curative potential in MDS.[10] Azacitidine is registered in the Netherlands for the abovementioned indication following the results of the randomised phase III AZA-001 trial.[11,12] We assessed the effectiveness of azacitidine for the treatment of transplant-ineligible patients with higher-risk MDS in Dutch clinical practice.[13] Median overall survival (OS) was 16.9 months in the azacitidine group compared with 7.3 months in the best supportive care only group, a difference of 9.6 months.[13] This difference was comparable with that observed in the AZA-001 trial.[11] Further, azacitidine was given for a median of 8.5 cycles, which was also comparable with the AZA-001 trial.[11,13] Despite the potential of azacitidine to prolong OS in a similar fashion, as shown in the AZA-001 trial, patients in Dutch clinical practice fared much worse than patients in the AZA-001 trial. The median OS was 24.5 months for azacitidine-treated patients in the AZA-001 trial and 16.9 months for azacitidine-treated patients in Dutch routine practice.[11,13] Several possible explanations could be put forward to explain the difference in OS: azacitidine-treated patients in our study had comparatively unfavourable features than azacitidine-treated patients in the AZA-001 trial, such as more frequent poor-risk cytogenetics (44 versus 28%) and therapy-related MDS (18 versus 0%).[11,13] Collectively, these results suggest that patients recruited in the AZA-001 trial may not be entirely representative of patients with higher-risk MDS from the general population. Therefore, findings from RCTs should be extrapolated with caution to patients from daily practice.

TREATMENT, TRIAL PARTICIPATION AND SURVIVAL IN AML

Contemporary findings from RCTs demonstrate that 40-50% of younger, and around 10% of older patients with AML can be cured.[2] However, as described above for MDS, the study populations of RCTs may not be

KEY MESSAGES FOR CLINICAL PRACTICE

1 **The proportion of patients with an unclassified MDS in the Netherlands decreased from 60% in 2001 to 36% in 2010. Careful assessment and subsequent documentation of morphological features in bone marrow specimens and blood smears are necessary to facilitate an accurate classification of MDS.**

2 **Cytogenetic assessment was not performed at diagnosis in almost half of all patients with MDS in the Netherlands. Cytogenetic analysis is a mandatory diagnostic procedure in MDS, as specific cytogenetic aberrancies—in combination with the percentage of blasts and the number of cytopaenias—are incorporated in the IPSS to predict clinical outcome and plan risk-adapted therapy in MDS. In addition, cytogenetic analysis is necessary for the classification of MDS with an isolated del(5q).**

3 **The effectiveness of azacitidine for treatment of patients with higher-risk MDS in Dutch clinical practice was comparable with findings from the AZA-001 trial, in terms of prolonging overall survival and the provided number of azacitidine cycles.**

4 **The overall trial participation rates among patients with AML age 61-70 and >70 in the Netherlands was 30% and 12%; respectively. In order to advance treatment strategies and improve patient outcome in AML, patients should be encouraged to participate in clinical trials. Sound information provided by the physician on the pros and cons of trial participation can lower the barriers for patients to participate in clinical trials.**

5 **Population-based cancer registries are of vital importance to determine the cancer burden and its evolution over time within a well-defined geographic area. In addition, population-based cancer registries can be utilised for guideline adherence concerning diagnostics and therapy, and to assess whether findings from RCTs translate into benefits for patients in daily practice.**

representative of the general patient population. Therefore, we investigated patterns of treatment, trial participation and survival among patients diagnosed with AML in the Netherlands from 1989-2012.[14] The application of alloHSCT in the Netherlands increased over time among patients with AML up to age 70, whereas patients above age 70 predominantly received supportive care only. More specifically, the proportion of alloHSCT in age groups 18-40, 41-60, 61-70 and >70 years was 24%, 8%, 0% and 0% in the period 1989-1994, as compared with 55%, 46%, 17% and <1% in the period 2007-2012; respectively. Generally, 90% of patients age up to 60 received intensive therapy (i.e. chemotherapy, autologous HSCT or alloHSCT) in the period 2007-2012, as compared with 75% and 33% among patients age 61-70 and >70; respectively.

In the overall series, around 60% of patients with AML up to age 60 participated in a HOVON or EORTC clinical AML trial whenever open for accrual in the Netherlands. Of those 40% who did not enter into a clinical trial, the vast majority (90%) received intensive therapy outside the setting of a clinical trial. Despite AML being a common disease of old age, with a median age of 68 at diagnosis in the period 2007-2012, trial participation decreased progressively after the age of 60, with participation rates of 30% and 12% among patients age 61-70 and >70; respectively. Patients in these age groups who did not enter into a clinical trial were treated less intensively outside the setting of a clinical trial, as compared with their younger counterparts, namely 73% and 25%; respectively.

As for relative survival, which is the observed patient survival corrected for the expected survival of a comparable group from the general population with respect to age, sex and period, it increased steadily in a span of more than two decades among patients with AML up to age 70. Five-year relative survival in the period 2007-2012 was 54, 38, 14 and 2% for patients with AML age 18-40, 41-60, 61-70 and >70; respectively, as compared with 28, 20, 5 and 1% in the period 1989-

1994. The steadily improved survival among patients with AML up to age 70 may be related to the increased use of intensive, potentially curative therapy over time. In order to advance treatment strategies and improve patient outcome, especially, but not exclusively, for patients with AML above age 70, specific clinical trials should be designed for those who are not eligible for current clinical AML trials.

CONCLUSION

Population-based cancer registries are of vital importance to provide insight on incidence and survival of MDS and AML at the population level. In addition, such registries can provide data complementary to that from RCTs that usually addresses a rather selected patient population, provided that those registries are well-established, include relevant parameters, cover the target population with high accuracy, and have an accurate follow-up. For all haematological malignancies diagnosed from January 1st, 2014 in the Netherlands, additional parameters are standardly included in the nationwide NCR. As such, the PHAROS registry covers the entire country, and is currently better known as the Hemato-Oncology Registry of the NCR.

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