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Recommendation Report MOAC-1 – ARCHIVED 2018

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Prognostic Value of the DNMT3A Biomarker in Cytogenetically Normal Patients with Acute Myeloid Leukemia

B. Leber, N. Ismaila, S. Kamel-Reid, M. Rutherford and the Molecular Oncology Advisory Committee

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The reviewed EBS report, which is available on the CCO Pathology and Laboratory Testing page, is comprised of 2 sections:

Section 1: Recommendations
Section 2: Evidentiary Base

Report Date: November 27, 2013

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A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Prognostic Value of the DNMT3A Biomarker in Cytogenetically Normal Patients with Acute Myeloid Leukemia: Recommendations

B. Leber, N. Ismaila, S. Kamel-Reid, M. Rutherford and the Molecular Oncology Advisory Committee

Report Date: November 27, 2013

RESEARCH QUESTION

What is the prognostic value of DNMT3A mutation screening in cytogenetically normal patients with acute myeloid leukemia (AML)?

TARGET POPULATION

AML patients with a normal cytogenetic profile

INTENDED PURPOSE

This recommendation report is intended to determine if testing for DNMT3A mutation in this patient population determines prognosis with standard indication and consolidation therapy, as a guide to choosing alternative treatment if appropriate.

INTENDED USERS

Clinicians, patients and funding bodies

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

RECOMMENDATION 1
DNMT3A mutation testing should be included as a biomarker test in cytogenetically normal AML patients.

Summary of Key Evidence for Recommendation
Four (8,10,13,15) of the eight studies (8-15) included in the systematic review reported a statistically significant difference in Overall Survival (OS) between DNMT3A wild type (DNMT3A-wt) and DNMT3A-mutated (DNMT3A-mut) populations favouring the non-mutated gene; the remaining four that did not provide statistical data did demonstrate a similar trend. The meta-analysis of these data resulted in an overall estimated hazard ratio 1.66 (95%CI, 1.23-2.24; p=0.0010) favouring patients that are DNMT3A wild type. This strongly suggests that the mutational status of DNMT3A has prognostic value. However, the interpretation of the meta-analysis using OS may be limited by the fact that two studies were omitted as complete information was not available.

Justification for Recommendation 1
The available evidence shows DNMT3A mutation status has good prognostic value in this patient population.

Qualifying Statements for Recommendation 1
This recommendation is based on evidence currently available. Despite the heterogeneous nature of the studies included, the likelihood of having a series of large homogenous studies done in this patient population is low due to the nature of the disease and its management.

FUTURE RESEARCH
Currently, there are no ongoing trials on DNMT3A mutation status in this patient population.

Funding
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Updating
All PEBC documents are maintained and updated
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Recommendation Report MOAC-1: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Prognostic Value of the DNMT3A Biomarker in Cytogenetically Normal Patients with Acute Myeloid Leukemia – A Systematic Review and Meta-analysis: Evidentiary Base

M. Gichuru, H. Messersmith, B. Leber, N. Ismaila, S. McNair, S. Kamel-Reid, Michael Rutherford and the Molecular Oncology Advisory Committee

Report Date: November 27, 2013

INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive cancer of blood stem cells and encompasses several specific subtypes (1). Cytogenetic abnormalities occur in approximately 55% of adult patients with AML (2) and are widely recognized as the most significant prognostic factor in determining the response to treatment. DNMT3A encodes for the enzyme DNA (cytosine-5)-methyltransferase 3A and is responsible for *de novo* acquisition of DNA-methylation patterns (3). Specifically, DNMT3A catalyzes the addition of methyl groups to the 5-position of the cytosine residue within cytosine-guanine dinucleotide (CpG), forming 5-methylcytosine (4). Concentrated islands of CpG dinucleotides are found in regions upstream of genes (5); aberrant DNA methylation of these regions result in altered expression of the downstream gene. There is increasing evidence that DNMT3A mutations play a significant role in AML pathogenesis and may also affect prognoses.

DNMT3A mutations have been found most commonly in patients with a normal cytogenetic profile. This is associated with the largest and most heterogeneous group that is associated with intermediate risk. As mutations in other genes such as FMS-like tyrosine kinase 3 (FLT3), nucleophosmin 1 (NPM1), and CCAAT-enhancer binding protein alpha (CEBPA) are now thought to influence the prognosis of sub-groups within this intermediate risk category (1,4,5), it is important to determine if there is also prognostic utility in determining the mutation status of DNMT3A as well.

Therefore, a systematic review of the literature on DNMT3A and its prognostic value in cytogenetically normal (CN) patients was proposed to determine its efficacy in terms of overall survival (OS) in a meta-analysis.

OBJECTIVES AND RESEARCH QUESTIONS

The objective was to determine the prognostic value of DNMT3A biomarker in cytogenetically normal (CN) patients with acute myeloid leukemia (AML).

METHODS

No previous guidelines or systematic reviews were done on this subject. Therefore, a systematic review of the primary literature was conducted for this evidentiary base document.

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and any associated Programs is editorially independent from the Ministry.

Literature Search Strategy

The primary search is up to date as of July 26, 2012. Published literature was retrieved via searching the following electronic databases: MEDLINE (1946 to July Week 3, 2012) with in-process records and other non-indexed citations and daily updates via Ovid (July 25, 2012); EMBASE (1980 to Week 29, 2012) via Ovid; and The Cochrane Central Register of Controlled Trials (2012, Issue 7) via Ovid. Terms used were related to AML (acute myeloid leukemia OR acute myelogenous leukemia OR acute myelocytic leukemia) and DNMT3A (DNA methyltransferase 3A OR DNA (cytosine-5)-methyltransferase 3A human OR DNMT3A protein).

Study Selection Criteria and Protocol

Studies must have included CN patients stratified to the intermediate-risk group. Pediatric AML was not included for analysis (<15 years of age); no upper age limit was specified. Comparators under investigation were normal cytogenetic risk groups defined with the DNMT3A mutation versus normal cytogenetic risk groups without the DNMT3A mutation (wild type). The exact nature of the treatment administered was not of primary interest but was documented if the study provided the information. Primary outcomes of interest include OS, complete remission (CR), cumulative incidence of relapse (CIR) and relapse-free survival (RFS). Co-occurring molecular aberrations, along with where the mutation was located in the gene, were documented for further research. Inclusion criteria encompassed systematic reviews, meta-analyses, clinical practice guidelines, randomized control trials, cohort studies (prospective and retrospective) or case-control studies with an analysis or subgroup analysis of DNMT3A biomarker status and investigated DNMT3A in patients with previously treated or untreated AML. Exclusion criteria was applied to articles published in a language other than English, were non-systematic reviews, letters, editorials, commentaries, or historical articles, or if patients had secondary AML.

Data Extraction and Assessment of Study Quality and Potential for Bias

One reviewer (MG) went through the various databases that were mentioned in the search strategy to identify relevant guidelines and articles. The same reviewer conducted title and abstract screening, and duplicates were removed. For each eligible study, the same reviewer would extract all the study data (including study design features, patient population, interventions, molecular exons sequenced and analyzed, co-occurring molecular aberrations with DNMT3A, and clinical outcomes).

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis would be conducted using the Review Manager software (6). For time-to-event outcomes, hazard ratios (HRs), rather than the number of events at a certain time point, would be the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, they would be derived from other information reported in the study, if possible, using the methods described by Parmar et al, 1998 (7). For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in Review Manager, would be used.

Statistical heterogeneity would be calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

RESULTS

Primary Literature Systematic Review

After removing duplications and the preliminary title and abstract screening, no existing systematic reviews or practice guidelines were found that addressed the prognostic value of the mutation in DNMT3A as a biomarker in AML patients with a normal karyotype. Three hundred and seven citations were identified from electronic searches. Two hundred and sixty-four articles were excluded after reviewing the titles and abstracts. Forty-three articles were potentially relevant to the review, but thirty-five did not meet the inclusion/exclusion criteria after full-text review. Therefore, eight articles met the criteria and were included (8-15). All the included trials were summarized to outline trial design, patient population, mean age, number of DNMT3A mutations, and clinical outcomes (Table 1).

Study Design and Quality

Two studies were prospective cohorts (8,14). The retrospective cohort studies (10,11,13,15) sampled patients from multiple trials and populations and, therefore, demonstrate a variety of treatments and therapies. Trials were primarily performed in an academic setting (university), hospital or other treatment centres. Blinding to patient allocation and data assessment was not specified, as the majority of trials extract data from banks of sample data.

Table 1. Characteristics of included studies

Study	Trial Design	Patient Population	Median Age (Range)		Number of DNMT3A Mutations		Clinical Outcomes
			DNMT3A-mut	*DNMT3A*-wt	R882	Other	
Hou (8) (2012)	Prospective	NTUH (n=500)	61 (16-87)	49 (15-90)	44	26	OS, CR, RFS
LaRochelle (9) (2011)	Retrospective	Toulouse University Hospital (n=288)	47 (20-63)	53 (18-65)	38	1	DFS, OS, CR
Ley (10) (2010)	Retrospective	Washington University (n=188) CALGB (n=94) trials: 9621, 9222, 9191, 9710	53 ± 14‡	48 ± 17‡	27	17	EFS, OS
Marcucci (11) (2012)	Retrospective	CALGB (n=415) trials: 9621, 19808, 8525, 8923, 9420, 9720, 10201	61 (22-82)	62 (18-83)	92	56	CR, DFS, OS
Patel (12) (2012)	Retrospective	ECOG E1900 phase III trial (n=398)	NR	NR	NR	NR	DFS, CR, OS
Renneville (13) (2012)	Retrospective	ALFA-9802 and ALFA-9801 trials (n=123)	47 (23-58)	48 (16-59)	30	8	CR, EFS, OS
Ribeiro (14) (2012)	Prospective	NR	50 (18-60)	41 (15-60)	46	26	OS, RFS
Thol (15) (2011)	Retrospective	SHG 0199 (n=332) SHG 0295 (n=157)	52 (30-60)	45 (17-60)	58	32	OS, RFS, CR

‡Age reported as Mean plus-minus standard deviation

ALFA = Acute Leukemia French Association; CALGB = Cancer and Leukemia Group B; CR = complete remission; DFS = Disease-free survival; DNMT3A = DNA methyltransferase 3A (mut = mutated, wt = wild type); ECOG = Eastern Cooperative Oncology Group; EFS = Event-free survival; OS = Overall survival; NR = Not reported; NTUH = National Taiwan University Hospital; RFS = Relapse-free survival; SHG = Sueddutche Hamoblastose Gruppe

Interventions

The included studies reported a variety of treatment regimens. Some studies included data from more than one clinical trial, documenting each treatment regimen. Induction chemotherapy varied in terms of cytarabine dosage (100 mg/m^2/d – 500 mg/m^2/d; days 1-7), the choice of anthracycline (i.e. daunorubicin or idarubicin; d1-3) and its respective dosage. Some patients received all-trans retinoic acid (ATRA), etopisode or mitoxantrone, or other chemotherapy drugs as induction therapy or secondary induction therapy. Induction chemotherapy was a week in duration for all patients with the standard cytarabine (days 1-7) and an anthracycline (days 1-3) schedule. Consolidation therapy differed substantially between studies, (high-dose cytarabine, mitoxantrone, oblimersen, or allogeneic or autologous stem cell transplantation). Specific information on treatment as was retrieved from the main body of the article the supplementary appendix or from the original clinical trial is included as a reference in the main article. Not every study reported appropriate doses and data.

Molecular abnormalities co-occurring with DNMT3A mutations

There is evidence suggesting that DNMT3A mutations may be found variably in combination with other known genetic abnormities in patients with AML (Table 2). Renneville et al, 2012 (13) was the only study to observe no statistically significant difference in the co-occurrence of FLT3ITD abnormalities ($p=0.99$) with DNMT3A abnormalities. All studies demonstrated statistically significant differences in the co-occurrence of NPM1 mutations ($p<0.001$) in patients with DNMT3A mutations compared to wild type patients. Four studies (9,10,11,15) observed no significant difference in co-occurrence of IDH2 mutations between both populations. Only Marcucci et al, 2012 (11) and Renneville et al, 2012 (13) observed statistically significant results in the co-occurrence of CEBPA mutations with DNMT3A mutations. Some studies were unable to report certain molecular abnormalities.

Mutations at the arg-882 (R882) codon in the DNMT3A gene are the most frequent because more than 60% of patients have a mutation at this site. Mutations were found within entire cohorts of the some of the reported trials, not the just in CN patients specifically. Only one study (12) did not report the spectrum of DNMT3A mutations observed.

Table 2. Mutational status of four genes in patients with *DNMT3A* mutations

Study												
	FLT3^{ITD}			***NPM1***			***IDH2***			***CEBPA***		
	Mut	Wt	p-value	Mut	Wt	p-value	Mut	Wt	p-value	Mut	Wt	p-value
Hou (8) (2012)	30	83	<0.0001	38	66	<0.0001	16	39	0.0016	3	63	0.0134
LaRochelle (9) (2011)	17	37	0.027	29	49	<0.0001	16	5	0.77	2	20	0.26
Ley (10) (2010)	25	48	0.003	37	27	<0.0001	7	13	0.15	NR		
Marcucci (11) (2012)	62	85	0.01	107	146	<0.001	24	51	0.79	7	58	<0.001
Patel (12) (2012)	52	37	<0.001	57	32	<0.001	NR			NR		
Renneville (13) (2012)	7	18	0.99	24	28	0.0006	5	14	NR	0	12	0.017
Ribeiro (14) (2012)	39	77	0.002	73	60	<0.001	13	23	0.086	1	7	0.69
Thol (15) (2011)	34	95	<0.003	56	107	<0.001	9	26	0.45	NR		

CEBPA = CCAAT-enhancer binding protein alpha; FLT3ITD = FMS-like tyrosine kinase 3 internal tandem duplications; IDH2 = Isocitrate dehydrogenase 2; mut = mutated; NPM1 = nucleophosmin 1, wt = wild type

Outcomes

The primary outcomes of interest examined were OS and CR, and are summarized in Table 2. All values were reported if available, or otherwise denoted NR (not reported). Although CIR was a primary clinical outcome, it was not documented in any of the retrieved studies. RFS (Table 3) was also recorded for future reference at the request of one of the clinical consultants.

Four studies (8,10,13,15) observed a statistically significant difference in the OS between DNMT3A-mut and DNMT3A-wt patients, with a worse OS in the mutated population. Conversely, the other studies (9,11,12,14) have only reported a trend towards improved survival in non-mutated versus mutated cohorts; however, no statistically significant differences were reported. Although the median OS in months was not recorded for some studies, the significance was documented. LaRochelle et al, 2011 (9) observed this difference in the intermediate risk group rather than a CN cohort, although 27/39 patients with DNMT3A mutations were cytogenetically normal. Furthermore, LaRochelle et al, 2011 (9) conducted a univariate analysis for OS for patients with a normal karyotype, yielding a p-value of 0.88 (p-value of the Log rank test). The p-value for multivariate analysis was >0.1; however, the hazard ratio and confidence intervals were not recorded – neither was significant. Renneville et al, 2012 (13) observed a p-value of 0.02 for a univariate analysis for DNMT3A mutated versus wild type and a p-value of 0.002 with multivariate analysis. Thol et al, 2011 (15) obtained similar results: in a univariate analysis, a p-value of 0.003 (HR=1.73; 95%CI, 1.21-

2.46); multivariate analysis resulted in p=<0.001 (no value recorded; HR=2.46; 95%CI, 1.58-3.83). Ribeiro et al, 2012 (14) did not analyze CN patients specifically, but conducted a univariate analysis for OS in CN patients (HR=1.255; p=0.216). Hou et al, 2011 (8) studied OS in young (<60 years of age) CN patients only, and determined that a normal karyotype is an independent variable using a multivariate analysis (HR=2.303; 95%CI, 1.088-4.876, p=0.029). Marcucci et al, 2010 (11) observed a trend towards significance (p=0.07) in OS after adjusting for age group (HR=1.25; 95%CI, 0.98-1.57, p=0.07), and did not observe a significant association with OS adjusting for other variables within the multivariate analysis.

The outcome data for CR were reported in 4 studies (9, 11, 13, 17). No statistically significant difference was observed in any of these studies except for Thol et al, 2011 (17). RFS was documented in three separate studies (8, 14, 15). Hou et al, 2011 (8) and Ribeiro et al, 2012 (14) were the only investigation to report any significant difference in RFS between DNMT3A-mutated patients and wild-type patients with a normal karyotype (p=0.004 and 0.033 respectively) while Thol et al, 2011 (15) observed insignificant results (p=0.32,).

The studies conducted by Ley et al, 2012 (10) and Patel et al, 2012 (12) did not provide enough information to construct hazard ratios for OS. The hazard ratios from multivariate analyses were used if studies provided that data; if not, data from univariate analyses for normal karyotype were used.

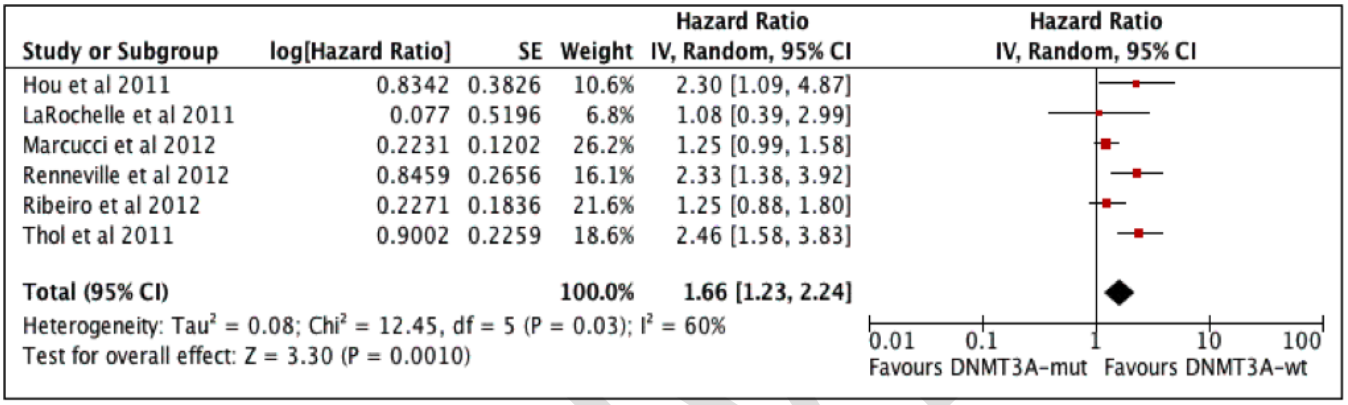
Table 3. Outcomes reported in the included studies

Study	Median OS	CR (% or Odds Ratio)	Median RFS
Hou (8) (2011)	DNMT3A-mut: 15.5 mo. (95%CI = NR) DMNT3A-wt: NR (95%CI = NR) p=0.018	NR	DNMT3A-mut: 6 mo. (95%CI = NR) *DMNT3A*-wt: 21 mo. (95%CI = NR) p=0.004
LaRochelle (9) (2011)	DNMT3A-mut: NR DMNT3A-wt: 24.7 mo. (95%CI = 0.87-2.19) p=0.17	DNMT3A-mut: 87% DMNT3A-wt: 81% p=0.48	NR
Ley (10) (2010)	NR (p=0.007)	NR	NR
Marcucci (11) (2012)	NR (p=0.07)	Odds ratio: 1.22 (95%CI = 0.75-1.96) p=0.42	NR
Patel (12) (2012)	DNMT3A-mut: 14.08 months DNMT3A-wt: 22.83 months (p=0.17)	NR	NR
Renneville (13) (2012)	DNMT3A-mut: 23% (95%CI = 0-39) DMNT3A-wt: 45% (95%CI = 34-57) p=0.02	DNMT3A-mut: 80% DMNT3A-wt: 90% p=0.24	NR
Ribeiro (14) (2012)	Hazard Ratio: 1.255 (p=0.216)	NR	Hazard Ratio: 1.524 (95%CI = NR) p=0.033
Thol (15) (2011)	DNMT3A-mut: 1.73 years DMNT3A-wt: 5.36 years HR=1.73 (95%CI, 1.21-2.46) p=0.003	DNMT3A-mut: 69% DMNT3A-wt: 82% P=0.023	Hazard Ratio: 1.23 (95% C.I.=0.81 – 1.88) p=0.32
CI = Confidence interval; CR = Complete remission; DNMT3A = DNA methyltransferase 3A (*mut* = mutated, *wt* = wild type); mo = Months; NR = Not reported; OS = Overall survival; RFS = relapse-free survival			

Meta-analysis

The response data from six of the eight trials were pooled for a meta-analysis (Figure 1). Two studies (10, 12) did not provide enough information to calculate the ln(HRi) and the se(ln(HRi)) for OS. The overall hazard ratio for OS was 1.66 (95%CI, 1.23-2.24), favouring the DNMT3A-wt population. However, significant statistical heterogeneity was identified (Chi^2=12.45, p=0.03, I^2=60%).

Figure 1. Forest plot of effect size for overall survival



DISCUSSION

Interventions

The treatment regimens varied considerably between trials, other than a minor variation on standard induction therapy with cytarabine (d1-7) + anthracycline or anthracenedione (idarubicin or daunorubicin, days 1-3) cycle (16). By contrast, there were large differences in post-remission consolidation therapy (high-dose cytarabine, autologous/allogeneic stem cell transplantation), and age restrictions for various treatment options. These looser criteria allowed a larger study population to evaluate. Pediatric AML was excluded from the investigation, as children normally do not possess the DNMT3A mutation (17). Some patients received several other chemotherapeutic medications: hypomethylating agents such as lenalidomide, alkylating agents such as lomustine, and purine analogs such as cladribine (18). This substantial variation in therapy between studies is a source of clinical heterogeneity, which may complicate the interpretation of the data. Only one study explicitly studied and reported an interaction between DNMT3A and response to a specific therapy (12). In this report, high-dose daunorubicin-induction therapy improved rate of survival compared to low-dose daunorubicin in DNMT3A-mut patients with NPM1 translocations, suggesting that high-dose anthracyclines may benefit cohorts with specific genetic abnormalities.

DNMT3A mutational profiling

Currently, only the FLT3ITD, NPM1 and CEBPA mutations are widely tested to determine prognosis in AML and have influenced several treatment decisions for CN patients (19). As DNMT3A mutation co-occurs with FLT3ITD and NPM1 mutations (10), this issue needs further analysis. Patel and colleagues (12) investigated patients with DNMT3A mutations and developed primary, comprehensive, mutational profiling for risk stratification and clinical management of AML according to OS. Although preliminary, this stratification scheme

combines cytogenetic classification with the more conventional risk-stratification system that can lead to further risk stratifying of different AML subgroups.

The molecular abnormalities co-occurring with DNMT3A mutations were reported within the cytogenetically normal subgroup of patients suffering from AML. For those with a DNMT3A mutation, it was observed that FLT3ITD and NPM1 genetic aberrations were significantly present across the majority of studies. However, Renneville et al, 2012 (13) did not observe significant co-occurrence in the FLT3ITD mutations with DNMT3A mutations. Patel and colleagues (12) observed significantly similar co-occurrences of DNMT3A with NPM1, FLT3, and IDH1 alleles ($p<0.001$ for all comparisons). In this report, Patel et al, 2012 (12) studied the frequency of somatic mutations within a test cohort of 398 patients, and the pair-wise interrelationships of the various mutations were presented in a Circos plot. The implications of these observations suggest that molecular abnormalities of the DNMT3A gene may complement specific genetic mutations in the pathogenesis of AML. The co-occurrence of IDH2 and CEBPA mutations with the DNMT3A mutations were quite variable. These differences may be due to the techniques used, which exons were sequenced, as well as biologic/clinical differences in the patient population studied such as age.

The DNMT3A mutation was found primarily at exon 23 of the gene, and was screened in each study. Specifically, the R882 codon of exon 23 harboured the majority of the mutations observed. Each study reported that over 60% of the mutations resided at the R882 codon within the CN patient cohort. The R882 codon is localized on the methyltransferase domain, which may explain the hypermethylation of CpG islands that contributes to downregulation of gene expression (9). According to the structural analysis performed by Yan et al, 2011 (5), R882 codon of DNMT3A likely participates in the homodimerization of DNMT3A, as it resides at the 3A-3A interfaces with two pairs of salt bridges between the proteins R885 and N876. It was also noted that R882 missense mutations were significantly associated with a higher white blood cell count compared to other DNMT3A mutations (9). This leads to the speculation that mutations at exon 23 are predominantly driver mutations within this population of acute myeloid leukemia patients. It is proposed that other prognosticators such as NPM1 and FLT3 mutations may be involved (20,21).

Mutational profiling of patients expressing the DNMT3A mutation may refine current prognostic models, further develop risk stratifications within the intermediate risk group, and assist clinicians with informing therapeutic decisions (4). Those screened for the co-occurring molecular aberrations with DNMT3A mutations may benefit from a more intensive chemotherapy for improving OS (22). This information may also help in understanding the biological characteristics of AML. Although the genetic information of AML is not completely understood, the molecular profiling of each CN patient leads to a better comprehension of the leukemic disease.

Outcomes

OS was the primary clinical outcome of interest investigated. Four of the eight studies observed a statistically significant difference in OS between DNMT3A-wt and DNMT3A-mut populations. The meta-analysis of these data resulted in an overall estimated hazard ratio 1.66 (95%CI, 1.23-2.24; p=0.0010) favouring patients that are DNMT3A wild type. This strongly suggests that the mutational status of DNMT3A has prognostic value. However, the interpretation of the meta-analysis using OS may be limited by the fact that two studies were omitted as the information was not available. It is unknown whether this omission affects the overall outcome.

Moreover, there was moderate statistical heterogeneity (I^2=60%) observed in the meta-analysis. This statistical heterogeneity likely resulted from distinct clinical heterogeneity between the studies in terms of multiple factors: different follow-up periods; differences in

the patient populations studied, such as age, overall health, disease type and status; and different therapies provided. LaRochelle et al, 2011 (9) observed patients that had experienced changes in treatment and care over the course of 9 years, which may have influenced the likelihood of discerning a difference between DNMT3A mutated versus Wild-type patients (p=0.17). Marcucci et al, 2012 (11) recruited patients from different clinical trials with a variety of patients and treatment regimens, but demonstrated no statistically significant differences. Another prognostic indicator is the age of the patient; Ribeiro et al, 2012 (14) recruited patients' ages 18 to 60 and observed no distinct difference between populations (p=0.216), similar to LaRochelle et al, 2011 (9) who had patients ages 18 to 65 years of age. The observation that DNMT3A seems to be of prognostic value with respect to OS is supported by the pooled estimate effect of the meta-analysis.

The rate of CR was not affected by the mutational status of the gene. LaRochelle et al, 2011 (9) and Marcucci et al, 2012 (11) observed similar results (p=0.48 and p=0.42, respectively) between populations, suggesting that both groups experienced BM cell maturation, approximately <5% BM blast cell counts and no evidence of circulating blasts or extramedullary leukemia (23). It is evident that DNMT3A mutations do not inherently hold any prognostic benefit with respect to CR. It is worthwhile to note that FLT3-ITD is another genetic mutation in AML that affects OS but not CR rate. Finally, no significant difference was observed for RFS clinical outcome.

CONCLUSIONS

In conclusion, assessing DNMT3A mutational status provides important prognostic information for AML patients with a normal karyotype. The six studies analyzed all demonstrated a better OS in DNMT3A-wt patients, with moderate to high heterogeneity. Further clinical research may further refine the estimated prognostic relevance of this biomarker. Clinicians wishing to make decisions or recommendations based on these results must understand the limitations of the available data.

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. With recommendation reports, this review is conducted by the Director of the PEBC. The Working Group is responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, MOAC members, and internal and external reviewers were asked to disclose potential conflicts of interest.

The authors, members, and reviewers reported that they had no conflicts of interest.

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Figure 2: Flow diagram of search result