Cellular Physiology and Biochemistry

Cell Physiol Biochem 2018;49:1589-1599

DOI: 10.1159/000493494

Published online: 14 September, 2018

Accepted: 5 September, 2018

Original Paper

A Bayesian Network Meta-Analysis Comparing the Efficacies of Eleven Novel Therapies with the Common Salvage Regimen for Relapsed or Refractory Acute Myeloid Leukemia

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Key Words

Acute myeloid leukemia • Chemotherapy • Complete remission • Overall response rate • Meta-analysis

Abstract

Background/Aims: Acute myeloid leukemia (AML) is a relapsed and refractory hematological malignancy with a lower morbidity but higher mortality. In addition to hematopoietic stem cell transplantation, chemotherapy is used as the front-line treatment. However, the diversity of available agents and the inconsistency of outcomes of relevant trials render treatment decision-making tough. Network meta-analysis (NMA) is an efficient statistical framework that makes a comprehensive comparison and provides a valuable clinical reference. ***Methods:*** All the potential trials were retrieved from the medical database and screened according to the inclusion and exclusion criteria. The main characteristics of each trial as well as the primary outcomes, including complete remission (CR), overall response rate (ORR), overall survival (OS), and event-free survival (EFS), were extracted. In addition, the network graph was plotted to illustrate the connections among the trials involved. Comparison results in the network were exhibited in a forest plot. Furthermore, the surface under the cumulative ranking curve (SUCRA) was introduced to rank the treatments for each endpoint. ***Results:*** A total of 11 trials were selected from 1,625 identifications. No significant difference in the common treatment was observed for the endpoints CR and ORR. In terms of OS, CPX-351 (HR: 0.77, 95% CrI: 0.63, 0.94) and HiDAC plus MK-8776 (HR: 0.80, 95% CrI: 0.68, 0.93) showed a superiority over the common salvage regimen in the short term, while HiDAC plus MK-8776 (HR: 0.80, 95% CrI: 0.70, 0.93) and Ara-C plus vosaroxin (HR: 0.86, 95% CrI: 0.74, 0.99) outperformed the common salvage regimen for the 3-year OS. In addition, clofarabine plus Ara-C (HR: 0.61, 95% CrI:

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0.53, 0.69) and CPX-351 (HR: 0.71, 95% CrI: 0.60, 0.83) were confirmed to be efficacious in enhancing the rate of EFS. ***Conclusion:*** Referring to the network outcome and SUCRA value, clofarabine plus Ara-C (CR: 79.05%, ORR: 80.02%) and Ara-C plus vosaroxin (CR: 75.42%, ORR: 73.43%) were potentially the top two choices for both CR and ORR. CPX-351 (1-year OS: 91.36%), HiDAC plus MK-8776 (3-year OS: 94.23%) and clofarabine plus Ara-C (1-year EFS: 97.34%) yielded the highest probabilities to be the optimal choices for 1-year OS, 3-year OS and 1-year EFS, respectively.

Introduction

Leukemia refers to a hematological malignant clonal disorder caused by excessive abnormal white blood corpuscles in the bone marrow [1]. Leukemia is generally classified into four types, chronic lymphocytic leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia and acute myeloid leukemia (AML), according to the clinical and pathological features. Among them, AML is a relapsed and refractory type, which is characterized by the halted differentiation and uncontrolled proliferation of myeloblasts, and serves as an immature precursor of monocytes and granulocytes [2]. Despite its low morbidity with 3.7 cases per 100, 000 persons, the mortality of this malignant neoplasm is quite high [3]. In 2005, a total of 147, 000 individuals died from this dreadful disease [4]. The overall survival (OS) of AML is an age-correlated distribution with an average of 8.3 years with induction therapy [5]. Under the influence of an abnormal immune system and hematological system, patients are prone to suffer from weight loss, fatigue, pyrexia of unknown origin, symptomatic anemia, lymphadenopathy, splenomegaly, hepatomegaly, and immunological cytopenias, and they are also susceptible to infection [6]. Nonetheless, while the direct precipitating factor is currently unspecified, genetic mutation, virus infection, and the influences of radiation and chemical substances, such as benzene, are confirmed to be relevant factors [7, 8].

Compared with hematopoietic stem cell transplantation and radiotherapy, chemotherapy is considered the front-line treatment for AML and consists of two phases, induction and consolidation therapy [9, 10]. Antimetabolites, such as methotrexate, cytarabine, decitabine, clofarabine and hydroxycarbamide; antineoplastic antibiotics, such as daunorubicin, doxorubicin and idarubicin; alkaloids, including vincristine and etoposide; mono-antibody agents, such as gemtuzumab ozogamicin (GO); and tyrosine kinase inhibitors, such as imatinib, are all common chemotherapeutic drugs used alone or in combination to treat AML [11].

Although clinical advances in AML have been achieved and the efficacy of chemotherapy is explicit, disease relapse remains an unsolved problem [12]. Additionally, the selection of a specific drug regimen has not been finalized considering the large amount of available drugs and the continuous release of new drugs. Since AML was defined early in the last century, one hundred years later, dozens of novel drugs or emerging drug combinations still spring up ceaselessly in an attempt to cure the disease completely or at least exert an improved efficacy. Fortunately, the 5-year OS increased from 11.9% in 1975 to 52.1% in 2002 for young AML adults and from 4.3% to 11.3% for the elderly (Surveillance Epidemiology and End Results. Fast Stats: Acute myeloid leukemia 5-year relative survival by year diagnosis and age at diagnosis/ death 1975-2002). To make a comparison, different therapeutic options had been evaluated by a large number of randomized controlled trials (RCTs), which have yielded some great results. Nonetheless, the paradox among these trials precipitated the situation into another dilemma. In a study by Burnett *et al*. in 2012, daunorubicin plus cytarabine (Ara-C) or clofarabine combined with GO decreased the 3-year cumulative relapse incidence (68% versus 76%, P = 0.007) and prolonged the 3-year OS (25% versus 20%, P = 0.05) significantly in comparison with the induction chemotherapy without GO [13]. However, in a 5-year follow-up trial reported by Petersdorf *et al*., the addition of GO to daunorubicin plus Ara-C exerted no influence on the improvement of the relapse-free survival rate (43% versus 42%, P = 0.40) and OS rate (46% versus 50%, P = 0.85) [14].

Due to discrepancies in the experimental design, baseline of subjects, administration dosage and other factors, the final outcomes vary widely. Network meta-analysis (NMA), a statistical tool, can utilize direct and indirect evidence and make a comprehensive comparison at the same time [15, 16]. Comparisons between treatments included in RCTs can supply

direct head-to-head evidence. However, it is generally impractical for researchers to conduct RCTs to compare all relevant treatments in a disease field, especially for new treatments. In this situation, NMA can be applied if both treatments have been compared to a common comparator. The assessment obtained from such an analysis is called "indirect evidence", which is the estimate of the efficacy of treatment A over B and can be measured by comparing trials of A vs. C and B vs. C. NMA is a tool to synthesize direct evidence and indirect evidence to assess the effect of several treatments.

On the basis of available data from relevant RCTs, a network meta-analysis would be a better solution to address existing inconsistencies and an efficient framework to compare the efficacies of multiple treatments simultaneously for relapsed or refractory AML patients.

Materials and Methods

Identification strategy

The relevant literature and eligible trials recorded in internet medical databases, such as Cochrane Library, Embase and PubMed, were retrieved with terms including the disease "acute myeloid leukemia"; drugs "cytarabine", "mitoxantrone", "etoposide", "idarubicin", "topotecan", "gemtuzumab ozogamicin", *etc*. as well as the publication type "randomized controlled trial", connected by the Boolean operators "OR" and "AND". In the case of any omission, the reference list of retrieved meta-analysis and systematic reviews was examined manually. Three internet databases were searched from October 1, 2017 to October 15, 2017 under the identification strategy described above for articles published between 1950 and 2017.

Inclusion and exclusion criteria

For all the studies identified, the inclusion and exclusion criteria were established to screen the qualified trials. First, the following inclusion criteria must have been met: (1) the trial must have been designed as an RCT, double blinded or open-labeled trial; (2) the enrolled patients must have been diagnosed with AML, either refractory or first relapsed; (3) the investigated comparison must have been carried out between an unconventional chemotherapeutic regimen, drug alone or drug in combination with an unspecific effect and a known salvage regimen, such as the drug combination of mitoxantrone, etoposide, and cytarabine (MEC) and the combination of cyclophosphamide, cytarabine, and topotecan (CAT); and (4) at least one comparable outcome must have been reported. In addition, exclusion criteria were applied to remove some exceptions as follows: (1) the data were from a phase I or single-arm phase II clinical trial; (2) the compared treatments disconnected from the giant component in the network graph; and (3) the trial was conducted to contrast the efficacies between different administration dosages of a single chemotherapy. The screening and identification of trials was independently accomplished by two staff members, who then jointly created the final list.

Data extraction and endpoint

As a token of the different trials, the main characteristics, such as the first author and year of publication, were recorded for each included trial. The blinding and diagnosis as well as the features of the trial itself were removed. For each arm, the intervention, sample size, age and male ratio were extracted along with all the reported numerical outcomes for further network analysis. The data of 1-year, 3-year OS and 1-year EFS were extracted by using *Engauge Digitizer* 4.1 to match the OS curve and EFS curve reported in papers. In addition, complete remission rate (CR), overall response rate (ORR) were extracted. According to the nature of AML prognosis and the availability of clinical data, 1-year OS, 3-year OS, 1-year EFS, CR and ORR were deemed the primary efficacy endpoints.

In general, the following three conditions were considered as CR, the disappearance of all signs of AML: (1) no anemia, hemorrhage, infection or infiltration of leukemia cells were observed as clinical symptoms; (2) for hematologic indicators, the counts of platelets and hemoglobin exceeded 100×10^9/L and 90 g/L, respectively, and the leukopenia or normal leucocytes were observed in blood; and (3) the regeneration of normal erythrocyte and megakaryocyte maturation was monitored with a normocellular number less than 5% in the bone marrow [17]. The case in which at least one condition mentioned above was met and the normocellular number was lower than 20% is recognized as an ORR. OS is a measure of the length of lifetime, while EFS indicates the time that a patient remains free from certain disease-related complications or symptoms.

Statistical analytical method

Among the four types of endpoints, CR and ORR are discrete variables measured by odds ratios (ORs), while OS and EFS are prognostic variables measured by hazard ratio (HR). 95% credible intervals (CrIs) were measured to judge whether the results were statistically significant. When value one was covered under the 95% CrI, the statistic was considered insignificant.

Prior to the implementation of NMA, a traditional head-to-head meta-analysis was conducted as a prerequisite to determine the model choice. Heterogeneity was estimated for each comparison in a fixed-effects model in terms of Cochran's Theorem. If the *P* value was less than the 0.05 significance level, the influence of heterogeneity was supposed be considered, and the random-effects model was fitted. After that, indirect data were calculated based on the raw data extracted from RCTs and the interconnection in the network, as demonstrated in the net plot. In the network graph, the information regarding the pooled sample size and number of comparisons was reflected by the node size and the line width, respectively. In addition, direct and indirect evidence was then synthesized to acquire the network data (as listed in the slash table), and the comparison of each treatment to the salvage regimen is exhibited in the forest plot. Furthermore, the surface under the cumulative ranking curve (SUCRA) for each endpoint were estimated and ranked, and higher scores denoted a higher probability of the treatment to be the most efficient solution. All data used were processed using R 3.3.3 software.

Results

Literature identification

As depicted in the flow chart (Fig. 1), 1, 625 records were identified from the PubMed, Embase and Cochrane databases. After removing 199 duplicates, the remaining 1, 426 eligible articles were further screened according to the inclusion and exclusion standards. In total, 1, 375 studies were not included, as they were irrelevant RCTs, meta-analyses, systematic reviews, phase I or single-arm phase II clinical trials, or interim trial reports. In addition, 51 full-texts were retrieved for more details, but another 40 studies were rejected due to insufficient data, inability to connect with other interventions, poor quality or any other reasons. Eventually, 11 trials were included to provide the primary evidence [18-28].

Characteristics of the included trials

Table 1 summarizes the basic information regarding all 11 trials disclosed between November 2004 and July 2017 and the baselines of the 2, 447 patients involved. In most cases, the prognosis was closely correlated with age, and the age of the patient could be a main confounder; therefore, all the subjects in the included trials were adults with an average age of 61 (18-89) years and a male ratio of 55.6%, and no pediatric RCTs were included. The network relationship plotted in Fig. 2 represents monocentric graphs using the salvage regimen as the sole kernel with an average degree of approximately 2. All eleven trials offered raw CR data, while seven trials provided information about ORR.

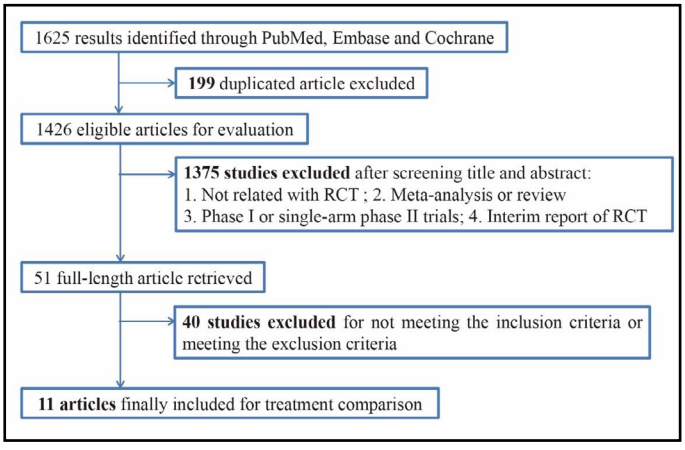

Fig. 1. Flow chart for the process of screening out the included studies. Abbreviations: MEC, drug combination of mitoxantrone, etoposide, and cytarabine; CAT, combination of cyclophosphamide, cytarabine, and topotecan; HiDAC, high-dose cytarabine.

Complete remission, CR

Except for MEC plus valspodar, the combination of high-dose cytarabine (HiDAC), idarubicin and AEG35156, and HiDAC plus MK-8776 (OR value less than one), the other 8 treatments were better than traditional chemotherapy in improving CR. However, none of these comparisons were conspicuous, as shown in Fig. 3. According to their SUCRA values listed in Table 2, clofarabine plus Ara-C (0.7905)

Table 1. Main characteristics of the included studies. *1 unit CPX-351=1.0 mg Ara-C+0.44 mg daunorubicin. **investigator's choices were: HiDAC/MEC/FLAG/FLAG-Ida/low or intermediate dose Ara-C/decitabine/azacitidine/hydroxyurea/supportive/anthracycline+etoposide/gemtuzumab ozogamicin. *** Abbreviations: OS, overall survival; EFS, event-free survival; MEC, mitoxantrone+etoposide+cytarabine; HiDAC, high-dose cytarabine; GO, gemtuzumab ozogamicin; CAT, cyclophosphamide+cytarabine+topotecan; FLAG, fludarabine+cytarabine+G-CSF

First Author	Year	Blinding	Diagnosis	Study Arm				Control Arm				Outcomes
				Treatment	Age (yrs)	Male (n)	Size (n)	Treatment	Age (yrs)	Male (n)	Size (n)	
Greenberg	2004	-	refractory or relapsed	MEC+Valspodar	-	-	38	MEC	-	-	40	CR,OS,EFS
Feldman	2005	-	refractory or 1st relapsed	MEC+HuM195	55.4±14.6	39	94	MEC	54.8±14.8	41	97	CR,ORR,OS
Giles	2009	double	1st relapsed	HiDAC+Laromustine	59(22-82)	-	177	HiDAC	60(25-84)	-	86	CR,ORR,OS
Litzow	2010	-	refractory or relapsed	Ara-C+liposomal daunorubin	52(27-85)	11	29	GO/CAT	53(25-78)	34	53	CR
Levis	2011	-	1st relapse	MEC+lestaurtinib	59(20-81)	-	112	MEC	54(21-79)	-	112	CR,ORR,OS
Schimmer	2011	open-label	primary refractory	HiDAC+idarubicin+AEG35156	62(24-77)	14	27	HiDAC+idarubicin	64(47-80_	8	13	CR,ORR
Faderl	2012	double	refractory or relapsed	Clofarabine+Ara-C	67(55-82)	114	162	Placebo+Ara-C	67(55-86)	101	158	CR,ORR,OS,EFS
Roboz	2014	open-label	refractory or relapsed	Elacytarabine	62(22-89)	115	191	Investigator's choice**	63(19-83)	101	190	CR,OS
Cortes	2015	open-label	1st relapsed	CPX-351*	52(18-65)	38	81	Investigator's choice	56(18-65)	19	44	CR,ORR,OS,EFS
Ravandi	2015	double	refractory or 1st relapsed	Ara-C+vosaroxin	64(20-80)	202	356	Ara-C+placebo	63(18-82)	192	355	CR,ORR,OS
Webster	2017	-	refractory or relapsed	HiDAC+MK-8776	60(37-72)	8	14	HiDAC	60(29-71)	9	18	CR,OS

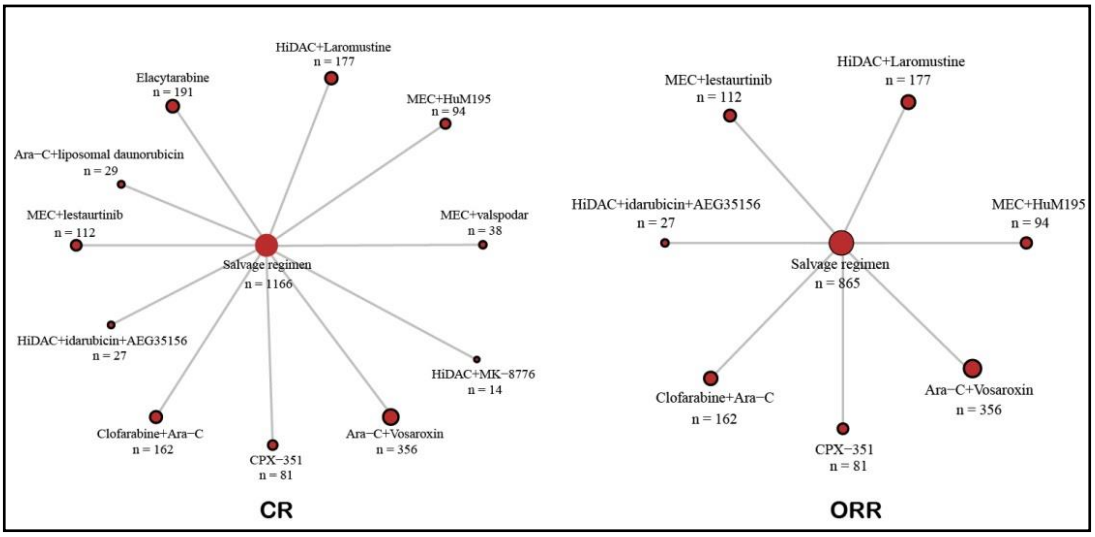

Fig. 2. Network structure for CR and ORR. The network plots show direct comparison of different treatments, with node size corresponding to the sample size. The number of included studies for specific direct comparison decides the thickness of solid lines. Abbreviations: MEC, drug combination of mitoxantrone, etoposide, and cytarabine; CAT, combination of cyclophosphamide, cytarabine, and topotecan; HiDAC, high-dose cytarabine.

had the highest probability of being the best choice, followed by Ara-C plus vosaroxin (0.7542) and MEC plus HuM195 (0.5802).

Overall response rate, ORR

Similar to CR, the outcome of ORR indicated that among the seven interventions, the combination of HiDAC, idarubicin and AEG35156 was the only one inferior to the salvage regimen. The advantages of the other treatments were not ensured with statistical significance, as shown in the forest plot in Fig. 3. In contrast to HiDAC combined with idarubicin and AEG35156, the difference in clofarabine plus Ara-C (OR: 10.7, 95% CrI: 1, 121.51) was noticeable, as listed in Table 3. Supported by the SUCRA value in Table 2, clofarabine plus Ara-C (0.8002) and Ara-C plus vosaroxin (0.7343) remained the top two, while HiDAC plus laromustine (0.7067) ranked third.

Overall survival, OS

In terms of OS, 1-year and 3-year outcomes were investigated as two time nodes. As exhibited in Fig. 4, a discrepancy in the efficacies of the different therapies manifested. For short-term OS, two novel drugs, CPX-351 (HR: 0.77, 95% CrI: 0.63, 0.94) and HiDAC plus MK-8776 (HR: 0.80, 95% CrI: 0.68, 0.93), were significantly better than the common treatment, whereas HiDAC plus laromustine (HR: 1.32, 95% CrI: 1.11, 1.59) and MEC plus valspodar

(HR: 1.22, 95% CrI: 1.03, 1.45) were much poorer. In accordance with the outcome of SUCRA, CPX-351 (0.9136), HiDAC plus MK-8776 (0.8867) and Ara-C plus vosaroxin (0.7651) were the top three for increasing the 1-year survival rate. Regardless of the four lost interventions in 3-year OS, HiDAC plus MK-8776 (HR: 0.80, 95% CrI: 0.70, 0.93) and Ara-C plus vosaroxin (HR: 0.86, 95% CrI: 0.74, 0.99) displayed outstanding efficacy over the salvage regimen, while iDAC plus laromustine (HR: 1.28, 95% CrI: 1.11, 1.48) and MEC plus valspodar (HR: 1.28, 95% CrI: 1.11, 1.47) performed poorly. Due to the absence of CPX-351, HiDAC plus MK-8776 (0.9423) and Ara-C plus vosaroxin (0.8308) ranked first and second.

Event-free survival, EFS

More informative than the OS, EFS measures the length of survival without interference from certain complications or symptoms. Among the three chemotherapies reported to be a relevant direct comparison, clofarabine plus Ara-C (HR: 0.61, 95% CrI: 0.53, 0.69) and CPX-351 (HR: 0.71, 95% CrI: 0.60, 0.83) could efficiently protect patients from associative illness. Nevertheless, MEC plus valspodar (HR: 1.83, 95% CrI: 1.33, 2.51) might reduce this rate significantly, as illustrated in Fig. 4. The SUCRA value in Table 2 for clofarabine plus Ara-C (0.9734) and CPX-351 (0.6932) further verified this result.

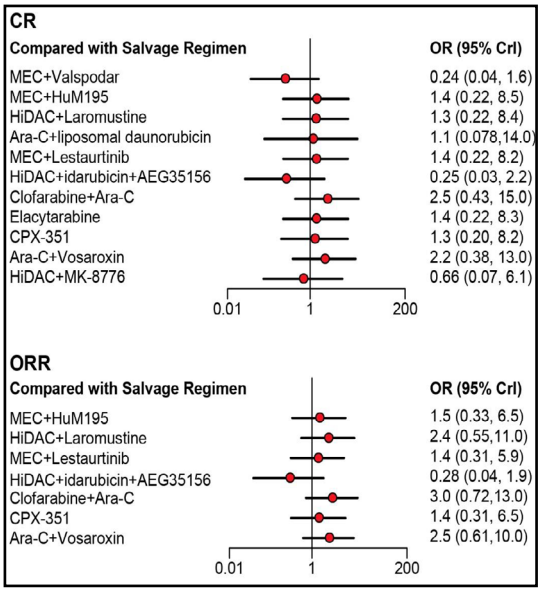

Fig. 3. Forest plots for CR and ORR. Odds ratios (ORs) with 95% credible interval (CrIs) indicate the relative efficacy. Abbreviations: MEC, drug combination of mitoxantrone, etoposide, and cytarabine; CAT, combination of cyclophosphamide, cytarabine, and topotecan; HiDAC, high-dose cytarabine.

Discussion

Other than the former relevant meta-analysis regarding the evaluation of routine treatments, we are the first to conduct an overall comparison among new selections using NMA, and this strategy and is expected to make a therapeutic breakthrough over traditional chemotherapies [29, 30]. In the scope of these eleven interventions researched, some were indicative of significant efficacies when compared with the conventional salvage regimen. The combination of clofarabine with Ara-C manifested an outstanding performance for improving the CR, ORR and 1-year EFS. Additionally, CPX-351 and HiDAC plus MK-8776 exhibited an advantage over the others in increasing short-term and long-term OS, respectively.

Clofarabine (2-chloro-9-[2-deoxy-2-fluoro-b-D-arabinofuranosyl] adenine), a novel deoxyadenosine analog, synthesizes the inhibitory efficacy of ribonucleotide reductase and DNA polymerase while combining the feature of fludarabine and cladribine to reduce toxicity [31]. In a myeloid-derived cytology experiment, the drug combination of clofarabine with Ara-C reflected a significant cytotoxin [32]. Furthermore, its safety and efficacy were also significantly good in a

Table 2. Surface under the cumulative ranking curve (SUCRA) results for CR, ORR, OS and EFS. Note: The scores show the relative efficacies of the treatments: a high score refers to a relatively high efficacy, while a low score reflects a low efficacy

Treatment	CR	ORR	1-OS	3-OS	1-EFS
Ara-C+vosaroxin	0.7542	0.7343	0.7651	0.8308	-
Clofarabine+Ara-C	0.7905	0.8002	0.541	0.5348	0.9734
CPX-351	0.5531	0.4712	0.9136	-	0.6932
Elacytarabine	0.5719	-	0.538	-	-
HiDAC+Laromustine	0.5694	0.7067	0.0412	0.0988	-
HiDAC+MK-8776	0.3719	-	0.8867	0.9423	-
MEC+HuM195	0.5802	0.4903	0.5125	-	-
MEC+lestaurtinib	0.5776	0.4547	0.235	-	-
MEC+Valspodar	0.1234	-	0.1205	0.1039	0
HiDAC+idarubicin+AEG35156	0.1468	0.6204			
Ara-C+liposomal daunorubicin	0.5228	-			
Salvage	0.4381	0.2807	0.4465	0.4894	0.3333

Table 3. Network meta-analysis results for CR, ORR, OS and EFS. Note: CR and ORR refer to complete remission and overall response rate. OS and EFS refer to overall survival and event-free survival. CR and ORR are represented in form of odds ratios (ORs) with 95% credible interval (CrI). OS and EFS are represented in form of hazard ratios (HRs) with 95% CrI, indicating the relative efficacy. Note that in the upper half of the table, column treatments are compared against row treatments, whereas in the lower half of the table, row treatments are compared against column treatments. A: Salvage; B: MEC+Valspodar; C: MEC+HuM195; D: HiDAC+Laromustine; E: Ara-C+liposomal daunorubicin; F: MEC+lestaurtinib; G: HiDAC+Idarubicin+AEG35156; H: Clofarabine+Ara-C; I: Elacytarabine; J: CPX-351; K: Ara-C+vosaroxin: L: HiDAC+MK-8776

Endpoints		Treatments												
		A	B	C	D	E	F	G	H	I	J	K	L	
CR	A	1												
	B	4.18 (0.62,27.94)	1											
	C	0.73 (0.12,4.39)	0.17 (0.01,2.39)	1										
	D	0.75 (0.12,4.53)	0.18 (0.01,2.44)	1.03 (0.08,12.68)	1									
	E	0.86 (0.07,12.81)	0.2 (0.01,5.53)	1.19 (0.06,28.79)	1.15 (0.06,29.08)	1								
	F	0.73 (0.12,4.39)	0.18 (0.01,2.39)	1 (0.08,12.94)	0.98 (0.08,12.55)	0.85 (0.03,17.81)	1							
	G	4.01 (0.46,36.23)	0.96 (0.05,17.81)	5.58 (0.33,91.84)	5.31 (0.32,91.84)	4.62 (0.15,130.32)	5.47 (0.33,92.76)	1						
	H	0.4 (0.07,2.32)	0.09 (0.01,1.31)	0.54 (0.04,6.75)	0.53 (0.04,6.69)	0.45 (0.02,9.49)	0.54 (0.04,6.62)	0.1 (0.01,1.58)	1					
	I	0.75 (0.12,4.44)	0.18 (0.01,2.41)	1.02 (0.08,12.55)	0.99 (0.08,12.55)	0.86 (0.04,18.36)	1.02 (0.08,12.81)	0.19 (0.01,2.92)	1.88 (0.15,22.65)	1				
	J	0.79 (0.12,4.9)	0.19 (0.01,2.59)	1.08 (0.08,13.74)	1.04 (0.08,13.74)	0.9 (0.03,19.69)	1.06 (0.08,13.74)	0.2 (0.01,3.29)	1.97 (0.15,25.03)	1.05 (0.08,13.87)	1			
	K	0.45 (0.08,2.59)	0.11 (0.01,1.43)	0.63 (0.05,7.69)	0.61 (0.05,7.54)	0.53 (0.02,10.59)	0.62 (0.05,7.46)	0.11 (0.01,1.77)	1.14 (0.1,13.6)	0.61 (0.05,7.46)	0.58 (0.05,7.39)	1		
	L	1.42 (0.17,13.6)	0.34 (0.02,6.42)	1.97 (0.12,33.78)	1.92 (0.12,33.12)	1.65 (0.06,48.42)	1.95 (0.12,33.45)	0.36 (0.02,8.08)	3.6 (0.22,62.18)	1.92 (0.12,33.78)	1.84 (0.11,33.12)	3.16 (0.21,52.46)	1	
ORR	A			1.46 (0.33,6.49)	2.41 (0.55,10.59)		1.36 (0.31,5.93)	0.28 (0.04,1.9)	3 (0.72,12.68)		1.4 (0.31,6.49)	2.53 (0.61,10.18)		
	B													
	C				1.65 (0.2,13.33)		0.93 (0.12,7.39)	0.19 (0.02,2.16)	2.03 (0.26,16.12)		0.96 (0.12,8.17)	1.72 (0.22,13.46)		
	D						0.57 (0.07,4.48)	0.12 (0.01,1.28)	1.25 (0.16,9.78)		0.59 (0.07,4.85)	1.05 (0.14,8.17)		
	E													
	F						0.21 (0.02,2.34)	2.2 (0.28,17.29)	2.2 (0.28,17.29)		1.03 (0.13,8.67)	1.86 (0.24,14.3)		
	G							10.7 (1,121.51)	10.7 (1,121.51)		5.05 (0.44,60.95)	9.03 (0.84,98.49)		
	H										0.46 (0.06,3.86)	0.84 (0.11,6.3)		
	I											-		
	J											1.8 (0.22,14.01)		
	K													
	L													
1 yr OS	A	1												
	B	4.18 (0.62,27.94)	1											
	C	0.73 (0.12,4.39)	0.17 (0.01,2.39)	1										
	D	0.75 (0.12,4.53)	0.18 (0.01,2.44)	1.03 (0.08,12.68)	1									
	E	0.86 (0.07,12.81)	0.2 (0.01,5.53)	1.19 (0.06,28.79)	1.15 (0.06,29.08)	1								
	F	0.73 (0.12,4.39)	0.18 (0.01,2.39)	1 (0.08,12.94)	0.98 (0.08,12.55)	0.85 (0.03,17.81)	1							
	G	4.01 (0.46,36.23)	0.96 (0.05,17.81)	5.58 (0.33,91.84)	5.31 (0.32,91.84)	4.62 (0.15,130.32)	5.47 (0.33,92.76)	1						
	H	0.4 (0.07,2.32)	0.09 (0.01,1.31)	0.54 (0.04,6.75)	0.53 (0.04,6.69)	0.45 (0.02,9.49)	0.54 (0.04,6.62)	0.1 (0.01,1.58)	1					
	I	0.75 (0.12,4.44)	0.18 (0.01,2.41)	1.02 (0.08,12.55)	0.99 (0.08,12.55)	0.86 (0.04,18.36)	1.02 (0.08,12.81)	0.19 (0.01,2.92)	1.88 (0.15,22.65)	1				
	J	0.79 (0.12,4.9)	0.19 (0.01,2.59)	1.08 (0.08,13.74)	1.04 (0.08,13.74)	0.9 (0.03,19.69)	1.06 (0.08,13.74)	0.2 (0.01,3.29)	1.97 (0.15,25.03)	1.05 (0.08,13.87)	1			
3 yr OS	A			1.46 (0.33,6.49)	2.41 (0.55,10.59)		1.36 (0.31,5.93)	0.28 (0.04,1.9)	3 (0.72,12.68)		1.4 (0.31,6.49)	2.53 (0.61,10.18)		
	B													
	C				1.65 (0.2,13.33)		0.93 (0.12,7.39)	0.19 (0.02,2.16)	2.03 (0.26,16.12)		0.96 (0.12,8.17)	1.72 (0.22,13.46)		
	D						0.57 (0.07,4.48)	0.12 (0.01,1.28)	1.25 (0.16,9.78)		0.59 (0.07,4.85)	1.05 (0.14,8.17)		
	E													
	F						0.21 (0.02,2.34)	2.2 (0.28,17.29)	2.2 (0.28,17.29)		1.03 (0.13,8.67)	1.86 (0.24,14.3)		
	G							10.7 (1,121.51)	10.7 (1,121.51)		5.05 (0.44,60.95)	9.03 (0.84,98.49)		
	H										0.46 (0.06,3.86)	0.84 (0.11,6.3)		
	I													
	J													
1 yr EFS	B	1.83 (1.33,2.51)	1						3 (2.13,4.23)		2.59 (1.82,3.69)			
	H	0.61 (0.53,0.69)	0.33 (0.24,0.47)						1		0.86 (0.7,1.06)			
	J	0.71 (0.6,0.83)	0.39 (0.27,0.55)						1.16 (0.94,1.42)		1			
	A	1	0.55 (0.4,0.75)						1.64 (1.44,1.87)		1.42 (1.21,1.66)			

phase I/II clinical trial [33, 34]. In the supportive phase III RCT, such a drug combination prominently outperformed the single medication for the CR, ORR, EFS and 4-month EFS rates without unexpected adverse events but did not significantly benefit the OS [19]. This limitation in OS might be a consequence of the advanced age of the recruited subjects, a hard-to-treat population with a median OS ranging from 2.4 to 8 months in general. Therefore, compared with other interventions studied on the no age-restriction adults, its strength in OS was relatively weaker.

To ameliorate the outcome of OS, CPX-351 and HiDAC plus MK-8776 seemed to be the optimal choices, as reported by phase II trials [18, 28]. Unlike other novel treatments, CPX-351, the combination of Ara-C and daunorubicin encapsulated in a liposome at a 5:1 molar ratio, is a formulation-improved chemotherapy that is expected to maximize the *in*

vitro synergistic effect and minimize the antagonistic effect via the plasma half-time extension function and the enhanced permeability and retention effect of liposomes [35-37]. MK-8776, a selective checkpoint kinase 1 (Chk1) inhibitor, can sensitize AML cells to Ara-C by prohibiting its activation of the Rad3-related protein (ATR)-Chk1 singling pathway, which could arrest the cell cycle and impair the cytotoxicity of Ara-C [38-40]. Thus, this kind of drug combination was also validated as an effective therapeutic approach.

However, some deficiencies of this NMA were inevitable. (1) Due to the investigation on the novel treatments, the relevant qualified RCTs were numbered, resulting in only one trial being included for each intervention, and were not error free. (2) To enlarge the scope of the study, a specific population study performed on the elderly was included, which might have been biased, as the prognosis of AML is age-dependent. (3) Restricted by the follow-up, some interventions were lost in the long-period endpoints, which made the outcome incomplete; for example, the longest follow-up time of all the included studies was less than 5 yr, which made it impossible to perform a statistical comparison of 5-year survival rates. (4) Due to the ambiguous category and missing data on related adverse events, the safety of each intervention was not taken into consideration even though it was as important as the efficacy. Overall, a more high-quality RCT on adults with a longer follow-up and more comprehensive endpoints should be carried out in future studies.

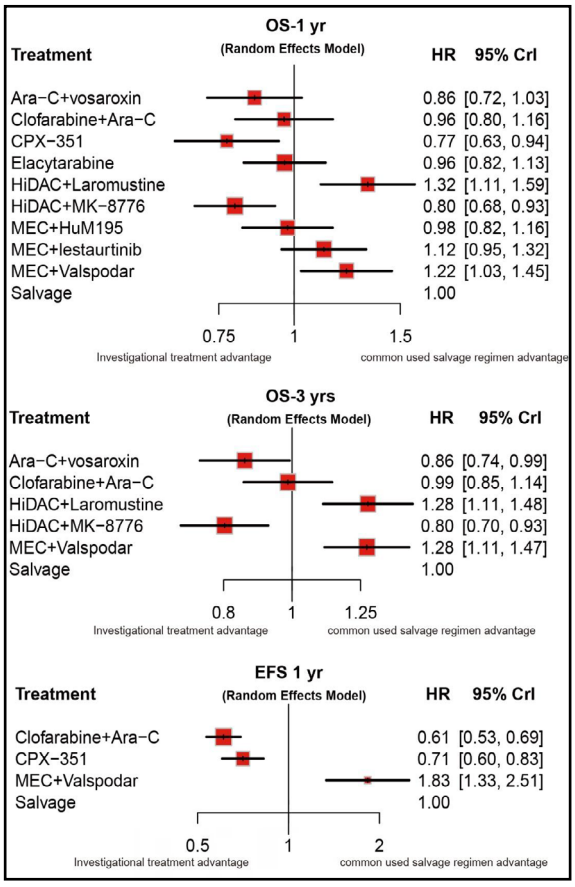

Fig. 4. Forest plots for 1-OS, 3-OS and 1-EFS. Hazard ratios (HRs) with 95% credible interval (CrIs) indicate the relative efficacy. Abbreviations: MEC, drug combination of mitoxantrone, etoposide, and cytarabine; CAT, combination of cyclophosphamide, cytarabine, and topotecan; HiDAC, high-dose cytarabine.

In conclusion, clofarabine plus Ara-C (CR: 79.05%, ORR: 80.02%) and Ara-C plus vosaroxin (CR: 75.42%, ORR: 73.43%) could be the top two choices for both CR and ORR. CPX-351 (1-year OS: 91.36%), HiDAC plus MK-8776 (3-year OS: 94.23%) and clofarabine plus Ara-C (1-year EFS: 97.34%) yielded the highest probabilities to be the optimal choices for 1-year OS, 3-year OS and 1-year EFS, respectively. Above all, no single drug combination can exhibit outstanding efficiency under all five endpoints. However, our NMA supplied a good reference for clinical decision-making considering all the common chemotherapeutic drugs. Physicians can combine the clinical condition of the patient, the therapeutic goal, the willingness of the patient and the NMA analysis results to make a better decision. Our NMA ultimately demonstrated the value of multiple treatments and provided a valuable clinical reference in terms of the CR, ORR, OS and EFS indicators.

Acknowledgements

This study was supported by National Natural Science Foundation of China (NSFC 81500173).

Disclosure Statement

The authors declare that they have no conflicts of interest.

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