

Short Communication

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Approach to AML Treatment. Survey Results from the 6th International Hematologic Malignancies Conference: Bridging the gap 2015, Beijing, China

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For the past six years, the Asia-Pacific Hematology Consortium (APHCON), through its Bridging the Gap (BTG) conference series has convened Asia's top hematologists and oncologists to share their practical knowledge and experiences. In addition to the high informational value of panelist and speaker presentations, we wish to learn directly from conference participants. This year in Beijing, we deployed a survey in hopes of discovering answers to the following questions: What are the common standards of care in Asia's hematology oncology community? Which of these are best practices? In which scenarios are the treatment strategies controversial or in disagreement? What educational or material needs remain to be met? This letter represents the first in a series of survey summaries that detail the state of the art in hematology oncology in the Asia-Pacific sphere. Our aim is to spark a conversation that addresses areas of opportunity for improving patient care and physician support.

In this letter we present the results of the first survey, focused on Acute Myeloid Leukemia (AML) (Table 1). We asked 16 questions regarding treatment preferences among 86 physicians from China and 27 physicians from other countries including Australia, India, Japan, Nepal, Thailand and the United States of America. The per-question response rate was 87% for Chinese physicians and 67% for the others. Unless we state otherwise, we report survey results as the percentage of respondents, excluding those who did not provide an answer to a particular question.

In cases of newly diagnosed AML, a wide margin of all survey respondents (91% China, 78% other) chose the Standard 7+3 induction regimen. A minority of non-Chinese respondents (17%) indicated a preference for high dose cytarabine from the outset. When asked specifically about AML induction in adolescents, again a majority of physicians in our survey (68% China, 60% other) recommended Standard 7+3. The remaining responses were split among clinical trials, cytarabine + daunorubicin + etoposide, and clofarabine + cytarabine. The less common implementation of these induction regimens may be due to several factors. First, a smaller amount of data supports alternative approaches versus decades of experience implementing the Standard protocol [1]. However, recent and ongoing clinical studies are adding to the body of evidence. A European trial (EORTC-GIMEMA AML-12), for example, found improved outcomes for patients under 46 years of age for higher dosages of cytarabine in conjunction with daunorubicin and etoposide [2]. This more aggressive induction raises the concern of availability of chemotherapy agents for higher doses or longer dosage periods. While Standard 7+3 remains the most common induction regimen, further studies, the availability of biosimilars,

and ongoing education and knowledge dissemination may shift the paradigm for AML induction in younger patients.

For older (>60 yrs) patients, a plurality of physicians (~48% of all respondents) would recommend hypomethylating agents (HMAs) for AML induction. Evidence is mounting that HMAs provide better outcomes for this age demographic in terms of increased survival and quality of life, with less treatment-related death, than do traditional chemotherapies [3]. Nevertheless, the remainder of physicians split their response between Standard 7+3, clinical trials, and intermediate doses of cytarabine. Decitabine is the most recommended HMA in China (77%), while respondents from other countries prefer Azacytidine (67%). This difference likely reflects regional variations in drug availability and physician training. Observations from both preclinical and phase II studies indicate these chemicals possess different activities and are not biologically equivalent. Yet, neither has shown a major efficacy advantage [3].

Targeted therapies using kinase inhibitors are beginning to show more promise in clinical settings, and are gaining ground in the West. Sorafenib is one such compound with activity against mutant FMS-like tyrosine kinase 3 (FLT3). The bulk of our survey respondents were split between those who recommend Sorafenib for FLT3+ AML and those who require more information on the drug before they add it to their treatment regimen, with about 44% of all respondents in each camp. Recent phase II trials incorporating Sorafenib report some efficacy in achieving complete remission (CR) in younger patients, and warrant further trials [4]. The drug has a propensity, however, to select for resistant mutants. Taking a cautious "wait-and-see" stance is consistent with the call for more clinical evidence from the United States' National Comprehensive Cancer Network (NCCN) [1].

A large majority of survey respondents (~90%) recommend

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Question	^{a,b} Responses				No Response
1. What is your induction regimen of choice for newly Diagnosed AML?	Standard 7+3 Induction	Clofarabine Based Therapy	High Dose Cytarabine	Clinical Trial	
	China 91%; Other 78%	2, 0%	4, 17%	2, 4%	4, 15%
2. What is your ideal induction regimen for adolescent AML?	Standard 7+3 Induction	Clofarabine/Cytarabine	Cytarabine/daunorubicin/etoposide	Clinical Trial	
	68, 56%	10, 5%	12, 20%	10, 15%	9, 26%
3. What is your induction regimen for elderly (>60 yrs) AML?	Hypomethylating agents	Standard 7+3 Induction	Clinical Trial	Intermediate dose Cytarabine	
	49, 44%	24, 22%	21, 17%	6, 17%	12, 33%
4. Which hypomethylating agent do you prefer to use for AML induction?	Decitabine	Azacitidine			
	77, 33%	23, 67%			14, 33%
5. Based on recent data, would you use Sorafenib as part of AML induction regimen?	I need more data	FLT3 positive AML	All AML patients	No	
	44, 45%	43, 50%	2, 0%	10, 5%	6, 8%
6. In the era of Sorafenib, do you recommend allogeneic stem cell transplant for FLT3+ve AML?	Yes	No			
	91, 86%	9, 14%			10, 22%
7. Would you recommend Sorafenib maintenance in post-allogeneic transplant setting?	Yes, only if FLT3 remains positive	Yes, in all patients	No		
	74, 55%	10, 15%	15, 22%		9, 26%
8. Do you recommend allogeneic stem cell transplant in CR1 AML?	Only in High Risk AML	MRD positive AML	FLT3 AML	All of the above	
	25, 12%	4, 6%	0, 6%	71, 75%	12, 41%
9. Would you recommend allogeneic stem cell transplant in CR1 AML with diploid cytogenetics?	Yes	Yes, only if MRD positive	No		
	43, 53%	51, 27%	5, 20%		14, 44%
10. Do you recommend allogeneic stem cell transplant in CR1 Secondary AML?	Yes	No			
	95, 94%	5, 6%			13, 41%
11. Based on recent data, would you use Gemtuzuman ozogamicin (e.g. Mylotarg) in AML induction?	Yes	No			
	38, 53%	62, 47%			14, 30%
12. Do you use NK Cell Therapy in treatment of AML?	Yes	No			
	28, 12%	72, 88%			21, 41%
13. Do you routinely offer intrathecal therapy to AML patients with CNS involvement?	Yes	No	Only if CSF < 5 Blasts		
	91, 76%	2, 24%	7, 0%		19, 37%
14. What is your induction regimen for APL?	ATRA/Arsenic	Daunorubicin/ATRA	Clinical Trial		
	78, 29%	19, 59%	3, 12%		14, 37%
15. If available, would you use oral versus intravenous arsenic?	Oral Arsenic	Intravenous Arsenic			
	74, 75%	26, 25%			15, 40%
16. Are you concerned about cardiac side effects of Arsenic Trioxide?	Yes, in all patients	Yes, only in older patients	No		
	60, 63%	33, 31%	7, 6%		16, 41%

^a Percentage of survey takers who did not respond to each question, i.e. the "No response" counts, were removed from the data prior to calculating the percent responses for the other answers. Thus all other response values are given as a percentage of affirmative respondents.

^b Two values are given for each possible answer: percent of Chinese respondents is listed first, followed by percent of non-Chinese respondents.

Table 1: AML survey questions and response rates.

Allogeneic Stem Cell Transplantation (SCT) for FLT3+ve AML. Several studies demonstrate a potential benefit of SCT in patients with poor prognoses due to FLT3 mutations [5]. Nevertheless, relapse was common in these patients. A majority of our respondents (74% China, 55% other) would recommend Sorafenib after SCT only if the FLT3 positive diagnosis persists, with a smaller group (10%, 15%) favoring Sorafenib after SCT in all cases. Nearly three quarters (~72%) of all respondents recommend SCT in all cases of CR1 AML, while most of the remaining physicians reserve this treatment for high-risk patients. For instance, among the physicians we surveyed, many would recommend SCT in CR1 AML with diploid cytogenetics (43% China, 53% other), especially in patients showing minimal residual disease (MRD, 51% China, 27% other). For CR1 secondary AML, the opinion in favor of SCT is nearly unanimous (95%).

Less popular treatments for AML included Gemtuzuman ozogamicin (GO, e.g., Mylotarg) or NK cell therapy. In both cases, over 50% of physicians would not recommend these options. Still, over a third of survey respondents would use GO. This drug has been voluntarily removed from the U.S. market following reports of some

harmful side effects. But physicians in the West and in Asia see a utility for the treatment, especially in older patients who cannot tolerate the toxicity of aggressive chemotherapy regimen [6,7]. Only about one quarter of all survey respondents were inclined to use Natural killer (NK) cell therapy in treating AML. NK cell therapies must overcome numerous limitations, such as *in vivo* survival and target specificity, before becoming a more widely used and viable treatment for AML [8].

CNS involvement in AML is rare, but we lack sufficient data to know just how infrequent or possibly overlooked this condition actually is. Most survey respondents routinely offer intrathecal therapy for AML patients with CNS involvement, especially physicians from China. Intrathecal induction is highly recommended by the NCCN guidelines [1]. Meanwhile, the results of a recent retrospective, single-institution study challenge the necessity of targeted CNS therapy versus modern approaches such as SCT [9]. Given the rarity of these cases, additional retroactive data analyses that consider past and modern treatments will be vital to clarifying the best approach.

We also asked physicians about their induction regimen for Acute

Promyelocytic Leukemia (APL). Ninety-five percent of all respondents recommended a course that explicitly includes all-trans retinoic acid (ATRA). This group was split between ATRA+arsenic trioxide (ATO, 78% China, 29% other) versus ATRA+daunorubicin (19% China, 59% other). Both are valid alternatives under varying circumstances, supported by considerable clinical data and recommended by the NCCN [1,10,11]. Recent non inferiority studies have shown that ATRA+ATO may offer advantages such as decreased adverse events and hematologic toxicity in low- to intermediate-risk APL patients [12].

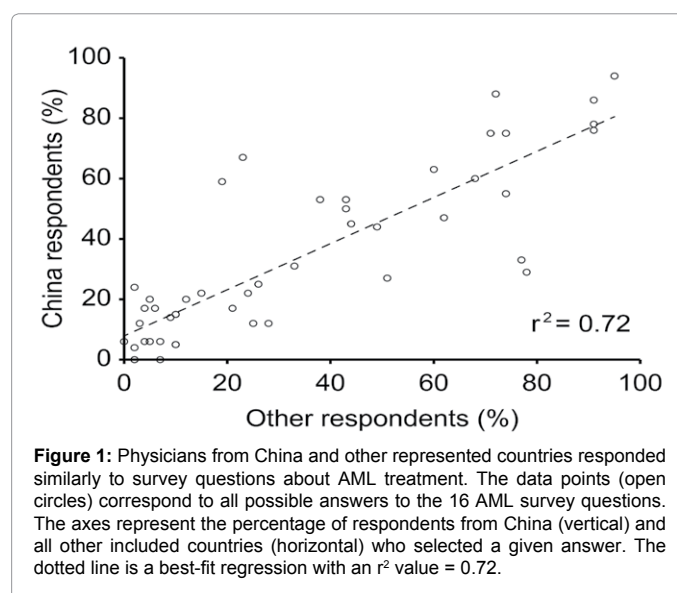
In administering ATO, 75% of all survey respondents say they prefer oral to intravenous arsenic. Over 60% of physicians are concerned about cardiac side effects of ATO irrespective of patients' age, and another 33% of respondents are concerned in older patients. Thus over 93% of all survey respondents expressed some concern over this widely employed and efficacious treatment. These trends were nearly identical between respondents from China and other nations, and underscore a desire among physicians for an ATO-based treatment with less potential for deleterious side effects.

Overall, the trends in treatment preference were quite similar among physicians regardless of nationality (Figure 1). Few questions showed a marked difference based on nationality: whether to use GO; which HMA to administer; what conditions warrant SCT in CR1-AML; and the use of ATO or chemotherapeutic in conjunction with ATRA to treat APL. The high level of global accord in the survey reflects successful communication of standards of care and the willingness of physicians of various backgrounds to integrate new ideas into their thinking. The high level of agreement allows us to readily identify questions of diagnosis and treatment that lack consensus, and to highlight areas that need more research, more clinical data, and better communication among our colleagues.

Patient care in burgeoning populations improves dramatically when more physicians are represented in the global knowledge base. We believe our survey takes a giant step toward giving underrepresented physicians a greater voice in the worldwide conversation.

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