Japan Adult Leukemia Study Group

JALSG

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目次

上海血液学研究所創立 25 周年記念会に出席して

愛知県がんセンター　名誉総長、NPO 法人　JALSG 支援機構理事長

大野竜三

上海血液学研究所創立 25 周年を祝う記念式典が 2012 年 10 月 20 日に開催され、1990 年以来の交流の誼で招待され出席した。APL に対する ATRA の効果を始めて報告した上海第二医科大学（現、上海交通大学）の血液研究所であり、時の中国厚生大臣が前所長の陳竺（Chen Zhu）博士であることもあって、盛大な記念式典であった。86 歳になられた初代所長の王振義（Wang Zhen-Yi）先生もご健在であり、2010 年に中国最高技術賞を受賞され、今も回診などを続けられているとのこと。記念誌に寄稿した「ATRA story in Japan: Journal of Clinical Oncology rejected our paper as“unbelievable”in 1991」（この号に添付）を是非ご一読いただき、当時の事情を知っていただければ幸いである。

中国厚生大臣：前所長の陳竺（Chen Zhu）博士

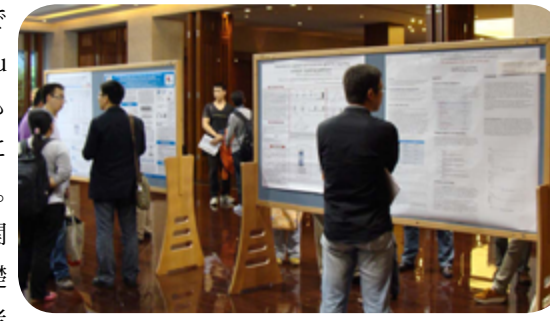
初代所長の王振義（Wang Zhen-Yi）先生

The 13th International Conference on Differentiation Therapy に出席をして

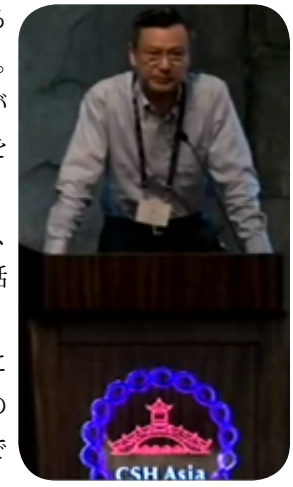
藤田保健衛生大学　恵美宣彦

10 月 21 日より 24 日まで中国蘇州で行われた第 13 回国際分化誘導療法会議に直江先生と品川先生とで出席してきました。大野先生は前日より行われていた上海血液研究所の記念の会に出られており、蘇州のホテルで合流となりました。

出発前は折からの日中関係の悪化により大変心配していたのですが、行ってみると特に不自由もない環境で快適に過ごすことができました。上海空港から会場の Dushu Lake Hotel まではタクシーで約 2 時間かかり、片側 6 レーンもある高速道路のその両側には建設中のアパート群が次から次に現れて、人口の多さと市場としての規模の大きさに驚きました。



ポスターセッションでは、私と品川先生が JALSG の APL 関係のポスターを出しましたが、ほかのポスターがほとんど基礎的な研究であったこともあり、質問に来てくれた中国の研究者は、cosolidation とは何かとか、ヒ素はどうやって投与するのかと言ったような質問がでて、説明するのに苦労しました。oral session では、海外の演者の間に、中国の若手の発表が混じり、玉石混合でしたが、この会を通じて、中国の若手を育てようとする姿勢が見えました。



大野先生は、高齢者の APL 治療に関して、直江先生は、STAT3/5 inhibitor の講演を、品川先生もポスターの内容を話しました。

3 日目の午後に、出席者全員で、世界遺産である拙政園にバスツアーとなりました。欧米の有名な研究者と若い中国の研究者がよい関係を作る意味でもよい機会と思いました。

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ASH 2012 での、JALSG 懇親会

宮脇先生より写真投稿

JALSG 懇親会は、先生方の発表が終わった月曜日 12 月 10 日の夜、1967 年に開業した老舗の南部料理のレストラン：Pittypat's Porch で開かれました。参加者は Award 受賞者の 10 名、大野先生、直江先生ほか , 総勢２５人が参加して下さいました。

ASH2012 に参加して

代表　直江知樹

今回の ASH では日大・入山先生が AML97 データを用いた t(8;21) における CD56 の意義を、済生会前橋病院・佐倉先生が ALL204-u の結果を、京都府立医大・滝先生が t(8;21) のデータについて日韓比較解析を、それぞれポスターで発表された。岡大・品川先生は APL204 の結果を口演で発表されるはずであったが急遽、小生が代役を務めた。初めての ASH 発表であり緊張したが、発表後の反響も大きくまずはホッとした。彼にとっては残念きわまりないことであろう。一日も早くお元気になられることを祈っている。

さて、ASH には出席するとかならず得られる何かがある。欧州やアジアからの出席者も多い。プレナリーやポスターに集まる聴衆の圧倒的な多さを眺めながら、内容のレベルの高さと熱気、International でありかつオープンであることがその理由であろう。このことは若手ほど感じるようで、朝 7 時に会場に集まる姿を見てさぞ驚いたことであろう。毎年口演に選ばれることは難しいかもしれないが、今後とも演題を多く出し続けること、そのことが JALSG 力をアピールすることになろうと確信を持った ASH であった。

施設紹介

横浜市立大学附属市民総合医療センター

横浜市立大学附属市民総合医療センターは、旧横浜市立大学附属浦舟病院を再整備し 2000 年 1 月にスタートしました。病床数は救急棟を含めて 726 床です。このうち血液内科は準無菌室 16 床を含む 30 床で、他に中央無菌室が 4 床備わっております。また、9 部署の疾患別センターと 18 の専門診療科を擁しており、高密度な総合医療を実践しております。現在血液内科のスタッフは血液専門医 7 人(指導医 4 人)を含む 8 人で、卒後 15 年以下の医師が 6 人と若手が多いのが特徴です。JALSG 運営委員は藤澤信部長で、PhALL208 プロトコール委員長も勤めております。2000 年からの新患患者数は急性骨髄性白血病 257 例、急性リンパ性白血病 72 例、慢性骨髄性白血病 111 例、骨髄異形成症候群 381 例、悪性リンパ腫 784 例、多発性骨髄腫 218 例などです。2000 年 1 月から 2009 年 12 月までの 10 年間の累計で、65 歳未満の急性白血病の完全寛解率は 82.5% で 5 年生存率は 58.4% でした。横浜市の人口は約 370 万人と非常に多く、近隣の施設からたくさんの患者さんをご紹介いただき JALSG の様々なプロトコールにも積極的に参加しています。

また、造血幹細胞移植も積極的に行っており、2000 年から 2011 年までに施行された症例数は 237 例で同種移植が 157 例、自家移植が 80 例でした。最近では年間 20-30 例の移植を行っております。急性骨髄性白血病の第一寛解期の同種造血幹細胞移植の 5 年生存率は 68.3% でした。横浜市立大学関連 4 施設での同種造血幹細胞移植が 2012 年 7 月に 1000 例に到達しました。今後は同種移植の症例数をさらに増やせるようにできればいいと思っています。

当院はみなとみらい、および横浜中華街に近く、ちょっと足を伸ばせば鎌倉・江ノ島もありとても立地に恵まれています。当院での初期研修、後期研修に興味をお持ちの先生がいらしたら、是非ご連絡をいただければと思います。

スタッフ写真：前列左から、田中、藤澤部長、桑原、後列左から沼田、本橋、立花、岸本、中嶋

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●第29回JALSG幹事会、平成24年度第2回直江班・小林班合同班会議、JALSG運営委員会が、行われました。

日時：平成24年12月15日（土）8：30-16：00

場所：名古屋大学医学部附属病院新中央診療棟　3階講堂

会議のあとで、集合写真をとりました。

会議予定

- 2013/2/23(土)　第17回JALSG研修会
  於：グランドプリンスホテル新高輪（品川）
- 2013/6/（土）　平成25年度第1回直江班・小林班合同班会議
- 2013/10/10(木)　日本血液学会学術集会
  於：ロイトン札幌

編集後記

今回は、海外出張コラムを載せました。是非先生方も、海外出張の写真や感じたことを書いていただければ投稿をお願いします。記事を集めるのに苦労をしています。今後とも御協力をお願いします。

教育・広報委員長　恵美宣彦

成人白血病治療共同研究グループ（JALSG）
事務局：〒431-3192 浜松市東区半田山1-20-1　TEL/FAX:053-433-4993　mail:jalsgsc@hama-med.ac.jp
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発行日　　：２０１３・１・１

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上海血液学研究所創立 **25** 周年記念誌寄稿文

ATRA Story in Japan:
Journal of Clinical Oncology Rejected Our Paper as “Unbelievable” in 1991

Ryuzo Ohno, M.D.
President Emeritus, Aichi Cancer Center, Nagoya, Japan

It was in June 1990, at the Second Joint Meeting of Japanese and Chinese Societies of Hematology held in Nagoya, when I first encountered the epoch-making results of all-trans retinoic acid (ATRA) on acute promyelocytic leukemia (APL) from Shanghai Institute of Hematology. Already in late 1988, we had read the astonishing article published in *Blood* by Huang et al., which stated that 22 of 23 patients achieved complete remission (CR) by ATRA alone[1]. Our concluding comment on this article was actually “hard to believe”, I must confess. In that era, APL was the most difficult leukemia to treat, and I often remarked that the hospital room treating APL patients resembled a field hospital, where patients were bleeding from every part of their bodies, their blood spilling all over bed-sheets and floor. Naturally, to read a report of 96% CR by orally administered Vitamin A for these ill-fated patients was not easy to believe.

During the meeting, Prof. Wang Zen-Yi presented the result of 90 relapsed or previously untreated patients with APL, and reported 88% CR in 76 patients who were treated with ATRA alone. Although 20 or so cases in the previous article was considered too preliminary, his 76 was an imposing number. At that stage, I felt convinced that this was true. Having been the chairperson of the Leukemia Study Group supported by the Ministry of Health and Welfare since 1988, I was eagerly searching for a novel therapy for leukemia, and decided to try ATRA for APL in this Study Group, of which Japan Adult Leukemia Study Group (JALSG) established in 1987 was main body. During the evening party, I asked around my Japanese colleagues about Prof. Wang’s presentation, but not everyone was positive. Prof. Wang had brought ATRA by himself and, at the party, so generously gave me a bottle of ATRA containing enough tablets to treat one patient.

After the meeting, I immediately wrote the protocol to treat relapsed or refractory APL, and got the approval of the Study Group to proceed in July. As for ATRA, I first tried to import them officially, but soon realized that the import of any drug via official route from China then was extremely difficult and time-consuming. Therefore, appreciating the generous offer by Prof. Wang, I looked for some acquaintances who happened to visit Shanghai for sight-seeing or business, and begged them to go to Rui-Jing Hospital to visit Prof. Wang, who again so generously gave me ATRA as a gift. Thus I was able to secure enough ATRA for the prospective trial. Without Prof. Wang’s help, we could not have carried on our APL

clinical study in Japan so early, following Shanghai and France.

By the way, 1990 for me was a very memorable year for another reason. My article, reporting the first prospective randomized study of G-CSF in AML patients, was published in *New England Journal of Medicine* that year[2]. This was the first clinical study from Japan ever published in this prestigious journal, and it made me internationally recognized in our field.

In October 1990, the first APL patient was enrolled from a hospital in Nagoya, followed by the second in Hiroshima in November, but they turned out to be failure cases. Both patients had relapsed and refractory APL with more than 10,000/μL leukocyte count, and both doctors who treated them reported to me that the drug rather aggravated APL by increasing the number of leukocytes, and stopped ATRA within a week. Later, we realized that these 2 patients plausibly had hyperleukocytosis by ATRA therapy, but this phenomenon was unknown at that time. One of them, a famous hematologist specializing in leukemia treatment, even said to me the ATRA story might be a fraud, but I remained unwavering.

The third patient was enrolled from Nippon University Hospital in Tokyo at the year end of 1990. This APL was relapsed and refractory to intensive re-induction chemotherapy, showing 5,100/μL leukocyte count and 35% leukemia blasts with Auer rods in bone marrow at the start. Toward the end of January 1991, I got a phone call from Dr. Toshiteru Ohshima who was one of the 3 founders of JALSG, and his excited voice informed that this third patient achieved CR by ATRA alone. The news immediately spread across our community, and successively more patients were enrolled. Our major problem was the drug supply, but Prof. Wang was always so generous to provide us ATRA as gifts.

By May 1991, 26 patients of age 8 to 74 were enrolled, but 4 patients received concomitant chemotherapy due to increasing leukocyte counts soon after ATRA therapy and, although all 4 achieved CR, were excluded from the evaluation. Thus, 18 (82%) of 22 evaluable patients achieved CR by ATRA alone, including two newly diagnosed elderly patients who achieved CR. Morphological evidence of differentiation was noted in all CR cases. Toxicities attributable to ATRA were minimal, and patients achieving CR received standard consolidation and maintenance chemotherapies.

We found that initial peripheral leukemia blast counts were significantly less in CR cases ($p < 0.01$). Seventeen patients with initial leukemia blast count of less than 200/μL all achieved CR, while only one of 5 patients with that of 200/μL or more did so. With this new observation which had not been reported from China or France, I wrote a manuscript reporting this amazing result obtaining 82% CR with ATRA alone in 22 patients with mostly relapsed/refractory APL by the first multi-center prospective study, and submitted it to *Journal of Clinical Oncology* in May 1991.

Editor's response, however, was very far from my expectation. Two reviewers simply rejected our manuscript with no chance for revision, by just bluntly commenting "unbelievable". Of course, I quoted not only the first paper by Huang et al. but also the paper

by Castaigne et al. from the French group in 1990, which reported 65% CR in 22 patients with APL [3]. Normally I never argue back against the final decision of editors when they reject our manuscripts, but against this decision I protested immediately as a member of American Society of Clinical Oncology. I wrote a cursing letter to then Editor-in-Chief, Dr. George P. Canellos, who happened to be a hematology oncologist, stating strongly that *Journal of Clinical Oncology* would doubtless regret to have regarded the ATRA treatment as "unbelievable". I am confident they did regret soon afterwards, because in that same year *New England Journal of Medicine* published the paper by Dr. Warrel et al., reporting 82% CR in 11 US patients with APL[4].

From June 1991, Hoffmann-La Roche in Switzerland started to provide ATRA to us, which I personally imported via an official route on behalf of the Leukemia Study Group of Ministry of Health and Welfare, and we initiated the second study of ATRA therapy on relapsed or refractory APL. Learning from the first study with Chinese ATRA, we planned, if initial leukemia cell counts were 200/μL or more, chemotherapy with daunorubicin (DNR) and behenoyl cytarabine (BHAC) was first given, and then ATRA was started. Of 44 enrolled patients of age 6 to 78, 2 received concomitant chemotherapy and were excluded from the evaluation, although both had achieved CR. Thus 36 (86%) of 42 evaluable patients achieved CR by ATRA alone. All 5 newly diagnosed elderly patients enrolled achieved CR. The manuscript of these 2 multi-center prospective studies was submitted to *Leukemia* in December 1992, and published in November 1993[5].

In 1992, JALSG started a multi-center prospective APL92 study with ATRA for newly diagnosed patients with APL, which was imported personally by me from Hoffman-La Roche. In this study, APL patients with initial leukocyte count less than 3,000/μL were treated with ATRA alone, and those with 3,000/μL or more received ATRA daily with DNR for 3 days and BHAC for 7 days. If patients' peripheral leukemia blast counts exceeded 1,000/μL during ATRA therapy, chemotherapy with DNR and BHAC was added. Of 109 patients aged 16 to 74, 97 (89%) achieved CR, and the predicted 23-month disease-free survival of CR patients was 81%. This study treating the largest number of newly diagnosed APL patients at that time was published in *Blood* in March 1995[6].

Meanwhile, Nippon Roche Co. initiated their own study on APL with ATRA monotherapy for the governmental approval with me as the chief investigator. Twenty-one patients were relapsed from or refractory to chemotherapy, but knowing such an astonishing results from our previous studies, the agency agreed to enroll 6 newly diagnosed elderly patients. Of these 27 patients, 82% obtained CR. Another 11 patients who relapsed from previous ATRA therapy were retreated with ATRA alone, but only 36% achieved CR. Thus, the Ministry of Health and Welfare approved ATRA for both relapsed/refractory and newly diagnosed APL in December 1994. I believe that this governmental approval of ATRA was the first in the world, except China.

I happened to be a member of the advisory committee for drug approval by the Ministry of Health and Welfare at that time, and I remember one episode during the approval process. All advisory members but one agreed with the proposed approval of ATRA on APL owing to its remarkable effectiveness. This one was an expert of teratogenicity who strongly argued against the approval, insisting that, because ATRA is a reference drug used in animal experiments which induces teratogenicity in all animals, ATRA should never be a drug for clinical use. Actually, before 1991 Hoffmann-La Roche had given up ATRA due to its teratogenisity, and instead provided 13-cis retinoic acid for clinical study. Great effort was needed to dissuade this expert, and I argued that childbearing by female APL patients was unthinkable even for chemotherapy because of teratogenicity, and that they would undergo artificial abortion by all means. I also added that APL was a dreadful disease with terrible bleeding tendency and without ATRA or chemotherapy patients would die within a month, and that patients with active APL would have no chance to deliver a healthy child. Finally with a condition that a strong warning against pregnancy is added, the expert agreed, and from January 1995, ATRA became available to all APL patients under National Medical Insurance.

The ATRA story of Japan, which originated from the generousity of Prof. Wang, contains a chapter on its great contribution to the expansion of JALSG. JALSG was established in 1987 by members of only 14 institutions with myself as chairperson and Drs. Masao Tomonaga and Toshiteru Ohshima as co-chairpersons, but when I became the chairperson of the above mentioned Leukemia Study Group of the Ministry of Health and Welfare in 1988, 9 other institutions belonging to this Study Group joined JALSG. Then, the publication of G-CSF study in *New England Journal of Medicine* in 1990 plus the spreading news of ATRA directed a spot-light on JALSG, especially because ATRA was only available in Japan for newly diagnosed APL through the JALSG APL92 study till January 1995. Therefore, the number of institutions belonging to JALSG was doubled to 51 with a total of more than 100 hospitals by 1996.

In order to enhance collaboration, I applied for an international collaborative study grant of the Ministry of Education between our group at Nagoya and Hamamatsu Universities and Prof. Wang's group at Shanghai Second Medical University. We were given a 2-year grant twice, starting from the fiscal year of 1993. With this grant, Profs. Tomoki Naoe, Kazunori Ohnishi, Akihiro Takeshita and other young doctors, as well as myself, were able to visit Shanghai Institute of Hematology, and we invited several young doctors from Shanghai. Profs. Chen Zhu and Chen Sai-Juan were the first visitors coming to Nagoya and Hamamatsu in 1994, which I understand was their first trip to Japan.

My visit to Shanghai with Dr. Takeshita in 1996 provided a rewarding addition to our ATRA story. Prof. Wang took us for a hospital round and introduced to me a Japanese patient with ATRA-refractory APL who came from Osaka to receive arsenic trioxide. The smear-slides of

his peripheral blood after the therapy, which Prof. Wang showed us, revealed differentiated neutrophils indistinguishable from ATRA treatment. Here, I encountered the amazing effectiveness of arsenic trioxide on APL for the first time.

After returning home, I planned a clinical study of arsenic trioxide on relapsed/refractory APL patients, and wrote a protocol. The institutional review board (IRB) of Hamamatsu University, however, did not approve the clinical study with arsenic trioxide, saying that preclinical toxicity data of arsenic trioxide was insufficient. In fact, the IRB was not courageous enough to allow us to use this well-recognized toxic substance clinically for the first time in Japan. Our protocol explicitly stated that the independent safety-monitoring committee would review all possible candidates for the treatment and judge whether the arsenic trioxide therapy would be the last treatment modality for each patient. The citizen members of IRB rather encouraged the clinical study for these desperate patients, but it took 3 years till the IRB finally approved the clinical study with arsenic trioxide which was provided by PolaRx in USA. Nonetheless we were the first to find that arsenic trioxide prolonged the QTc interval while receiving this treatment[7].

Today more than 80% of Japanese patients with APL are cured with ATRA-based therapy, with additional arsenic trioxide and tamibarotene, a synthesized retinoid[8, 9]. Moreover, we calculated that ATRA cuts national medical costs by approximately one billion Japanese Yen annually, owing to its low adverse events including lower incidence of infection and thrombocytopenia, as compared with the chemotherapy era[10].

Thus, patients with APL worldwide are greatly indebted to the Shanghai Institute of Hematology, and with pleasure and special gratitude I join the ranks of international researchers celebrating its 25th anniversary in 2012.

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