

Hematopoietic Stem Cell Transplantation and Chemotherapy for Patients with Hematological Malignancies in Kyushu University August 1- October 29, 2006

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Situation: The fellow of Takeda Science Foundation (TSF)

I am hematologist; work at Maharat Nakhon Ratchasima Hospital, Thailand. I received grant for studying 3 months in Japan from the medical association of Thailand supported by Takeda Science Foundation. My objective of study was Hematopoietic stem cell transplantation and chemotherapy for patients with

hematological malignancies in Kyushu University August 1-October 29, 2006. Many things in Japan are very interesting, life style, culture, developed technology, tourist place and my new knowledge.

I had many supervisors Ass. Prof. Abe Yasunobu, Ass. Prof. Muta Koichiro and Prof. Harada Mine (shared with other doctors in Prof. Harada group). I had a lot of friends, fellow of hematology, Dr. Sada Eriko, Dr. Ohtsuka Rie, Dr. Idutsu Kensaku, Dr. Kamezaki kenjiro and Dr. Tachikawa Yoshimichi.

My job in the Kyushu Hospital; I rounded patients in hematological ward and cleaned unit (stem cell transplant unit) with Hematological fellow, Sada Sensei, who is my friend, good mood, kindly, very clever, hardworking, an interpreter in many cases. I could speak little bit of Japanese language but could not read Kanji word. However I can round every case with other



ข้าพเจ้า และ คุณพ่อ คุณแม่ของข้าพเจ้าจากขวา
พญ. วัชรินทร์ ยิ่งสิทธิ์ศิริ นายบรรพต-นาง มริสรา ยิ่งสิทธิ์ศิริ

doctors. In the second week, I had my first patient who I took care with Dr. Kamezaki Kenjiro, who was kindly and good at stem cell transplantation. I had homework about reading the EBMT Handbook; I read it thoroughly in 3 week (22 Aug 2006) after that I summarized some parts of the book.

On Monday, I rounded ward with Ass. Prof. Abe at 9AM morning and at 3 PM afternoon stem cell transplant unit conference, on Tuesday 8.30 AM morning grand round the hematological ward with Prof. Harada and in the 5 PM evening round ward and see the slide bone marrow blood smear with Ass. Prof. Abe, on Wednesday 10 AM morning round ward with Ass. Prof. Muta and in the 5 PM evening hematological conference with Ass. Prof. Abe, Ass. Prof. Muta, on Thursday 1 PM afternoon conference about basic science, 3 PM grand round stem cell transplant unit with Prof. Harada, on Friday evening 5 PM round ward with Ass. Prof. Abe, on holiday visit my patients by myself.

The doctors in Kyushu hospital work very hard, start from 8 AM until 10 PM and do anything by themselves, for example, drawing blood from the

patients, giving medication and/on blood products to the patients, typing lab and treatment in computer and writing recorder, insurance and moving patients in wheel-chair or bed to other ward.

I am very impressed by good relationship between doctor and patient. It seems the doctors take care of their relatives. For example, I had one situation which I was very impressed, the woman in adult age who had EBV related lymphoma receive chemo-therapy and stem cell transplantation. During treatment, she had many complications from her disease and did not respond to medication. Her doctor work from 8 AM until at least 11 PM, no lunch time, took care of her and comforted her mother all of day. But any human has his own destination and time of life. The day when Taiphun occurred in September (18/9/2007) has heavy storm and rain, her clinical syndrome was too poor and her doctor took care of her all time and did not go home. On the final day of her life, it was very sad, all doctors in our group came to Kyushu Hospital for taking care her and supported her family until 11 PM. Every doctor and her family sent her body together. Before that her mother



Kyushu Hospital Kyushu University



Prof. Dr.Harada Mine

thanked every doctor. I appreciated both doctors, Ass. Prof. Abe Yasunobu and Dr. Sada Eriko. It was very sad event and I was very impressed by relationship between doctors and their patients. In my opinion I can't see the same event in other countries.

In Kyushu Hospital, the inner patient ward of medicine is very clean, there are rooms for 4 patients and separate room for high risk infectious patient (post chemo, neutropenia). The first time of my hematology conference, of 22 patients, just one had fever! ? I asked Dr. Muta "Why don't the patients have fever", he replied to me "because of the clean ward". I was very interested in that because in Thailand many patients have fever and sepsis and death but in Kyushu many patients have no fever after treatment with chemotherapy and they can receive stem cell transplantation.



แถวหน้าซ้ายไปขวา Dr. Ohtsuka Rie, Dr. Watcharin Ying-sitsiri, My supervisors Ass. Prof. Muta Koichiro, Ass. Prof. Abe Yasunobu

แถวหลัง ซ้ายไปขวา (Fellow of hematology), Dr. Kamezaki Kenjiro, Dr. Tachikawa Yoshimichi, Dr. Idutsu Kensaku, Dr. Sada Eriko

The stem cell transplant unit (clean unit) of Kyushu University, is sterile ward, 2 gates for sterile area. Every one when come in must wash his hands. There are 32 separate rooms with filtration with positive pressure. Every day, there are 28-30 patients in clean unit. I love these place because few patients die from hematological malignancies. If there is one death, it will be very serious. It is much more different from my experience (in Siriraj Hospital, and Udonthani and Maharat Nakhon Ratchasima Hospital). I very appreciate about the doctors and the health system of Japan.

With the help of my senior friend, Thai-surgeon, the first day I met the cafeteria of Kyushu Hospital, was the 7th of September, 2006. Firstly I thought Kyushu Hospital had no cafeteria because I saw every one have a lunch box on the table and ate it in 15 minutes and worked again. About the lunch boxes, someone prepare them from home while others buy them in the shop of hospital and I deposited the secretary of the laboratory room to buy it every day. S The cafeteria usually sells cheap foods with good taste.



Inner patient's room

I was very excited in my **new experience for stay in the Fukuoka city**. After finishing my activity from Kyushu Hospital in the evening even very few days in a month because almost all day the working hours usually lasted until 8 PM, I usually walked to the nearest shopping mall, behind the hospital. It took 15 min from the hospital to "You-Me Town (its Japanese language = the dream town)". Then I went to supermarket, buying some frozen foods, frozen prawns. I surveyed the cost of food the prawn was cheaper than squid and pork, probably Fukuoka city was close to the sea. I could see the ocean from the building of hospital. Every thing in Fukuoka was expensive than that of Thailand about 6-12 times, for example 1 plate of rice 400-800 yens (128-256 baht), noodle (MAMA) in the cup 190 yen (60 baht), public telephone 2 min/100 yen (32 baht).



Dr. Sada Eriko and me at Momoshi beach

In holiday I could go around the city by subway, very easily and safely. I often bought one-day ticket because it was cheap (600 yen/day) and I often lost way. I went to tenjin for sight seeing, shopping, meeting people, which was like Siam-square in Bangkok. Tenjin is the centre for shopping of Fukuoka city and centre of subway, train and bus. I went to "Daimaro shopping mall because some friends talked with me about it. I was disappointed by Daimaro shopping mall, it looked old and similar to other places.

I went to Hakata, the center of bus and train. I went to the cheap electric appliances shop "Yo do ba shi". It sells all of the electric appliances but most of them are expensive than that of Thailand except mobile-phone.

The first time, I had the dinner outdoors been Aug. 4, it was expensive but good experience. The seller could not speak English; I pointed the picture in front of the seller-counter. She gave a little machine to me when my food was already cooked, the little machine would have voice" beep-beep" then the seller would look at me. I had a hot rice with pork and egg but I wanted to eat noodle. I thought about the picture and looked at it again probably it was my mistake when pointing. Nowadays I can buy food by myself and I like Japanese food very much.

Sight seeing, the first time, I went to Momochi beach with my friend, Sadasung and his friend (Dr. Tinnouchi Mikako). Momochi was small beach but nice landscape. In the beach, someone were playing volleyball, someone were fishing but we did just walking, sight seeing and taking photographs. We saw the man play saxophone on the hill near the beach, it was very nice. Then we went by car again for getting our dinner. We

had the dinner at the Japanese restaurant near the sea at Marinao. We had the famous Japanese food “Okonomiyaki”. The Okonomiyaki restaurant had a table with hot electric pan for frying, the waiter serves fresh meat, fish egg, vegetable and flour then we cooked them on the pan. It was very delicious. After finishing, we went to play the Sky wheel, the biggest of Asia. We could see Fukuoka city in night time, the beautiful neon lights around the town and good weather, no rain, not cool.

I went to Nakasu (Hakata ward) with my friend, Sada Erigo by bus. It was very easy, comfortable and cheap (180 yen). The bus station was in front of Kyushu Hospital, most buses go to Tenjin. On the same road before Tenjin is Nakasu. I would like to go to Nakasu because it's recommended for traveler and I would like to eat Ramen noodles at Yatai. Ramen is the noodle look like “Ba-mee” in Thailand. The famous food of Fukuoka is Ramen.

We walked past Nakasu shopping center, the place you can buy anything with low price. I thought “Wow!! I met the shopping center for buying some things to Thailand”. Then we walked straight to many of Yatai food stalls, close to Naka River. My friend chose the ramen food stall and ordered food for us, surely Ramen noodle, one bowl of boiled meat ball, and one bowl of meat ball, beef, pork and grilled intestine. After being full, we walked by side of the river to the Hakata Riverain for dessert. The Hakata Riverain is the shopping mall sell brand- name, the 5th floor of the building sells international food. Because it has beer garden, German restaurant and USA restaurant. We had some desserts, very delicious, and sat down opposite the garden. I came back to my room by sub way.

I would like to explain about Tenjin, Nakasu and Ramen. I copy some words from the guide of Fukuoka city in the internet.

Tenjin (Chuo Ward) is Kyushu's number one downtown area, offers department stores, super market, fashion boutiques and many restaurants. Shop during the day, eat and drink at night. Everyday especially on weekends, Tenjin attracts people from all over Kyushu who want to take part in its excitement. It's very big place look like Siam square in Thailand but bigger. I have gone to Tenjin for 2 times.

Nakasu is the western Japan's biggest entertainment district. At night, it becomes a colorful maze of neon lights with lamps from yatai (food stalls) along the Nakasu River providing a charming row of lights. Enjoy the nightlife, take walk by the river, and look at neon lights from the building along the river. I loved this place but in this season it always rains, good for bringing an umbrella if want to walk out side.

The styles of ramen noodles vary wildly throughout Japan, but in Fukuoka tonkotsu ramen is the king. Made with a base derived from pig-bone, its noodles float in an opaque white soup with a distinctive (and addictive) taste and body. Ramen shops are everywhere throughout Fukuoka, ranging from state-of-the-art restaurants with electronic ordering systems to old-fashioned yatai (food stalls). I like ramen very much. It's delicious and not expensive 600 yen/bowl. The ramen noodle looks like “ba-mee” but bigger and a little bit softer, the soup is dense and a little bit salty. A seasoning consists of sesame, pink-pickled ginger, pepper and pickle. I dressed soup with sesame, very good taste, I like it very much.

Aso is volcano at Kumamoto, I went to Aso with my friends, Dr.Piya (Thai-surgeon), Dr.Shaun (Chinese-surgeon) and the important man of this trip Nobuhiro Torata because he was the only one Japanese, drove car, led tour and had very good manner. Aso is very beautiful, I can not explain. I have never seen the volcano before.

Tropical storm (Tai-phun) 18 August-17 October 2006, there had been Tropical storms (Tai-phun), very strong wind and heavy rain. I stayed in the building of my dormitory and hospital, I did not hear anything and felt safely. I appreciated the warning for Tai-phun and the strong buildings.

My new knowledge: Stem cell transplantation (SCT)

- Almost all hematological malignant cases treated by SCT, no limit of patient's age but limit donor's age, not more than 55 years.

- Collect stem cell from peripheral vein, not from the central vein, good result, adequate CD34 Stem cells.

- AlloSCT CD34 minimum $2 \times 10^6/\text{kg}$.

- AutoSCT CD 34 minimum $1 \times 10^6/\text{kg}$.

- Premedication before PBSCT: Methyl prednisolone 125 mg IV in 15-30 min.

- Central line after SCT transplant: hyperalimentation high calories

- Prevent veno-occlusive disease (VOD): Ursodeoxycholic acid 100 mg x 3 times/day start day -14 and LMWH 75u/kg day-6

- Acyclovir for prevent herpes

- Cyclosporine A for graft-versus-host disease (GVHD) twice a day, total 3 mg/kg to trough level 200 ng/ml, when patient has hematological response and

can eat the big tablet of cyclosporine, we can change form of drug.

- Check chromosome by bone marrow

- Check chimerism by peripheral blood

- Eosinophil rising is awareness about GVHD

occurrence

- MMF = immunosuppressive drug

- FK 506, Cyclosporin A: induce HypoMg

- BM for check chromosome

- Peripheral blood for check chimerism, CD3 T cell

- Hypercalcaemia after stem cell transplantation

=> disease relapses

- Case Multiple Myeloma

Autologous SCT: Melphalan (L-PAM) 200 mg /m² D2, no TBI

(In renal deficiency, amyloidosis reduce dose L-PAM 100 mg /m²)

Side-effect: mucositis

Auto + Allo: high TRM

Auto + Auto SCT: better

- Autologous SCT: Lymphoma, Multiple myeloma

PBSC 2 wks (D 10) engraftment

- noninherited maternal antigen (NIMA)



Mother



Father



patient 1



Donor 1



Patient 2



Donor 2

Patient receives blood or injury with blood of mother in fetal time, then if mismatch of mother, patient can tolerate.

- Choose SCT donor:

1. Relative allo stem cell
2. NIMA
3. Non- relative allo stem cell

Hematological Malignancy

- SIL-2 receptor (normal 400-700) for detecting T cell lymphoma, for screening Lymphoma in Japan. F/U disease by SIL-2 receptor. For example, (real case) the patient had just thickening of mucosa of intestine and thymus enlargement but no other lymph node enlargement and lab SIL 2 receptor was very high which diagnosed T cell lymphoma.

- Regimen of T cell lymphoma (resistance):
CHOP x 3 then CHAPS x 2 then autologous SCT

- THP-COP regimen used in patient who has problem about heart function

THP = Pirarubicin 50 mg/ m²

- T cell lymphoma Rx

CHOP x3 -> non-response, change to CHASE

CHASE regimen: Cyclophosphamide day-1

Ara C day-2-3

VP-16 day-1-3

Dexa day-8-10

- T cell lymphoma, Intestine after chemotherapy, usually results bowel stenosis, Rx by gastroscopie dilatation 3 times if failure removes mass

- The Ara C syndrome, it often occurs in Japanese patient who receives high dose Ara-C 3 g/ m² day-1, 3, 5. The Ara-C syndrome is erythematous rash, prevent by Methylprednisolone 150 mg/ day.

- AML M5a: 11q23+
- ATL Rx with CHOP-V-MMV
- NHL B cell Rx:

R-CHOP x 6 -> CR-IPI low: stop Rx -> 1st Relapse ->

Auto SCT

- IPI high: Auto SCT

- NHL T cell Rx:

CHOP x 6 then AutoSCT

- ATL Rx

CHOP x 3 courses-response continue CHOP until 6 courses

- Refractory -> CHASE 2-3 courses -> Allo SCT

- ATL/L (acute phase)

Regimen look like "CHOP"

CPA 150 mg/m²/day day-1-5

PSL 100 mg/m²/day day-1-5

ADR 50 mg/m² day-1

VCR 2 mg day-1

Other

- Platelet concentration 10 U = 70,000 yens (22,400 bath)

- MAP = Leukocyte-poor blood with radiation

- PAIgG (Platelet antibody IgG) lab positive in

ITP

- Treatment of ITP, fewer experience about splenectomy and vincristine. I talked with other hematologists in Thailand, splenectomy is performed in refractory cases or in bleeding in vital organs. Here treatment with high dose steroids then intravenous immunoglobulin (IVIG) and then Rituximab.

- Dose of G-CSF: AA 400 ug/m², Lymphoma 50-100 ug/m²

- â-D glucan (glycoprotein, light protein): lab for fungal infection

- MMF (mycophenolate mofetil) induce pure red cell aplasia

- Carbocysteine: Use for reduction of edema

from steroid. A neurologist has problem about amyloidosis and sleep apnea. He has pitting edema from steroid and he uses Carbocysteine for reducing edema.

- POEM has VEGF+
- Blood drawing: needle with wing+extension tube + vacuum tube
- Poly cythemia Vera found Jak2: Val 617 Phe (GTC -> TTC)
- C7- HRP = Ag of CMV +ve > 1/ 15,000 WBC
- Aplastic anemia: increased erythropoietin

- Virus association hemophagocytosis syndrome related with DIC (VAHS)

- HOMA-R
- = IRI immunoreactive insulin (*micronU/ml*) x FBS (mg/ml)/405 (<1.6 normal, >2.5 refractory insulin)
- Patients eat glucagons, then take their blood for checking insulin level at 0, 6, 10 min
- LDH type 1, 2 : leukemia, lymphoma
- LDH type 3, 4 : lung, liver
- LDH type 1, 5 : red blood cell