Introduction

The Network for Children with Chronic Myeloid Leukemia (CML) was established ten years ago. At that time, there were few places where information could be shared among patients and their families because patients with CML were quite rare. Since issues that children with CML have are different from adults, we established a separate network for children. Then, Ms. Onosaka and Ms. Maruyama who have had CML started to manage the network. As we talked with them, we learned about their experiences and the pathology specific to children. There are very few pediatric CML patients in Japan. We wrote this booklet hoping that the information could be shared with patients and their families.

As patients of CML ourselves, we are trying to make time to engage with the activities of our network while managing our other responsibilities. Above all, we have many supporters, health professionals including doctors and pharmaceutical companies. There must be people who do not know about this CML patient network or who carry the burden by themselves. We hope to deliver our messages to them: providing solid information and friends through publication. We hope to nurture the power to live by sharing wisdom like an *izumi* (a spring) that flows.

Izumi-no-kai, Hidehito Tamura
(Society for CML patients & families)

Understanding CML in Children

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1) Background of CML

Chronic myeloid leukemia (CML) was first reported in 1845 by a pathologist, Rudolph Virchow. The Philadelphia (Ph) chromosome was discovered in 1960, and in 1973 reported that it arises from a reciprocal translocation between chromosome 9 and chromosome 22. Then, a chimeric BCR-ABL gene accounting for the development of CML was found in the Philadelphia chromosome. Imatinib, a molecular targeted therapy for BCR-ABL positive CML, was developed by Brian Druker at the end of the last century. As such, CML has always been at the forefront of leukemia's history, from discoveries of the disease, causative chromosomal translocation and genetic abnormalities to the development of molecular targeted therapy.

After 20 years of launching the molecular targeted drug, imatinib, CML is no longer considered a serious disease requiring hematopoietic cell transplantation. The number of transplantation cases for patients with CML has sharply fallen since 2001 when imatinib became a treatment option. This means that one therapy, imatinib, has taken the place of more serious treatment, transplantation. However, unlike transplantation, CML is difficult to completely cure with tyrosine kinase inhibitors (TKIs) such as imatinib, which must be continued to intake. There are problems specific for children such that side effects of taking TKIs for decades and duration of the effect of the drug are unknown, and the costs of regular visits, examinations, and treatments are high. Further development of therapies is desired.

2) Epidemiology of CML in Children

CML primarily affects adults in their 40s and 50s, and develops in approximately 7 to 10 persons per million each year. CML is rare in children and accounts for approximately 3% of all cases of childhood leukemia. Approximately 20 children annually become new CML patients in Japan.

Association with radiation has been reported as a cause of CML, but there seems to be no causal relationships with drugs, chemicals, and infections with pathogenic factors such as viruses. The cause is unknown for almost all patients with CML except for radiation technologists and A-bomb survivors.

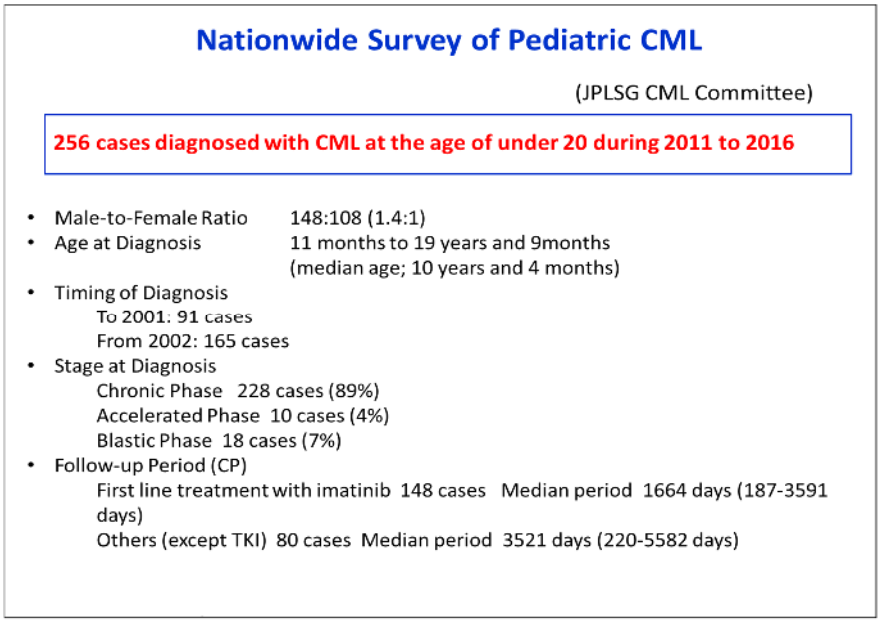

Figure 1

Although they are not recent, the results of the CML11 study conducted in 2011 by the Japan Pediatric Leukemia/Lymphoma Study Group (JPLSG) are shown below. Two hundred fifty-six patients under 20 years of age were diagnosed as having CML and enrolled in the study for 16 years between 1996 and 2011. Therapy was determined and provided at each facility.

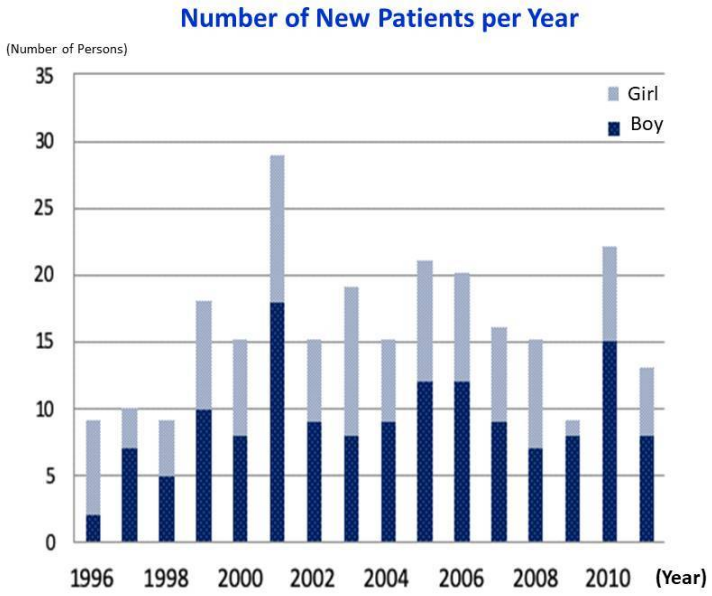

Figure 2

The male-to-female ratio was 1.4:1, and ages ranged from 11 months to 19 years. The percentages of stages at the primary onset were 89% for the chronic phase (CP), 4% for the accelerated phase (AP),

and 7% for the blastic phase (BP), with the advanced phased being approximately 10%. There were 10 to 20 new pediatric patients each year in Japan.

It should be noted in the age distribution that CML also occurs in infancy. Some patients were 11 months or 1 year old. As infants develop CML, although CML typically takes up to 10 years to develop, the mechanism of CML development in children may differ from adults. From the age distribution of pediatric patients, half are prepubescent. This is important for treatment. Children need different treatments from adults because children grow up with the disease. This is why pediatric-specific research is needed while therapies for them are according to those of adults. Patients at the ages of 15-19 years are fewer in number because they first visit hematologists, not pediatricians.

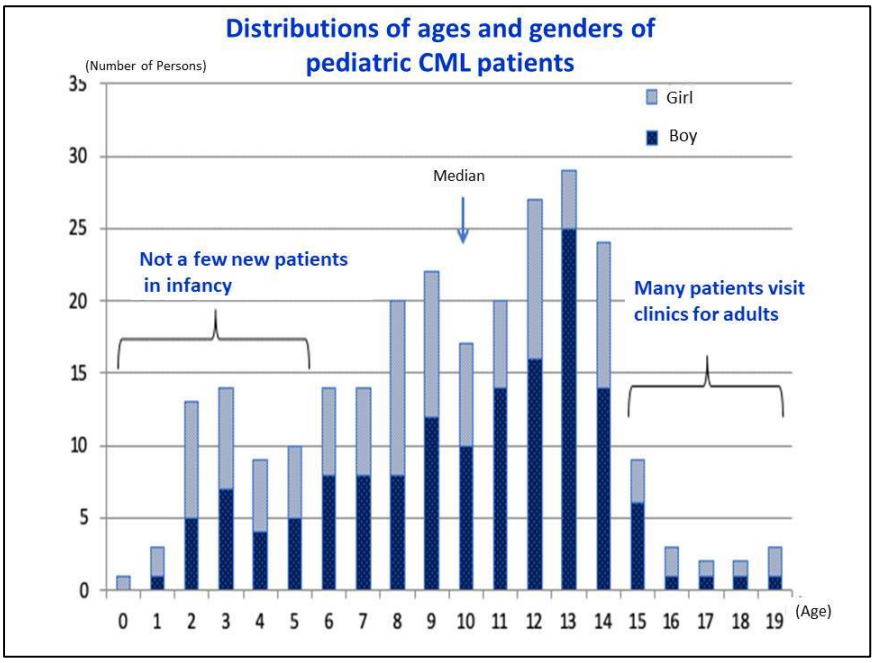

Figure 3

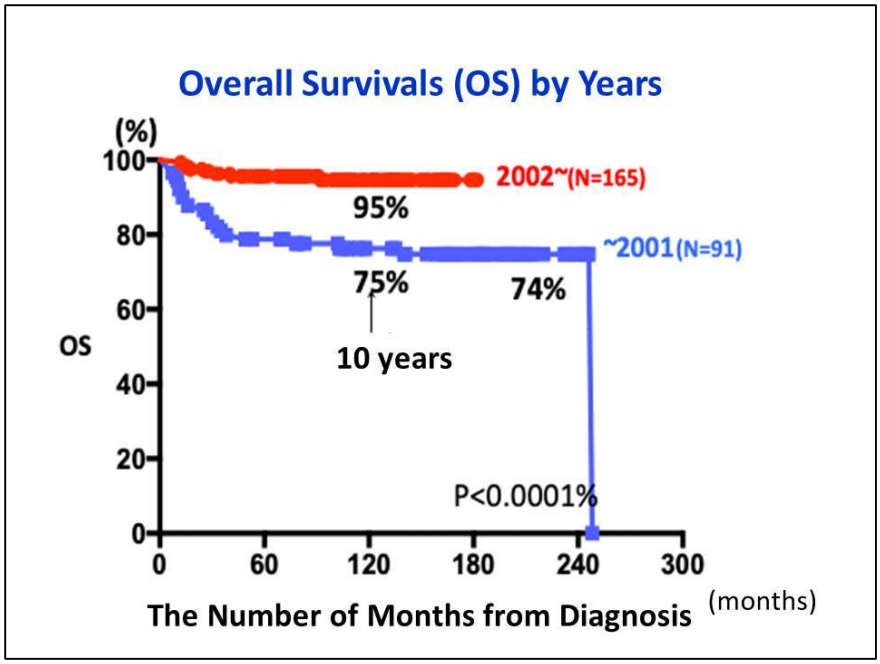

Figure 4

The numbers of patients with CML before and after December 2001, when imatinib was approved, specifically to 2001 and from 2002, are 91 and 165, respectively. Figure 4 shows the comparison of the overall survival before and after the approval. The 10-year survival was 75% from 1996 to 2001, and increased to 95% from 2002.

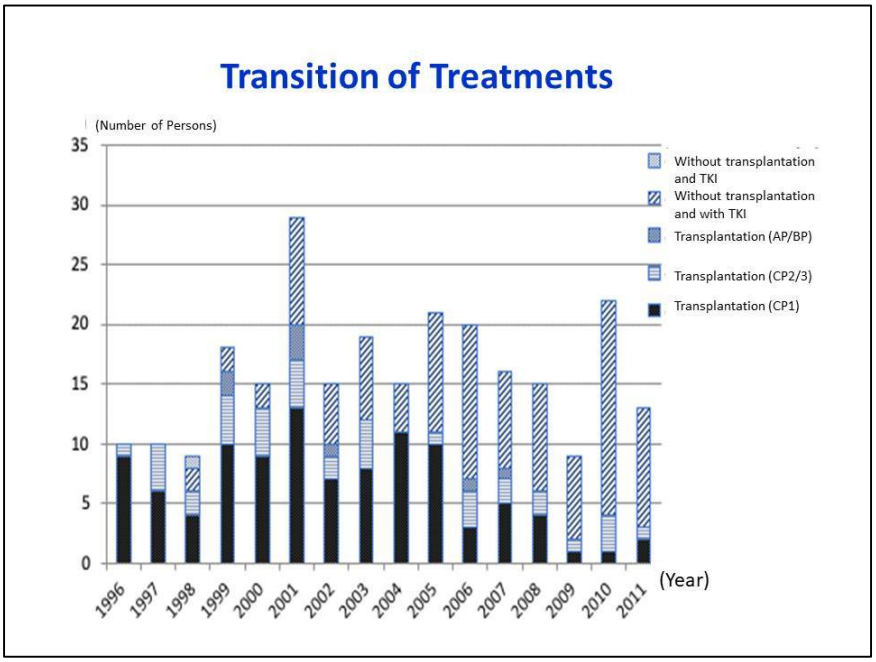

Figure 5

Next, we describe changes in the treatment, which are the major factors in improving the prognosis of patients with CML. Figure 5 shows the transition of treatments. Before the launch of imatinib in the 1990s, interferon (IFN) was used to treat patients in the chronic phase, but that was not enough to maintain the chronic phase, and hematopoietic cell transplantation was required. Since the approval of imatinib, the numbers of patients who need transplantation have dropped sharply, and more patients have been maintaining the chronic phase with oral TKIs alone. After 20 years of TKI therapies, including imatinib, most patients diagnosed with CML in the chronic or accelerated phase at the initial onset could start treatment with one of the TKIs. Only those in the blastic phase are considered to have transplantation from the start of treatment.

3) Onset Mechanism of CML in Children

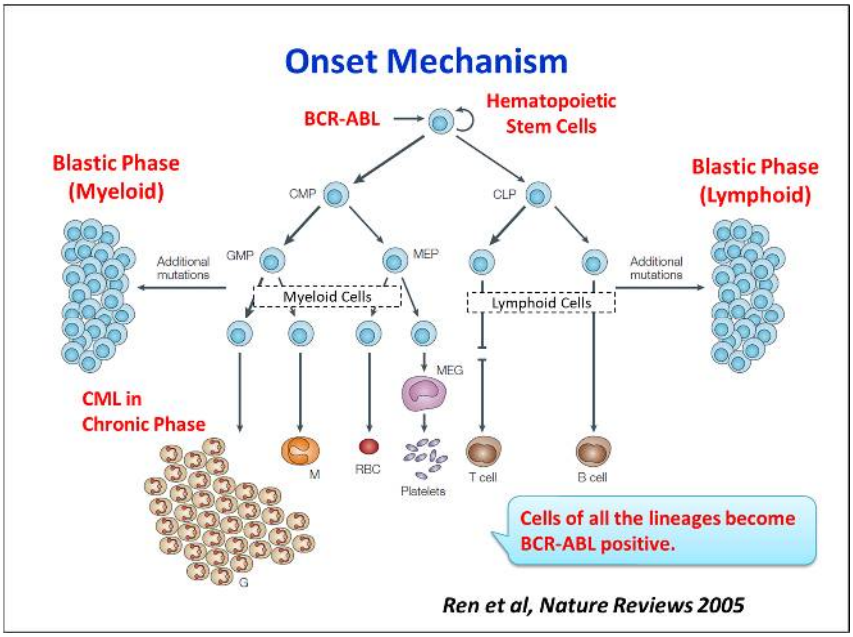

Figure 6

Blood cells are made in the bone marrow. Bone marrow has hematopoietic stem cells, which are the source of all blood cells, and differentiate into white blood and red blood cells and platelets. Once BCR-ABL genes develop in hematopoietic stem cells for some reason, hematopoietic stem cells start to abnormally proliferate while maintaining their differentiation potential. As a result, the numbers of platelets and white blood cells, especially neutrophils, increase aberrantly, and the spleen starts to swell. This is the chronic phase. Leukemia cell growth is triggered by an enzyme called tyrosine kinase produced by BCR-ABL genes, and TKIs inhibit the growth of leukemia cells by suppressing tyrosine kinase activity. Without appropriate treatment with TKIs, leukemia cells of CML eventually lose their differentiation potential, and the number of immature leukemia cells increases. This is the accelerated

phase. CML is characterized by the disease progression from chronic to accelerated and blastic phases, and hematopoietic transplantation is required in the blast phase.

4) Diagnosis of CML in Children

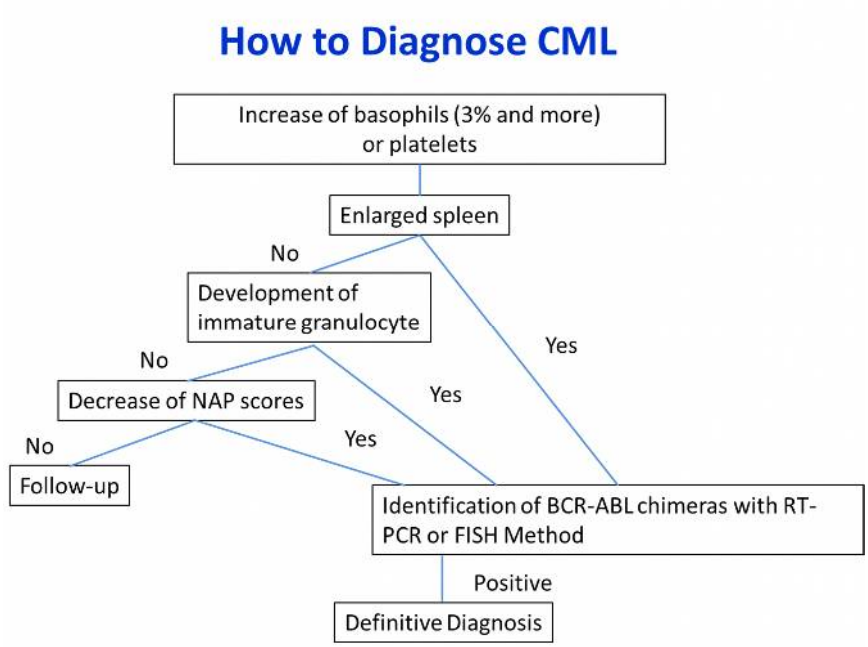

Figure 7

We see the differences between CML in children and adults at diagnosis in Figure 7. Symptoms are less likely to appear in children than adults, delaying their diagnoses. Let's see this difference in terms of white blood cell counts and the presence of an enlarged spleen.

In the IRIS study, a well-known clinical trial of adult patients with CML, the median leukocyte count at diagnosis was 17,900 /μl. However, the corresponding count in children investigated by the CML committee was 150,000 /μl, which is 10 times the count in adults. The enlarged spleen, which is one of the notable clinical presentations in CML, is found in 23% of adult patients but in 76% of pediatric patients. CML in children is often found when disease conditions have progressed. Approximately 10% of patients develop a complication, leukostasis, which is caused by congestion of the leukocytes due to the increase of leukocyte counts to hundreds of thousands /μl. Various symptoms including abnormal vision, priapism, dyspnea, headache, and body pain may appear, and then treatment must be promptly started.

The diagnosis of CML in children is often delayed because children do not have opportunities for regular check-ups including blood tests as adults do, and pediatricians are not familiar with CML so that they do not notice it without the enlarged spleen.

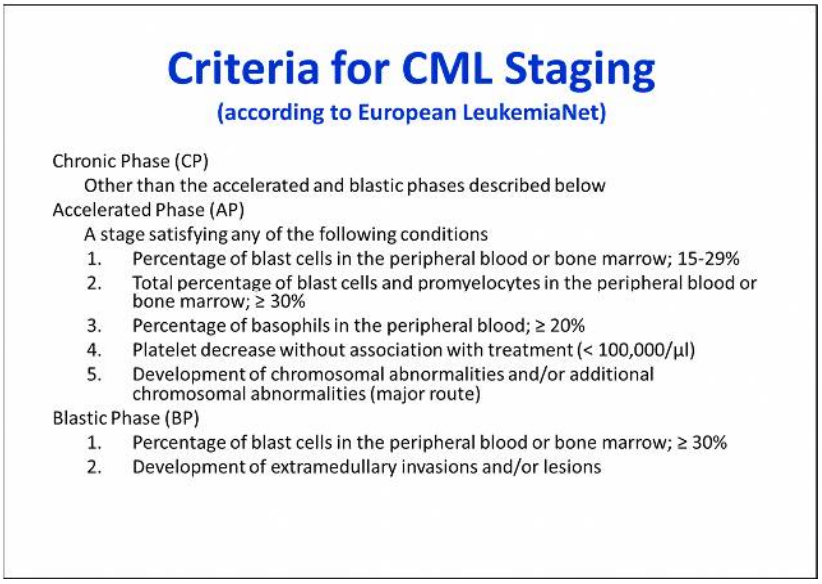

Figure 8

The question is when the disease develops. CML takes a long time for the onset. In adults, it takes about six years from emergence of the Ph chromosome in stem cells to the detection of the abnormalities by detailed examination, and two more years to find worsened results in blood tests for screening or enlarged spleen. Increases in basophils and platelets and a decrease in the neutrophil alkaline phosphatase (NAP) score is first detected in blood tests.

To diagnose CML, after a blood test finds increased numbers of basophils and platelets, the spleen will be examined to determine if it is enlarged. If the spleen is enlarged, a geneic test will be carried out for identification of CML. However, even if the spleen is not enlarged, CML cannot be excluded. If a type of young neutrophils, immature granulocytes, increase, CML is suspected and genetic testing will be performed. If BCR-ABL chimeric genes exist, the diagnosis is CML.

After CML is diagnosed, the next step is to determine the disease stage, which is crucial for deciding the most appropriate therapy. The criteria defined by the European Leukemia Net (ELN) is used to determine the stage. The early stage is the chronic phase (CP), which accounts for most patients with CML. Disease progression is slow and takes 5 to 6 years to evolve into the accelerated phase (AP). AP is the stage between the chronic and blastic phases (BP), during which the fraction of immature cells called blast cells in the peripheral blood and bone marrow increases. The speed of progression gradually increases, and the disease progresses to BP within 6 to 9 months. During BP, the number of blast cells increases and conditions like acute leukemia present. Even when conditions

in the peripheral blood and bone marrow indicate CP, patients would be diagnosed with BP if they have an extramedullary mass. Thus, patients should be scrutinized at the onset if they have a mass.

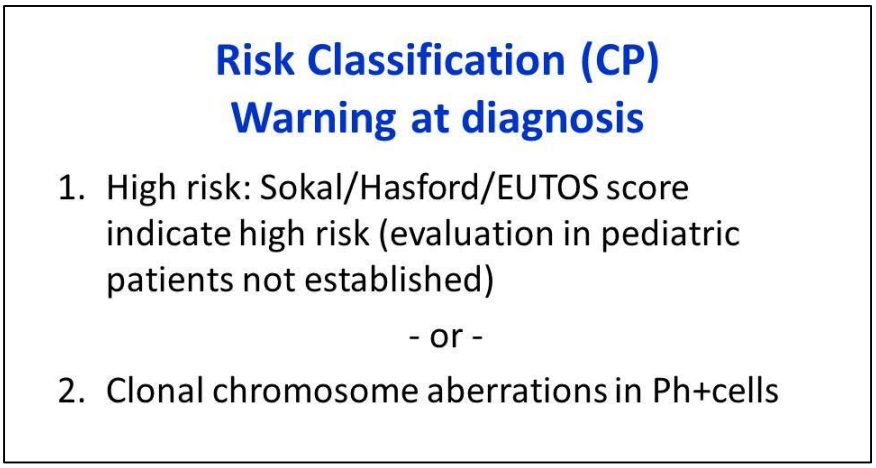

Figure 9

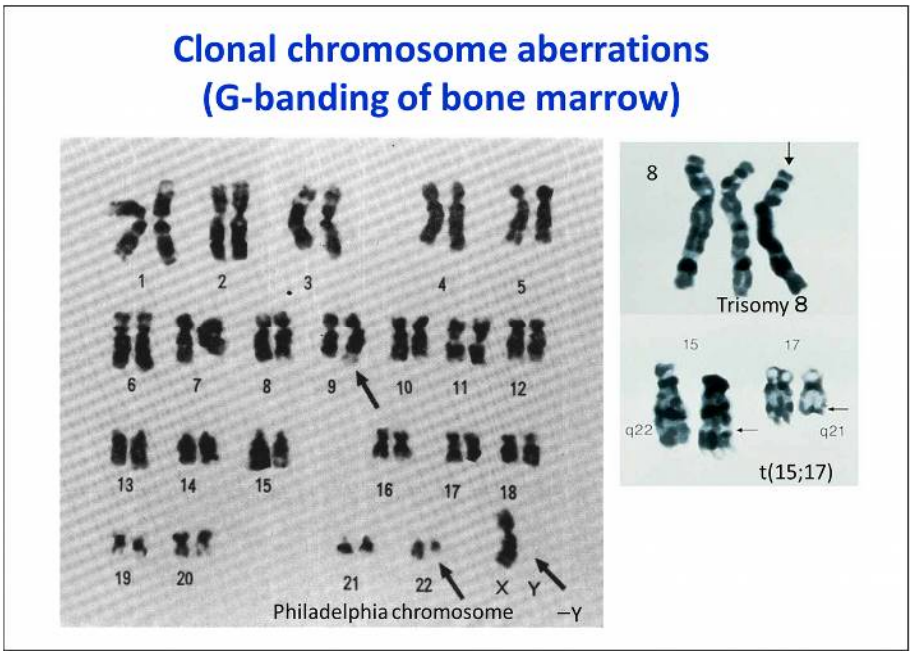

Figure 10

The ELN recommendations have a rating termed warning at diagnosis. Thus, patients must be evaluated whether the risk scores, which are calculated from the size of the spleen and the number of blood cells, are in the high-risk group (although the criteria for adults could not be applied to children), or if cells with Ph chromosome have other chromosomal abnormalities. When other chromosomal abnormalities such as those shown in Figure 10 are found, the disease might have progressed within the range of CP. Therefore extra caution should be taken, as it is more likely to progress to AP or BP.

5) Treatment for CML in Children

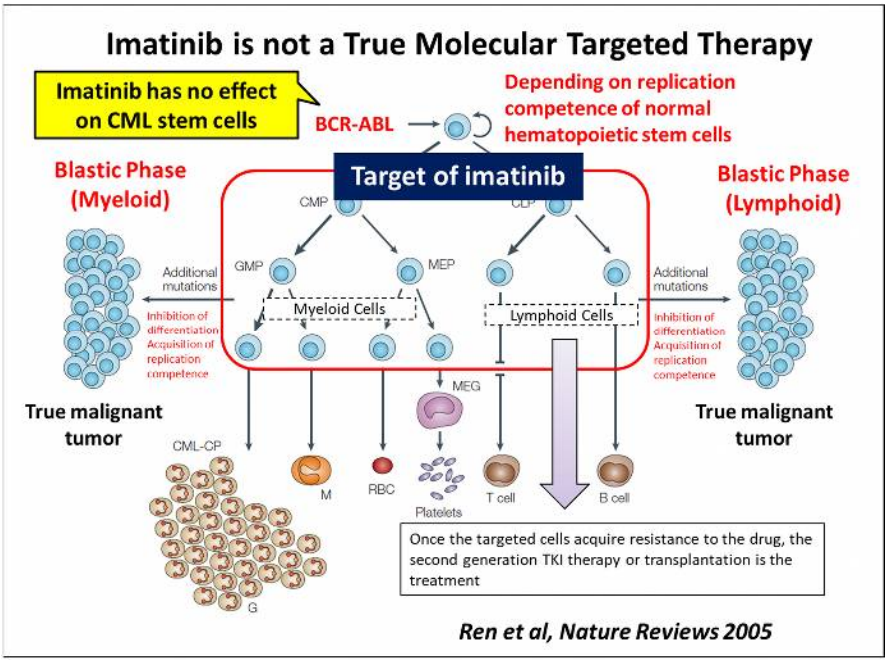

Figure 11

Imatinib is a type of TKI, which is molecular targeted therapy. TKIs block the active sites of tyrosine kinase in cells and inhibit the growth of Ph-positive cells having enhanced tyrosine kinase activity. TKIs do not target CML stem cells, which are the foundation of all cells. They target the early differentiated cells. By inhibiting the early cells, the cells that might turn into BP can be eliminated, and CP without clinical symptoms can be maintained. Since this procedure cannot eliminate the foundation, the disease relapses if TKI therapy ceases.

Response Evaluation Criteria and Therapeutic Strategy for Newly-Diagnosed and TKI-Intolerant Patients

Timing of Evaluation	optimal	warning	failure
At start of treatment		High-risk or Clonal chromosome abnormalities in Ph+ cells	
3 months after the start	BCR-ABL1 ≦ 10% and/or Ph+ ≦ 35%	BCR-ABL1>10% and/or Ph+ 36 to 95%	CHR not reached Or Ph+ > 95%
6 months after the start	BCR-ABL1<1% and/or Ph+ 0%	BCR-ABL1 1 to 10% and/or Ph+ 1 to 35%	BCR-ABL1>10% and/or Ph+ > 35%
12 months after the start	BCR-ABL1 ≦ 0.1%	BCR-ABL1>0.1 to 1%	BCR-ABL1>1% and/or Ph+ > 0%
Any time	BCR-ABL1 ≦ 0.1%	Clonal chromosome abnormalities in Ph- cells (-7 or 7q-)	Loss of CHR Loss of CCyR Conformed loss of MMR BCR-ABL1 mutation Clonal chromosome abnormalities in Ph+ cells
Therapeutic strategy	No switch required	More frequent monitoring should be continued and a therapeutic switch is required if response is failure	• In CP without T315 mutation, when the treatment starts with nilotinib or dasatinib, a switch to dasatinib or nilotinib is required, respectively. • When the disease stage progresses to AP or BP, or T315 mutation is detected, allo-HSCT is recommended.

Figure 12

Imatinib was the first-developed TKI and was approved for use in Japan in December 2001. Then, improved versions of imatinib called the second-generation of TKIs, dasatinib and nilotinib, were added. As of 2019, one of these three types of TKIs is used first when CML develops. The effect of the TKI used is determined by examination of levels of decrease in Ph chromosome and BCR-ABL genes in the bone marrow and peripheral blood respectively. The ELN criteria shown in Figure 13 are used to evaluate the effectiveness of the therapy.

After start of the TKI, effectiveness of the drug is evaluated every three months. The evaluation is performed using hematological response (HR), cytogenetic response (CyR), and molecular response (MR). In HR, complete hematologic response (CHR) means that blood counts in the peripheral blood have become normal. In CyR evaluated by the bone marrow chromosome test, a partial cytogenetic response (PCyR) means that the rate of Ph chromosome is reduced to 35% or less, and a complete cytogenetic response (CCyR) means complete disappearance. In MR evaluated in peripheral blood, major molecular response (MMR) means that the rate of BCR-ABL gene is 0.1% or less evaluated by the quantitative PCR (International Standard Method: IS)At present, the minimal treatment goal is to

maintain the MMR. MR can be measured in an extremely small amount with $MR^{4.0}$ of less than 0.01%, $MR^{4.5}$ of less than 0.0032%, $MR^{5.0}$ of less than 0.001%, which are collectively called deep molecular response (DMR) representing very deep remission.

Now, we will show the actual results of treatment based on the data. In the CML11 study, an analyis of 148 patients who started the first treatment with imatinib is included. The characteristics of patients are surmarized above in Epidemiology of CML in Children (figure 1). The median age was 10 years old. Since it was just after the launch of imatinib methods of treatment and follow-up varied from facility to facility. The recommended dose of imatinib was 260 mg/m^2 or more calculated from the adult dose, and approximately two-thirds of patients started with a dose that was greater than sufficient. The median follow-up period of this study was 1664 days, nearly five years, and some patients were followed for as long as 10 years.

First, we show the outcome of treatment and the prognosis by the achievement rate at each evaluation point.

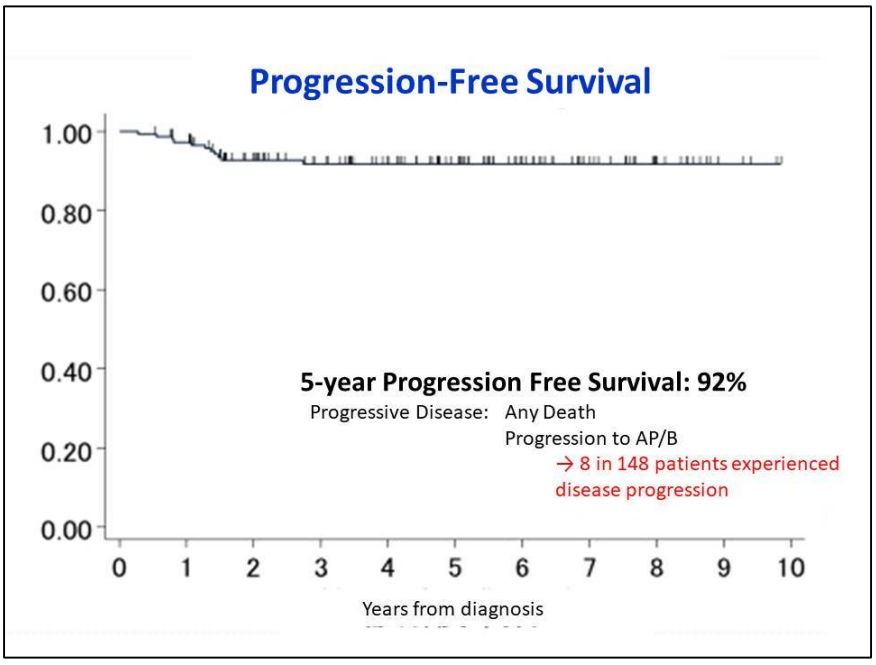

Figure 13

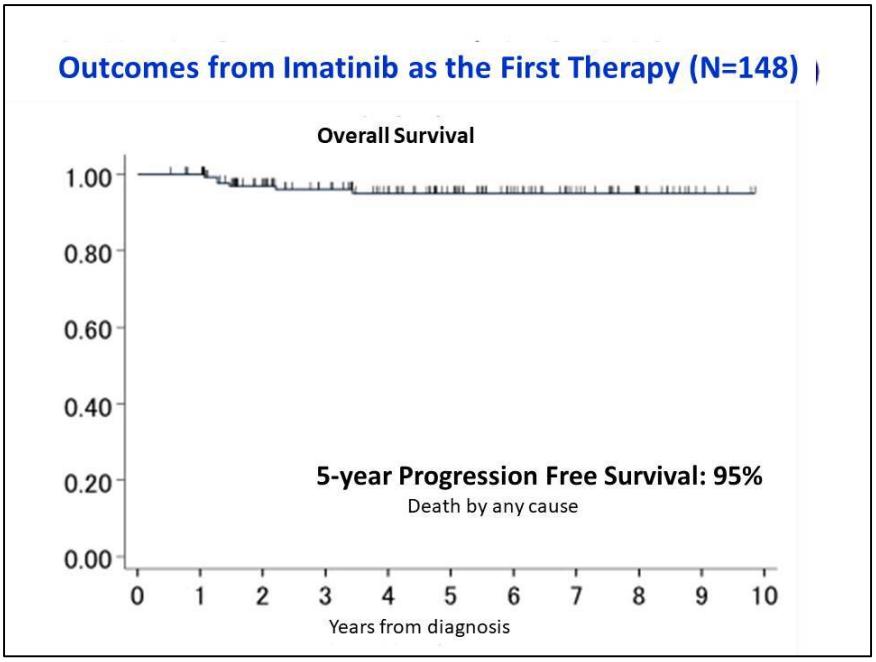

Figure 14

Five-year overall survival was 95% and progression-free survival, that is the percentage of the patients who maintained CP without progression to AP or BP, was 92%.

Recent analysis has found that the reduction rate of BCR-ABL genes is useful for predicting the prognosis. In particular, reduction in the first three months after starting treatment is important, and the data from adults has showed that if the BCR-ABL genes are reduced to a sufficient level at three months, good treatment response is likely to continue thereafter. Reports have indicated that earlier reduction in BCR-ABL genes is likely to result in a better long-term prognosis in children in the same manner as adults. A good start of treatment is important for a good outcome.

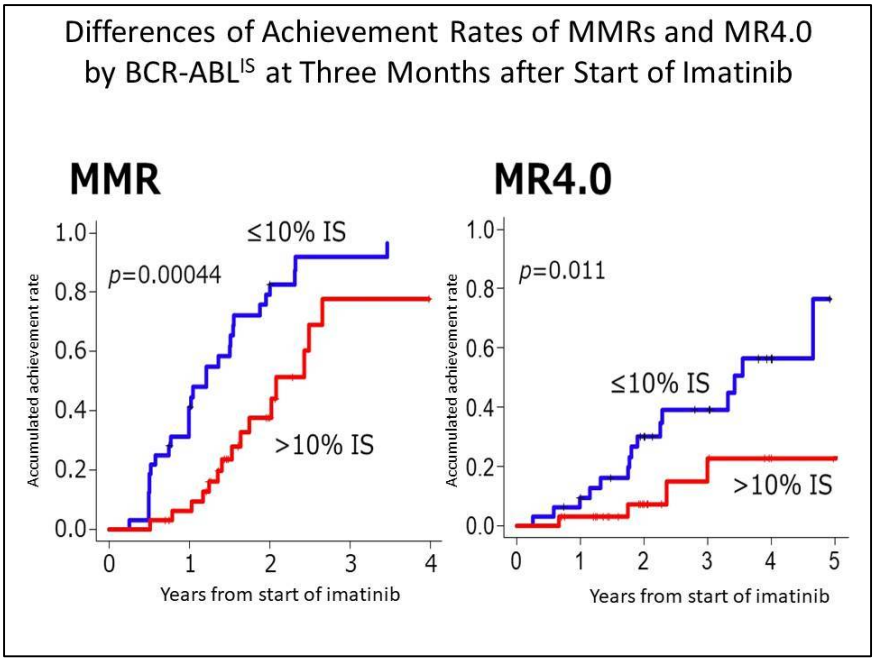

Figure 15

The JPLSG has been conducting a CML08 study since 2009 to investigate courses of chronic CML patients receiving various types of treatment, which was scheduled to be completed in October 2019. Preliminary analysis of interim results from 78 enrolled patients indicates that a deeper remission was achieved when BCR-ABL genes were reduced in the early stage with TKI treatment.

Since imatinib had a dramatic impact on CML treatment, development of improved TKIs followed. Studies in adults have shown that dasatinib and nilotinib, second-generation TKIs, showed better treatment response than imatinib. Thus, any of the TKIs, imatinib, dasatinib, or nilotinib, can be used for the first therapy.

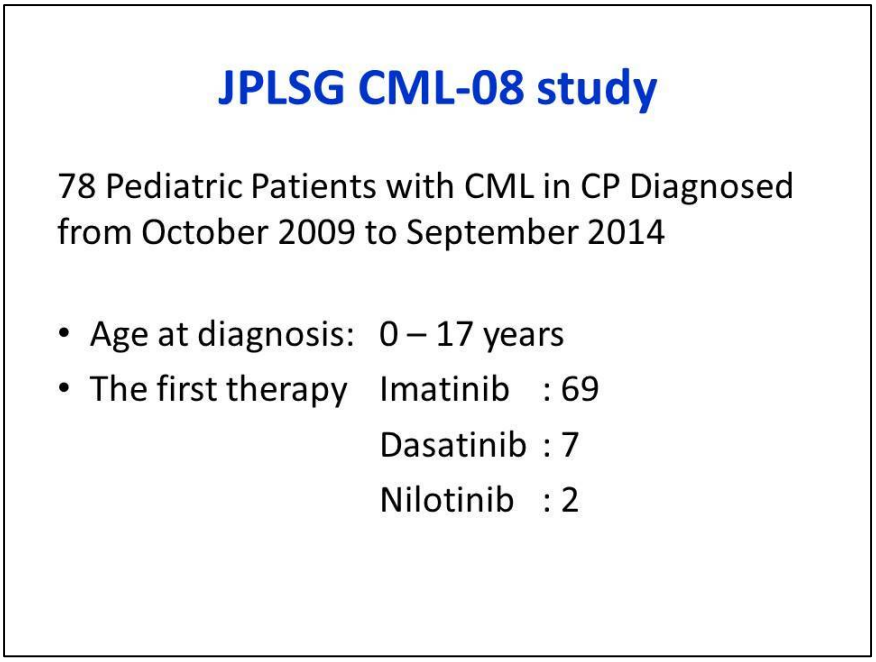

Figure 16

Second-generation TKIs have not yet been widely used in children worldwide. In Japan, second-generation TKIs are used in more than half of the 78 patients being followed up in CML08. Dasatinib and nilotinib were chosen for some patients from the beginning, and quite a few who started with imatinib have switched to other drugs or therapies due to poor response or intolerance with side effects. Some patients have switched treatments as many as 6 times. These findings indicate that children can obtain the same level of treatment reaponse from second-generation TKIs as adults, which are equal to or greater than from imatinib. However, it is still unclear which of the two drugs, dasatinib or nilotinib, is better for treating children. To answer this question, the CML Committee in June 2019 began the CML17 trial to compare dasatinib and nilotinib in pediatric patients with CML in CP and AP at the first onset. Despite the trial, the treatments are expected to be highly effective. This trial investigates which treatment is less likely to cause side effects and which is easier for children to continue.

Patients in AP at the first onset are being enrolled in the CML17 trial. Analysis has confirmed that imatinib responds well and provides good outcomes in adult patients in AP as well as those in CP. Therefore, ELN guidelines recommend that patients in AP should start treatment with TKIs in the same way as those in CP. Although the number of pediatric patients in AP at the first onset is small and thus there is no data, the expectation is that the treatment strategy for adults could also avoid hepatopoietic cell transplantation in children.

In addition, second-generation TKI bosutinib and third-generation TKI ponatinib have been launched. Neither is yet widely used in children. The expectation is that ponatinib will be effective for patients with cell mutation T315I. First- and second-generation TKIs are not effective for patients with the mutation. A clinical trial, PedPona19, similar to CML17, began in June 2019, to confirm ponatinib safety for pediatric patients.

6) Adverse events with TKIs in children

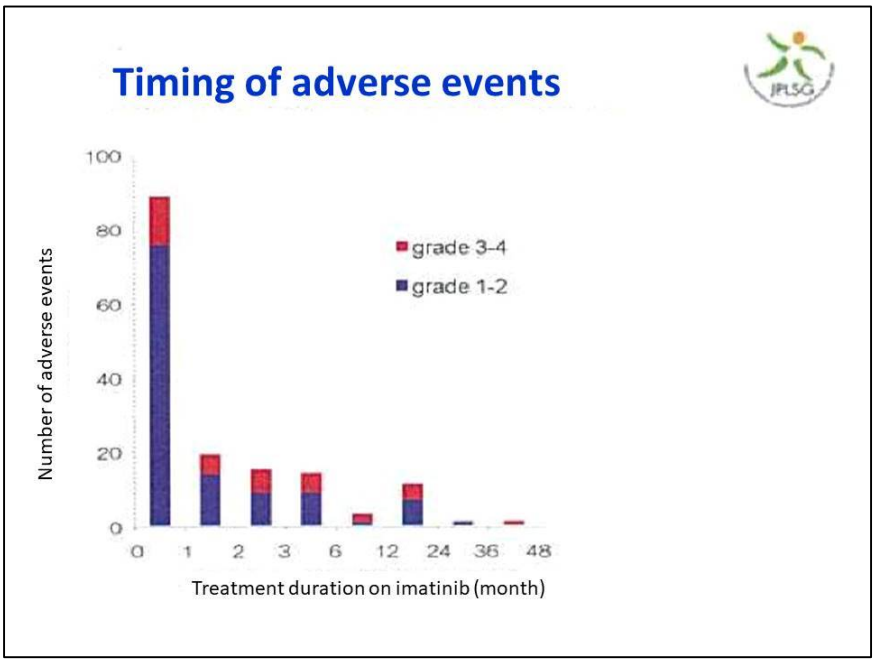

Figure 17

TKIs are excellent drugs for treating CML, but they are not free from adverse events (AEs). AEs can occur often in the first one to two months after starting TKI therapy in adults, and a similar pattern is found in children in a preliminary analysis in the CML08 study as presented in Figure 17.

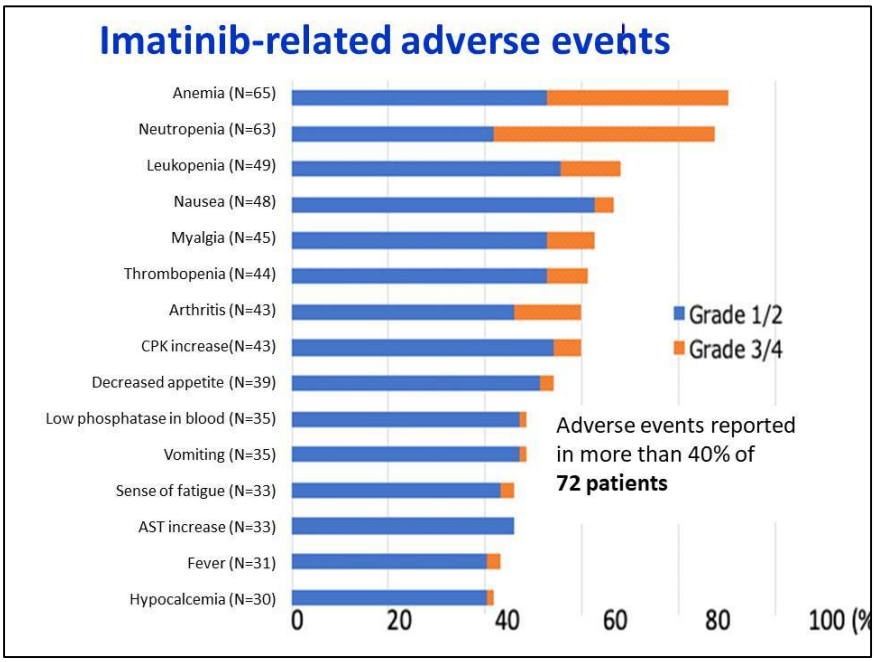

Figure 18

Figure 18 shows a list of specific AEs. In adults, digestive symptoms such as nausea and vomiting and systemic swelling are commonly reported in addition to cytopenia. Children may have elevation of an enzyme called creatinine kinase (CPK), which is released from muscles along with myalgia reported more commonly than in adults. Myalgia and arthralgia are also commonly why many patients switched to other drugs and could not continue imatinib.

Growth disturbance is another concern that cannot be overlooked for TKI therapies in children. This is explained below in Figure 19 using growth curves.

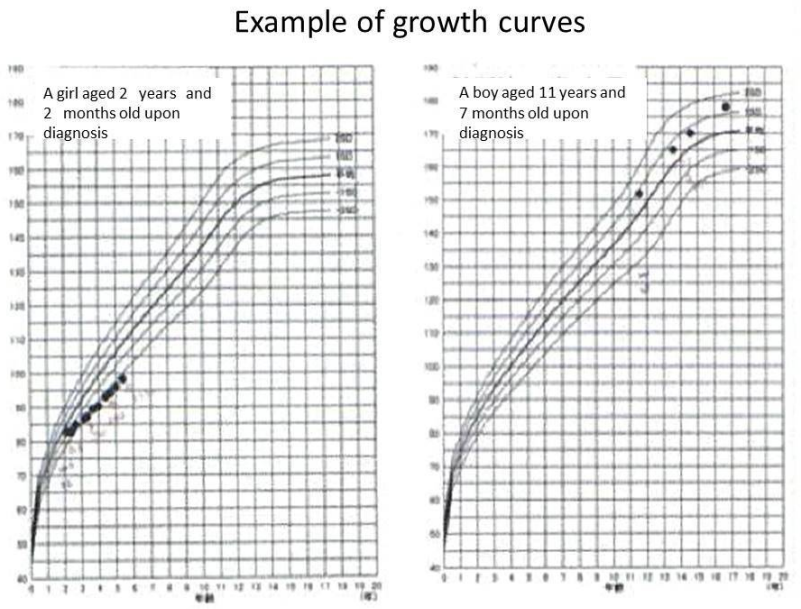

Figure 19

In a 2 years and 2 months old girl on the left in Figure 19, height growth initially followed average growth curve but began to fall below average after she started taking TKI. Meanwhile, an 11 years old boy on the right in Figure 19 indicates no sign of growth disturbance. Observing the growth curves of many child patients showed that growth disturbance might be less likely to occur in pubertal and postpubertal children and thereafter while it is more likely in younger prepubertal children.

As explained, prepubertal TKI may raise a concern for possible FTT, but some children on TKI may catch up with growth in later years.

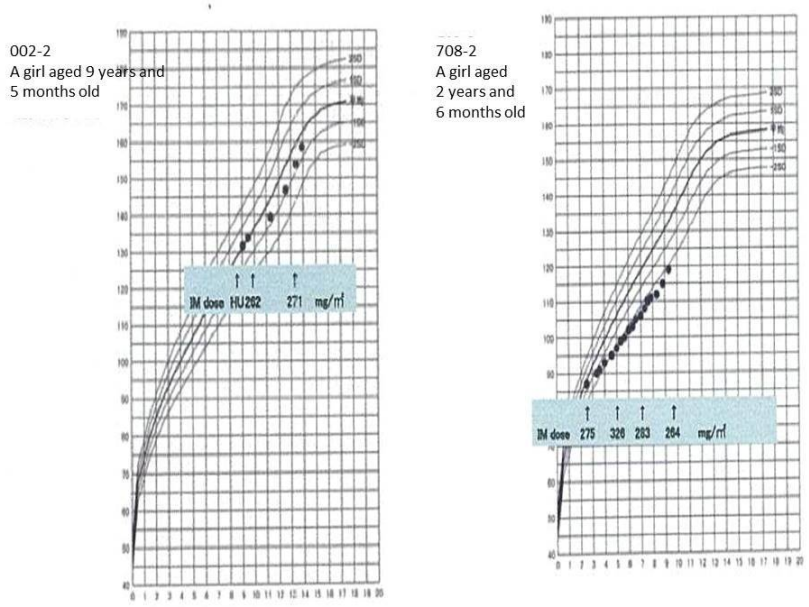

Figure 20

A 9 years and 5 months old girl on the left in Figure 20 received TKI before puberty. Her height growth initially fell below the curve but later increased. In another girl aged 2 years and 6 months old on the right in Figure 20, her curve initially fell but stabilized a few years later.

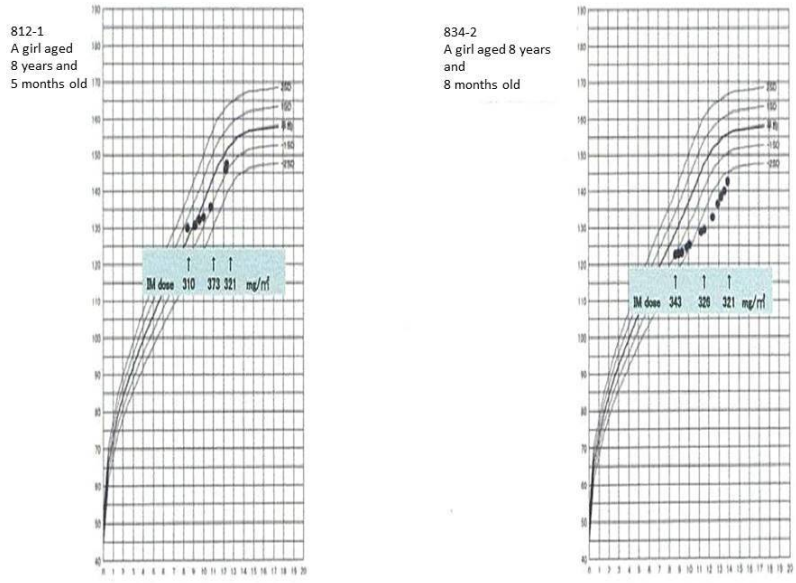

Figure 21

Height growth initially fell but gradually increased for both the 8 year and 5 month old girl on the left in Figure 21 and the 8 years and 8 months old girl on the right in Figure 21. The belief is that prepubertal imatinib affects bone and causes growth disturbance but recovers with the growth spurt

from the sex hormone in puberty.

The medical community has gained an overall picture of AEs associated with second-generation TKIs in children. Figures 22 and 23 show AEs reported from patients taking dasatinib and nilotinib from the preliminary analysis for the CML08 study.

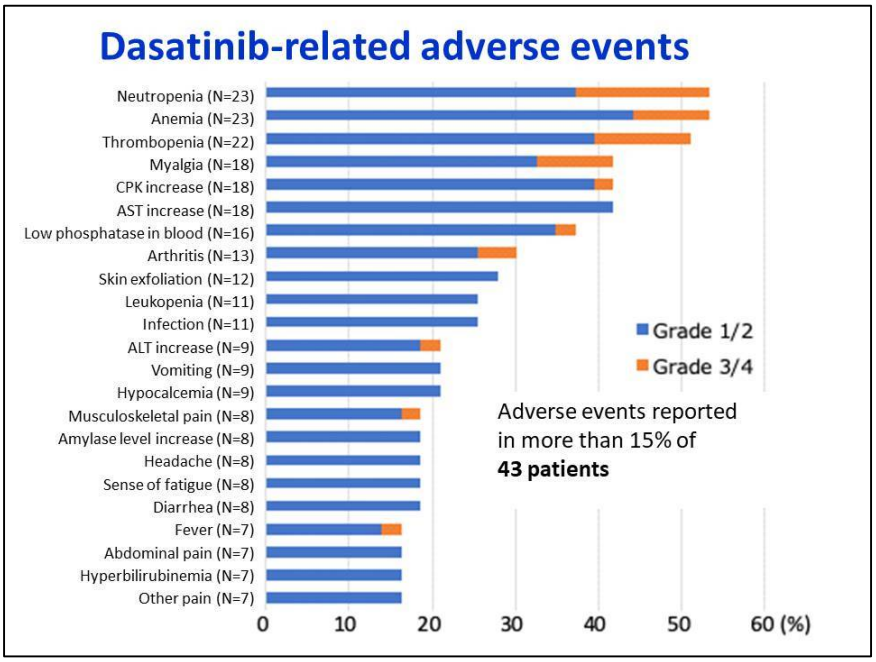

Figure 22

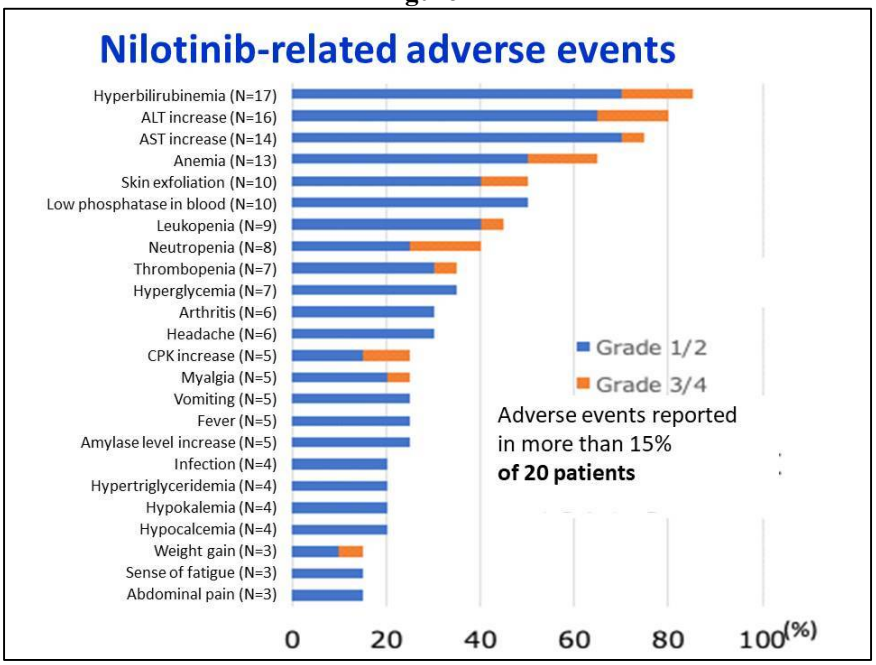

Figure 23

As in imatinib, AEs include cytopenia, myalgia and CPK increase associated with dasatinib, while hyperbilirubinemia has been reported in many patients taking nilotinib. In addition to these AEs, TKI

medication may cause issues over a long time, including the effect of chronic TKI medication on growth and immunity during their childhood and the effect of long-term medication on pregnancy and income issues when they become adults.

It was gradually found in recent years that some patients who respond well to TKIs achieve deep molecular remission (DMR), which means they achieve fairly deep remission and can eventually withdraw or even stop using TKIs. One clinical study designed to allow TKI withdraw in adult patients who maintained DMR like $MR^{4.0}$ or $MR^{4.5}$ over two years, which resulted in 40 to 60% of the patients discontinuing TKIs for the next several years.

Worldwide data for children was not previously available. A study for TKI withdrawal in CML children (STKI-14 study) was completed in December 2018, and the results will be shortly available. These studies set up conditions to allow TKI discontinuation, which essentially required patients to maintain DMR over two years as mentioned earlier. It is very important after all to continue adequate treatment from an early stage and achieve DMR so as to meet the stopping conditions as early as possible. AEs are more likely with TKIs and could be hard at an initial stage, but side effects often become less severe as patients continue TKIs. The appropriate dose level should be maintained by evaluating the drug efficacy based on effect evaluation criteria.

7) Hematopoietic cell transplant in children with CML

This section looks at the current status of hematopoietic cell transplantation, which was the indispensable treatment option before the advent of TKIs. If the disease is in progressive state, TKI medication may not be able to fully contain the progression. If disease onset begins as a BP like acute leukemia, transplantation is considered from the beginning of the treatment. In addition, even if the disease onset is in a CP, CML may not respond well to TKIs. If the treatment fails to achieve the desired effects, the more radical approach of transplantation may have to be considered. TKIs may not be continued because of a side effect, and chronic TKI therapy may not be economically feasible. Hence, opportunities remain to choose a transplant therapy for various reasons.

Currently, hematopoietic cell transplant is recommended exclusively for the following cases:

- BP
- Patients poorly responding to TKI therapies even in CP or AP or cannot continue the therapies due to a side effect
- Patients with gene mutations known that are refractory to TKIs

Transplant therapy can be chosen after considering the following therapy risks:

- TKIs cannot be taken as instructed, and the response to treatment may be poor.
- TKIs cause AE, which can compromise the quality of life.
- The patient himself/herself strongly wishes for the transplantation therapy.

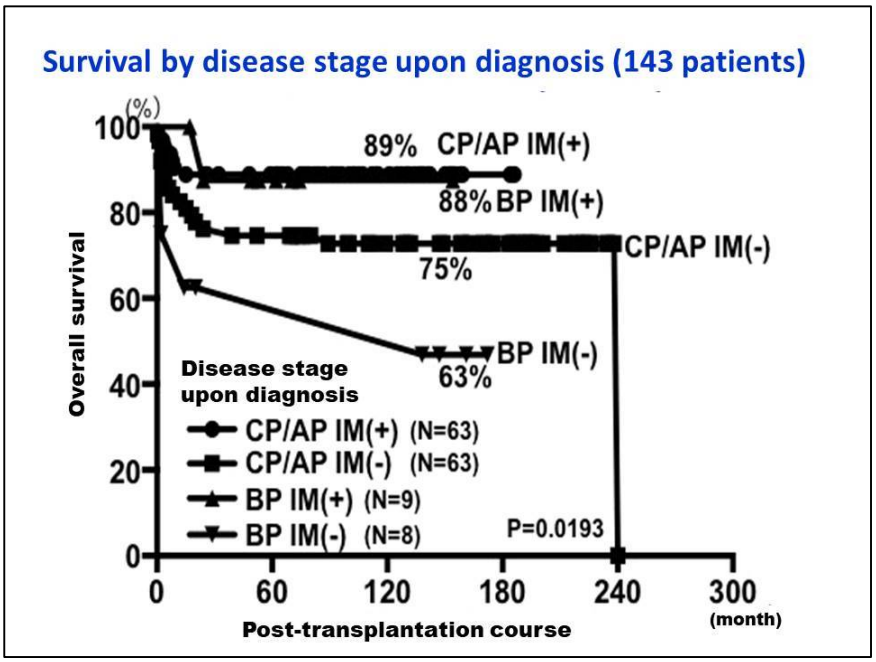

Figure 24

As explained above, only a limited number of patients can choose transplantation. This could mean that the condition in those patients before receiving transplantation is more severe. A high proportion of these patients have conditions that cannot be well controlled because TKI is not sufficient for them.

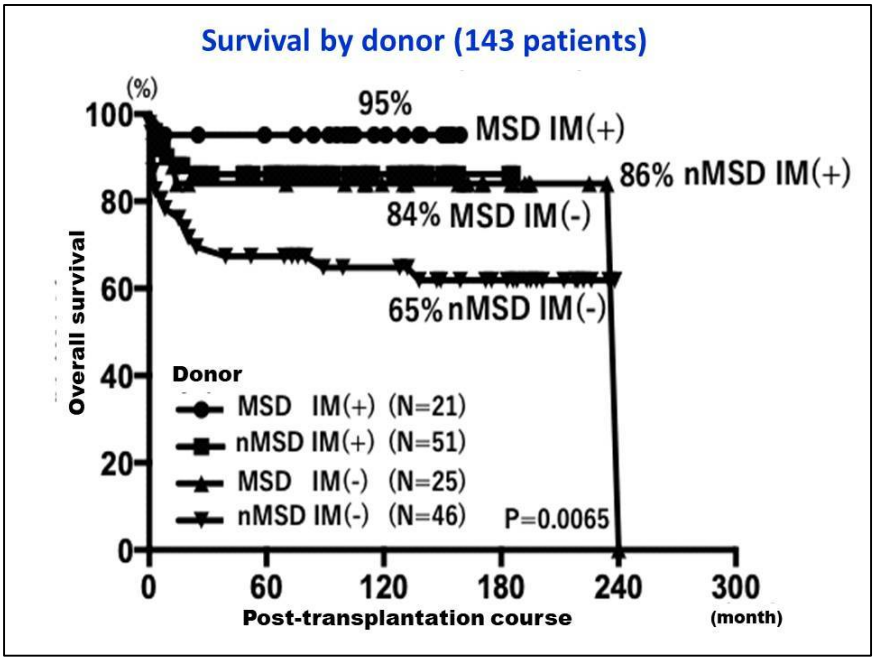

Figure 25

Figure 25 shows the results of hematopoietic cell transplantation therapy based on data from the CML11 study. The study evaluated patients from 1996 to 2011, during which the TKI era began. During this period, imatinib was the only TKI used in all patients before transplantation.

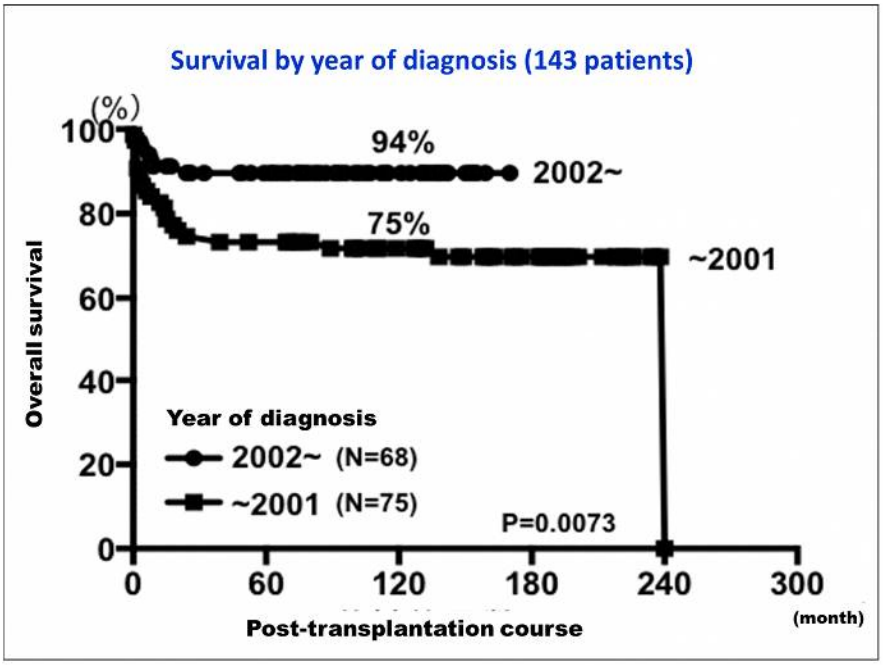

Figure 26

Figure 26 shows the survival rate by year of diagnosis before and after imatinib became commercially available. The 10-year survival rate of patients from 2002 to 2011 was 94%. The rate was 75% from 1996 to 2001. Simply comparing these results is not possible because patient medical histories may differ, but the change between these rates possibly indicates not only that CML could be kept in CP with imatinib but also that the results of transplantation itself have also improved.

The survival by disease stage at diagnosis shows nearly 90% even in BP if treated by imatinib, which shows practically no difference from survival in CP/AP with imatinib and even better than survival in CP/AP without imatinib.

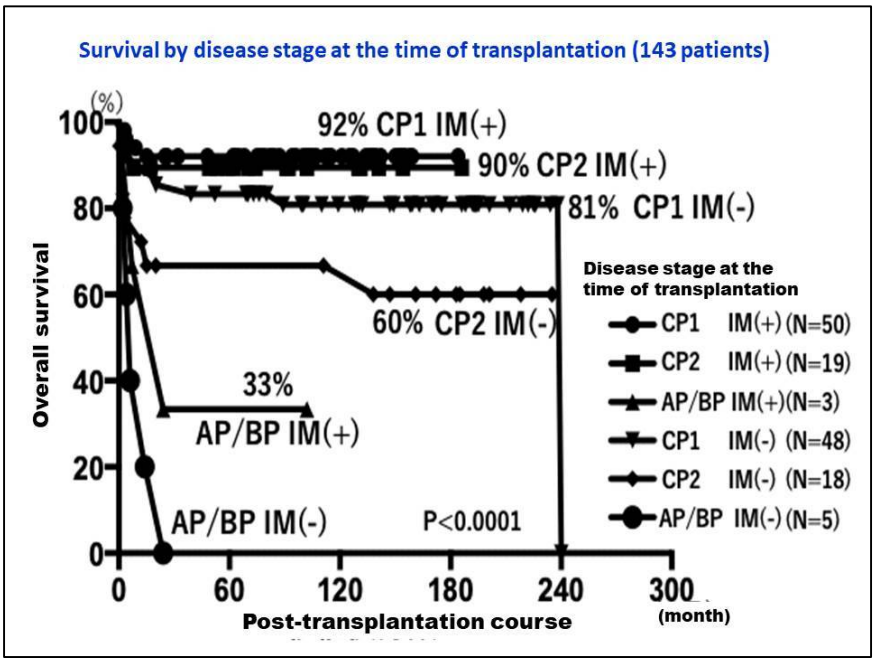

Figure 27

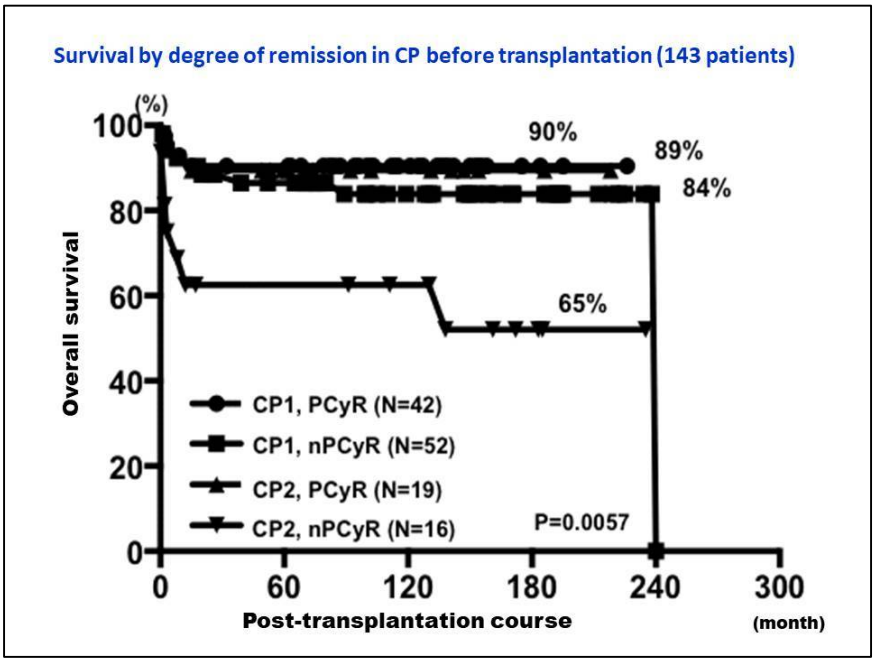

Figure 28

Figure 27 shows the survival by disease stage at the time of transplantation. CP1 represents patients who remained in CP from the primary onset until the time of transplantation. CP2 includes patients who experienced AP or BP and then transferred to CP by therapy before transplantation. AP/BP represents patients whose disease state progressed to AP and BP and thus had to undergo the transplantation. Patients in CP1 achieved favorable results of 10 year survival of 92% with imatinib or 81% even without imatinib. Meanwhile, in AP/BP, good results cannot be expected regardless of

with or without imatinib. In CP2, the survival rate is 60% for patients without imatinib, but patients on imatinib could significantly extend their survival up to 90%. This may indicate that patients at CP2 before transplantation improved, but remission might have been deeper with imatinib for those patients as compared to without imatinib. Then, let's see how deep the favorable remission state should be. As shown in Figure 29, a good result can be expected for patients at CP1 regardless of the depth of remission. Patients at CP2, whether or not PCyR is achieved before transplantation, can have a great difference in the results of 89% vs 65% 15 years post-transplantation. Providing therapy to target at least this level of remission depth before transplantation seems desirable.

Donors

From an HLA-matched sibling, the survival rate can be 84% without imatinib and 95% with imatinib. From a donor of not fully HLA-matched family members and other donors including unrelated donors through a bone marrow bank and an umbilical cord blood bank, the survival rete was 65% without imatinib. The survival rate increased to 86% with imatinib, which is as good as that after transplantation from a donor of HLA-matched sibling in the era before imatinib. This could be because pre-transplantation therapy with imatinib may work and also because transplantation technology itself has improved over time.

What has significantly changed with transplantation at the same time when imatinib was introduced could be an introduction of weak preconditioning type of transplantation reduced intensity stem cell transplantation (RIST) or mini-transplantation.

Among the 143 patients who had transplants in the CML11 study, 32 RIST patients were assessed. Most patients who choose RIST are patients in CP1. The introduction timing of RIST coincided with imatinib introduction, and all patients, excluding one, patient, received imatinib for pre-transplantation therapy. Approximately 10% suffered from graft failure, and although some patients relapsed, most had molecular relapse. Two of the 32 patients died.

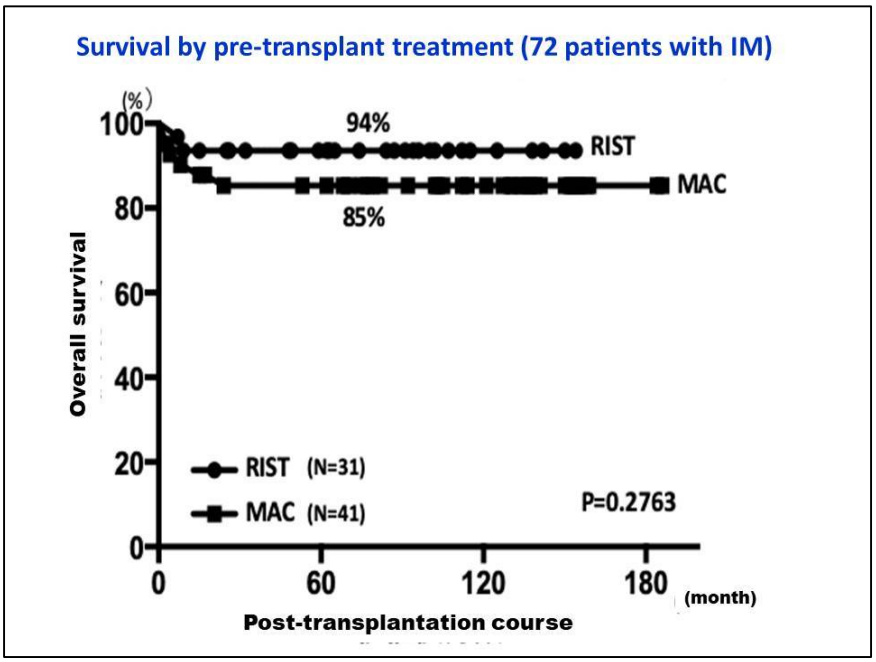

Figure 29

Figure 29 compares patients who underwent transplantation after conventional disruptive bone marrow pretreatment myeloablative conditioning (MAC) with those who received RIST. The comparison is done in 72 patients on imatinib to ensure that patient background is comparable. Many patients with RIST had transplantation in favorable conditions in the first CP as mentioned earlier, and the population reached excellent survival rate at 94%. When transplantation is possible in a relatively favorable condition, and not in the progression stage, a favorable prognosis with RIST appears possible to expect.

Returning to the topic of the entire transplantation, we will consider some conditions that may improve the results. Events reported from 143 patients who had transplants were summarized by transplantation with and without use of imatinib and by disease stage at the time of transplantation. Overall, approximately 10% of patients had graft failure, and this proportion remained unchanged even after imatinib was introduced. RIST also had 10% of patients with graft failures. Generally, approximately 10% of all patients have graft failure regardless of changes in the types of therapeutic approaches and transplantation pretreatment. This could predict that prevention of graft failure may serve as a step towards further improvement in the result of transplantation. Stem cells from the donor may fail to properly engraft, and some patients had to undergo second transplantation without a sufficient interval from the previous transplantation in the pre-TKI era, where not a few developed treatment-related complications and eventually died from the complication. In contrast, in the TKI-era, if the transplantation is performed in CP, it is often possible to maintain CP by resuming TKI even if the disease recurs. Then the situation of having to repeat transplantation as before has been avoided.

During the era where imatinib was not used, many patients relapsed in BP, and the presence or absence of relapse used to dictate the survival rate. After the imatinib era, however, relapse became less common. Even if relapse may occur, most patients experience it in CP. Thus post-transplantation relapse now does not affect the life prognosis. Death after transplantation can be attributed to transplantation complications and transplant-related death. Most causes of deaths are directly related to the transplantation including infectious diseases caused by the transplantation and organ impairments associated with anticancer drugs. Therefore, measures to eliminate complications of transplants are more important than relapse of disease.

What is needed to be more careful about transplantation includes late stage relapse and secondary cancers. Patients who receive transplantation from a related donor are more likely to achieve a successful outcome, but reportedly the possibility of relapse remains even in the late stage. This is thought attributable to the level immune response to leukemia called graft-versus-leukemia (GVL) that may be weaker than in a patient receiving transplantation from an unrelated donor. For patients receiving transplantation from a related donor, the rate of relapse does not diminish even after 10 years and the likelihood of relapse remains. A patient in the CML11 study experienced a relapse after transplantation from a sibling and underwent a second transplantation but developed a third relapse in CP five years after the second transplantation, inevitably requiring the initiation of a TKI. Though transplantation is generally seen as curative treatment, some medical professionals are skeptical about the eradicating nature of transplantation notably in the case of transplantation from related donors. Moreover, it has been confirmed that four transplanted patients with MAC developed secondary cancer. Despite complete recovery from CML, regrettably some patients died of secondary cancers. The onset was after 10 years from the transplantation. Transplanted patients themselves need to remain cautious and alert for a long time and continue follow-up observations.

8) Summary for CML therapies in Children

This section summarizes children following therapy primarily based on the guideline from the Japanese Society of Pediatric Hematology/Oncology (for 2016). This guideline is in line with the ELN guideline for adult patients. The acceptance criteria were presented earlier, and the response to a TKI is evaluated at every 3-month time point after starting therapy. At every time point, medical assessment is made to categorize the remission state in the following manner for prescribing the appropriate medication and dosage.

- Optimal: Treatment is sufficiently working, and the current therapy can be continued.
- Warning: The disease state is slightly questionable, so frequent testing should be done and if the treatment is poorly responded, then changing the therapy should be considered.
- Failure: The current therapy is not working and needs to be changed immediately.

If a patient feels that the TKI is not achieving the desired response after initiation, the first step is checking that the patient is taking the prescribed dose. Physicians presume patients are taking the dose as prescribed, so if the TKI is not working then a physician could consider dose increase. However, sometimes patients have not been taking the prescribed dose. This is unlikely in younger children as their parents and guardians control their medications, but above the age where patients can control medication by themselves, attention is needed as some patients may forget to take drugs or may stop taking the drug without telling their doctor.

It has become clear that some patients can maintain very deep molecular remission with TKI therapy owing to BCR-ABL assay tests that have been improved to be able to detect even a smaller amount as drug development advanced. Drug discontinuation is considered when patients respond to a therapy and maintain deep molecular remission for at least two years. Unfortunately, after drug discontinuation, the percentage of patients who relapse within a few months is not low. If patients resume a TKI at an early stage of relapse, their disease condition can immediately return to a deep molecular remission, Thus if TKI is discontinued, extremely careful follow-up observation is needed. TKI must not be discontinued at personal discretion, but should be withdrawn under careful control in an organized clinical study.

If the disease condition progresses or if the drug effect is not sufficient even though taking a drug for a certain period, a test for BCR−ABL gene mutation analysis is recommended. Drug effects to some extent can vary with mutation type, so patients on imatinib may receive a dose increase or switch to another drug, depending on the presence or absence of any mutation and, if present, the type of mutation. For switching from imatinib, if a patient is in CP and patient's BCR-ABL does not have a gene mutation called T315I, which is refractory to first- and second-generation TKIs, either dasatinib or nilotinib can be the choice for those who started the therapy with imatinib. Those patients who started with either nilotinib or dasatinib will be switched to one of these two drugs not previously used. There are also separate assessment criteria after switching to another drug from imatinib. Assessment every three months is generally the protocol as in the case of primary onset, but the optimal criterion is somewhat more loosely defined than for primary onset. For selection of either nilotinib or dasatinib, no data yet directly compares these two drugs for determining drug selection.

When the disease progresses to AP and BP, hematopoietic cell transplantation is recommended. Transplantation is currently the choice when second-generation TKI-refractory T315I mutation is found. If safety in children is demonstrated in the near future, a third-generation TKI ponatinib may be considered before transplantation.

If a patient is in AP at the time of the primary onset, the patient will start TKI monotherapy as in the

case of CP, but at a dose different from CP. If the effect is poor, transplantation is immediately considered. For BP, if the condition is acute leukemia-like, accordingly chemotherapy with a combination of a TKI should be used for treatment to bring the condition to second CP for the transplantation. When only extramedullary masses are found, ideally a certain therapy should be provided to resolve the masses before transplantation.

In any case, once promising results become available from the ongoing worldwide TKI discontinuation studies primarily on adult patients, the target for pediatric CML therapy may drastically shift from “Maintenance of the chronic phase with continued TKI administration” to “successful withdrawal of a drug to maintain remission” as the next step.