Expert Insights in Acute Lymphoblastic Leukemia: Current Challenges and Future Directions

Slide 1.

Dr. Charles Schiffer: Hello. I am Charles Schiffer, and I am a Professor of Medicine and Oncology at Wayne State University School of Medicine and the Karmanos Cancer Institute in Detroit, Michigan.

I am pleased to welcome you to this continuing education activity entitled, “Expert Insights in Acute Lymphoblastic Leukemia: Current Challenges and Future Directions.”

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I would like to thank the joint sponsors of this activity, Robert Michael Educational Institute and Postgraduate Institute for Medicine. I would also like to thank Enzon Pharmaceuticals for providing an educational grant for what I think will be a very exciting program.

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Today’s format will be slightly different than a standard didactic program. Each faculty speaker will present for approximately 20 minutes. And after each presentation, I will facilitate a 10-minute discussion amongst the panelists here.

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At this time, I would like to introduce our panelists. Acute lymphoblastic leukemia (ALL) is a disease that spans the entire age spectrum. I think it is, therefore, appropriate that we have two adult oncologists and two pediatric oncologists, because the approaches are often somewhat different. We can certainly learn from each other and probably, particularly, from our pediatric colleagues.

Dr. Deborah Thomas is an Associate Professor of Medicine at the MD Anderson Cancer Center in Houston. Dr. Dan Douer is an Associate Professor of Medicine at the University of Southern California in Los Angeles. Dr. Lewis Silverman is Assistant Professor of Pediatrics at Harvard Medical School and Dana-Farber Cancer Institute and Children’s Hospital in Boston. Dr. Stephen Hunger is Ergen Family Chair in Pediatric Cancer and Director of the Center for Cancer and Blood Disorders, Chief of the Section of Pediatric Hematology, Oncology and Bone Marrow Transplantation and Professor of Pediatrics at the University of Colorado School of Medicine and the Children’s Hospital in Aurora, Colorado.

Slide 5.
And now, Deb Thomas will give our first presentation on treatment challenges in Philadelphia chromosome–positive ALL (acute lymphocytic leukemia). Deb?

**Dr. Deborah Thomas:** Thank you, Dr. Schiffer.

**Slide 6.**

Here are my disclosures.

**Slide 7.**

Philadelphia-positive ALL is actually a disease that is fairly unique in character. Though it spans the age spectrum, as Dr. Schiffer indicated, it is much more common in adults, and it represents the most common karyotypic abnormality in approximately 20% to 30% of adults with ALL. It also represents a diagnostic challenge because it can often be confused with bilineage leukemia, particularly as it has a propensity to express myeloid marker at CD13 and -33, and it is not uncommon to have a patient referred with a diagnosis of AML (acute myelogenous leukemia). Unfortunately, this disease also has a propensity to occur in older patients. The incidence of Philadelphia-positive disease increases with age over 50 to over 50%.

**Slide 8.**

Lest we forget, in the pre-imatinib era, the outcome of chemotherapy was extremely dismal. Patients who underwent intensive chemotherapy regimens have a 2-year disease-free survival, which on average was less than 20% in the absence of allogeneic stem cell transplant.

**Slide 9.**

The advent of tyrosine kinase inhibitors (TKIs), in particular, imatinib, in the treatment of Philadelphia-positive ALL in patients who had been treated previously and had relapse or refractory disease was significant. Initially, this agent was tested in chronic myelogenous leukemia, and then applied to the patients who had more advanced disease. As you can see from this slide, it has significant biologic activity with a complete remission rate of approximately 20%, but the responses were of short duration.

**Slide 10.**

The challenges that we face today, although we have made advances through the use of TKIs, are as follows. How do we now optimize frontline chemotherapy? How do we incorporate the TKIs? Should they be administered alone or in combination with
Chemotherapy, and which TKI is the optimal one now that the second-generation and subsequent generations have been developed? I will discuss some of this in the talk.

Also, the treatment of elderly patients with Philadelphia-positive ALL represents a challenge, not only because this population tends to have a higher incidence of developing imatinib resistance, but it also has a decreased ability to undergo potentially curative strategies such as allogeneic stem cell transplant.

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When imatinib was first incorporated into frontline therapy, the optimal dosing and combination regimen was varied amongst different investigators. Both concurrent and alternating administration regimens have been developed and I will discuss some of these a little further.

**Slide 12.**

One of the first regimens developed was actually a concurrent regimen that most of you are familiar with, and that includes the hyper-CVAD (hypofractionated cyclophosphamide, vincristine, doxorubicin) and imatinib regimen, which we developed at MD Anderson. Initially, imatinib was administered concurrently with the intensive phase of the chemotherapy in a syncopated regimen mainly to avoid potential myelosuppression and reduction in dose intensity of the chemotherapy regimen.

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When we determined that it was feasible to combine them concurrently, we actually increased the dose of the imatinib and administered continuously after the induction phase, and we also extended the maintenance phase further. This was based in part on the data that were emerging on the dose-response relationship in chronic myelogenous leukemia.

This regimen is actually quite active. All patients who have active disease tend to respond to the treatment. There is fairly little in the way of toxicity that is different, compared with the hyper-CVAD regimen alone. In addition, a significant proportion of patients, almost 60%, can achieve a complete molecular response, which is of significance in the fact that this was not usually seen with chemotherapy regimens alone.

**Slide 14.**

The addition of imatinib to the hyper-CVAD regimen has improved survival with longer follow-up and longer duration of monitoring.
Slide 15.

This includes, also, remission duration.

Slide 16.

But other regimens have also been developed by other investigators, including the Japanese and German groups, which have identified potentially alternating and concurrent regimens, which may also be efficacious, besides the hyper-CVAD and imatinib regimen.

These regimens have been developed for patients who are younger and also for patients who are elderly. I will discuss the younger-age studies first because these exclude patients who are 55 years of age or older and generally include patients who undergo allogeneic stem cell transplant first complete remission.

The Japanese study is a similar study to ours, which also shows significant improvement in outcome in terms of complete remission rate and disease-free survival with the addition of imatinib to the standard regimen.

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In addition, the Germans performed a sequential analysis of two consecutive studies looking at the use of imatinib in an alternating fashion, mainly because of concerns of toxicity, followed by a concurrent regimen. What they determined with the complete molecular remission rate was much higher with the concurrent regimen. Whether this translates into long-term disease-free survival was unable to be assessed as these were not randomized trials, and the majority of patients went on to allogeneic stem cell transplant first remission.

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Some of the interesting data, which were presented at ASH (American Society of Hematology) this year, provide food for thought: how imatinib is used for the younger patients in terms of combination chemotherapy. There was a randomized study that looked at use of imatinib with minimal chemotherapy, predominantly vincristine and dexamethasone, and randomizing that to patients who had received hyper-CVAD and imatinib, similar to the regimen we originally designed.

The complete remission rate was very significantly high in both arms. The hyper-CVAD and imatinib regimen was more effective in clearing minimal residual disease by PCR (polymerase chain reaction). However, despite the fact that the majority of patients went on to allogeneic stem cell transplant, there was no difference in outcome in terms of long-term survival, although both regimens were superior to
that observed with the previous chemotherapy and imatinib-naïve regimens.

Slide 19.

The elderly population, as I stated earlier, represents a significant challenge in terms of treatment options. Often, these patients do not tolerate intensive chemotherapy, and we saw this evidenced in the German trial that Professor Ottmann conducted. This randomized trial looked at the use of imatinib as a single agent, during the induction phase, randomized to patients who also received chemotherapy. As might be expected, the complete remission rate was much higher with the imatinib regimen compared with the chemotherapy regimen. But the long-term disease-free and overall survival rates were very similar for the two approaches.

The use of imatinib with high-dose corticosteroids has also been implied by other European groups, and you can see on this slide that there are significantly improved outcomes with this particular approach. However, you can see that the relapse rate is approximately 40% to 60% across these studies, and that probably accounts for the increased relapse rate, particularly with the use of imatinib in these patients who develop resistance.

Slide 20.

The most common mechanism of resistance to imatinib is that development of ABL-kinase domain mutations, particularly -- the one of most concern is the T315I, which conferred resistance both to the first- and second-generation TKIs.

There are other mechanisms of action that are relevant, but they have been less well studied. There is ongoing research to identify how significant they are in terms of the implications of disease relapse and the absence of ABL mutation, particularly the mechanism of BCR-ABL independence, such as via SRC, which has led to development of other TKIs.

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What is the significance of the ABL mutations? Well, there are several investigators that have identified that these can be present in patients who are treatment-naïve and at the presentation of disease, including the T315I, which suggests this may be a separate mechanism than resistance induction specifically by TKI therapy, and it can be observed in up to 40% of the patients prior to any treatment.

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Although the investigators have not determined any significant impact on outcome with complete remission rate, molecular complete remission rate, or long-term
survival, there is a concordance in that these patients can often relapse with the similar mutation that was identified at diagnosis. The difference is that the proportion of mutation that involves the disease presentation is very low at the diagnosis and represents over half of the alleles once the patients have disease recurrence.

**Slide 23.**

The incidence and kinetics of development of these mutations are similar whether patients are presenting with de novo disease or have been previously treated with imatinib-based chemotherapy as demonstrated in this slide. The most common ABL mutation is actually not the T315I, but the P-loop mutation. These particular mutations also are generating alternative TKI therapy.

**Slide 24.**

One of the new second-generation inhibitors that have been developed is dasatinib, which is now FDA-approved for the treatment of imatinib-resistant Philadelphia-positive ALL. It has significantly more potency against ABL than imatinib, and it also has significant activity against imatinib-resistant cell lines. But as I mentioned already, it has no activity against the mutations that affect ATB binding, which is the T315I or the F317L.

**Slide 25.**

The phase I and phase II studies of dasatinib have shown encouraging complete responses. Remember, this 31% response rate is in patients who have had prior imatinib therapy.

**Slide 26.**

Now the challenge is how to decide how to incorporate dasatinib into frontline therapy for ALL. There are several studies that have been updated at ASH recently. One of them uses dasatinib in combination with a hyper-CVAD regimen similar to the imatinib and hyper-CVAD regimen I detailed earlier. And Dr. Ravandi presented an update of the outcome of this study, which shows favorable complete remission rates, a molecular complete remission rate of approximately 50%, and short follow-up. There is, again, a similar side effect profile, except we do see a higher incidence of potential hemorrhaging, complications, and pleural effusions because of the different toxicity profile of this agent. Longer term follow-up will be needed to determine whether this is superior to the imatinib and hyper-CVAD regimen.

**Slide 27.**
There was another provocative study that was presented at ASH this year, looking at single-agent dasatinib in patients of all age groups and particularly used in a twice-daily dosing. This separate abstract was presented previously, but an updated long-term follow-up of approximately 11 months compared with the previous presentation shows a continued 100% complete remission rate, but still a 26% incidence of relapse rate, particularly with a high incidence of T315I mutations. They were significantly prognostic in this study, but begs the question of what the role of chemotherapy is in subsequent treatment of these patients.

Slide 28.

Another study using a second-generation TKI in Philadelphia-positive ALL, particularly the elderly group, demonstrated a significant activity of 95%. The median follow-up is fairly short. There was only one relapse, and the regimen was fairly well tolerated. So this, again, speaks to the fact that TKI therapy with minimal therapy may be a particularly relevant strategy for the older patients.

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Nilotinib is another second-generation inhibitor, which is a derivative of the parent compound, imatinib. It has similar mechanisms of action, but it does have activity in imatinib-resistant cell lines, and phase II studies have been conducted and show some preliminary activity. To date, this agent has not necessarily been combined in frontline chemotherapy regimens.

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Of significance is the first- and second-generation differences in terms of sensitivity to TKI therapy with the ABL mutations. And preferentially, ABL mutation monitoring may be relevant in determining the sequence of TKI therapy, which should be administered to patients who have recurrent disease.

Slide 31.

This has led to the development of specific ABL inhibitors that have not only the mechanism of inhibiting ABL but also can inhibit SRC, aurora kinases, and, specifically, T315I. How these agents will be incorporated in future therapy programs remains to be seen.

Slide 32.
To shift gears a little bit to talk about the role of stem cell transplant in first complete remission for Philadelphia-positive ALL. In the pre-imatinib era, it was clear that this was an indicated procedure in patients who had an identifiable donor and no contradictive morbidities that prevented this modality and who had maintained their remission rate long enough to undergo this procedure. It has been confirmed in two prospective clinical trials.

**Slide 33.**

When we looked at our data with the imatinib and hyper-CVAD regimen in the patients, in particular, one third who underwent allogeneic stem cell transplant complete remission, the results for the stem cell transplant arm is actually quite favorable. The patients who have undergone this modality had a very low incidence of complications and very low relapse rate compared with the patients who had been treated just with continuous chemotherapy.

**Slide 34.**

When we initially looked at the outcome of stem cell transplant in first remission, again, comparing these patients who were selected based on availability of donor, younger age, and ability to maintain the remission of a sufficient duration, we saw no significant difference in outcome by transplant.

**Slide 35.**

However, with longer follow-up, and as I presented last year, we are seeing a difference, which has a trend towards statistical significance in patients who undergo allogeneic stem cell transplant in first complete remission.

**Slide 36.**

This is somewhat confounded by the fact that the median age of the patients who undergo stem cell transplant is 37 versus 53 in the patients who do not. As we have already demonstrated, the patients who are older with Philadelphia-positive ALL tend to have more resistant disease.

**Slide 37.**

Dr. Douer will talk a little bit more about the MRC/ECOG (Medical Research Council/Eastern Cooperative Oncology Group) trial and its influence on patients with Philadelphia-negative ALL. But just to demonstrate that this trial has also analyzed the influence of imatinib and stem cell transplant in Philadelphia-positive ALL in adults. Patients were treated with induction followed by consolidation.
intensification with high-dose methotrexate, and then underwent allogeneic stem cell transplant with either a match-related or -unrelated donor.

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During the course of this study, as imatinib was being developed and incorporated into therapy, the imatinib was initially placed earlier and earlier into the regimen: first, postinduction, and then during the induction phase. As might be expected, the complete remission rate increased with this intervention. However, despite the fact that 60% of the patients underwent stem cell transplant first remission, this appeared to have no impact on long-term survival. The addition of imatinib also had no impact on survival. These results are difficult to explain.

Slide 39.

However, the potential for disease recurrence after stem cell transplant has been evaluated closely and, potentially, a maintenance strategy might be of relevance. Imatinib given to patients who develop PCR positivity for *BCR-ABL* after allogeneic stem cell transplant were potentially salvageable if they eliminated their *BCR-ABL* by PCR within 6 weeks. If they did not clear their disease, they universally relapsed.

So potentially, intervening prior to development of PCR positivity would be a rational strategy. Again, the question becomes what is the optimal TKI therapy to incorporate at this time.

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We have, in Philadelphia-positive ALL, still work ahead of us. We still do not have answers to some of the questions that I raised earlier in the talk. One of them is how do we optimize frontline chemotherapy. The addition of TKI therapy is clearly indicated. Concurrent approaches with TKI therapy and chemotherapy appear superior to -- particularly for imatinib to that of alternating regimens, which is still -- the optimal TKI still remains to be determined. Perhaps patients who have mutations identified at diagnosis should receive specific agents that have demonstrated sensitivity, particularly T315I, and the newer agents might be of relevance.

The mechanisms of action and resistance without *ABL* mutations identified need to be explored further because there are patients who do have disease recurrence without this mechanism. Novel agents such as Hsp90 (heat shock protein 90) or histone acetylase inhibitors or other agents might be of relevance in terms of approaching these patients.
Finally, the role of allogeneic stem cell transplant first complete remission. I do not think we have enough data to support omitting this in the majority of patients. Perhaps additional studies will identify risk stratifications that could be applied. I think the only way to answer this would be to do a randomized study that incorporates allogeneic stem cell transplant and also follows with TKI maintenance phase therapy. Thank you.

**Slide 41.**

**Dr. Schiffer:** Thanks very much. That was a very comprehensive presentation on a difficult disease -- very difficult disease. I would like to start off the discussion really talking about what you ended with, the point about transplant, because in the past, once we identified Philadelphia chromosome-positive ALL, we used the combination of chemotherapy and a TKI to get us to transplant. Do you think the transplant should still be done in all people who are young enough and have donors?

**Dr. Thomas:** Yes. I think at this point -- initially, when we were first evaluating the data, I was less convinced. But as I followed the patients longer, we have not achieved a plateau on the curve, so to speak, in the patients who are receiving TKI therapy and chemotherapy alone. But we are seeing that in patients who have undergone allogeneic stem cell transplant first complete remission.

The patients who would also receive maintenance therapy, however, after transplant, beg the question was the TKI responsible for that outcome.

**Dr. Schiffer:** So is there a different perspective from the pediatricians?

**Dr. Stephen Hunger:** Well, I think we look at Philadelphia chromosome–positive ALL at least a little bit differently because there is a subset of younger children with lower white counts that actually has a relatively favorable prognosis in the pre–TKI therapy era. So prior to the development of imatinib, you could identify groups of children with a 45% to 50% cure rate with chemotherapy alone.

We have also conducted a study of intensive chemotherapy plus imatinib with very exciting early results that we are continuing to follow. I think we do believe that there may be a subset of patients who exhibit a very good early response who may not need to undergo stem cell transplantation in first remission.

However, I think we have to be very cautious, and the points Dr. Thomas has made are very relevant, that all these data are relatively immature, and we need longer follow-up to make definitive conclusions.

**Dr. Schiffer:** Lew?

**Dr. Lewis Silverman:** Yes, I would agree with that entirely. I think within pediatric ALL, we are at the moment of transition in this issue in which there are these exciting data that are out there that maybe we are going to be able to identify subsets
of patients who can be treated with chemotherapy and a TKI alone, but I do not think we are there yet. I do not think we have the long enough follow-up yet to say this is our standard of care.

**Dr. Schiffer:** What do you think those clues would be at the moment in terms of who you can avoid transplant in?

**Dr. Hunger:** Well, the strategy we have taken in our newly opened trial, first of all, combines a second-generation TKI, in this case, dasatinib, with intensive chemotherapy, and looks at the patients’ early response to therapy. So those patients that have a very good early response to therapy would not be candidates on this trial for alternative donor transplant. We are recommending matched-sibling donor transplant for all patients that have a matched-sibling donor.

**Dr. Schiffer:** Dan, do you have any thoughts from the adult perspective?

**Dr. Douer:** Well, the disease is most common in patients that are over 60 that, even pre-imatinib era, would not be candidates for transplantation. So if imatinib is improving the outcome without transplantation, it does give some hope to these patients even without transplantation. Obviously, I think transplantation should not be omitted in those patients who can receive. But those who cannot might benefit. There is one other study from Italy showing that you can actually get good remissions with imatinib and steroids only. So you might not even need to give intensive chemotherapy that some of these patients cannot get. Not only can they not get the transplant, they cannot get the intensive chemotherapy.

So I think overall, by having imatinib, we will be able to improve the outcome of these patients. If they can have a transplant, fine, but perhaps even without transplantation.

**Dr. Schiffer:** Yes, let me pursue that. Sure, you can get remissions with a TKI and lesser chemotherapy in older patients, but there are lots of older patients who are fit for regular-intensity chemotherapy. And I would wonder what you do in those patients. Would you administer standard, relatively intensive chemotherapy in combination?

**Dr. Thomas:** Well, in our institution with the imatinib and hyper-CVAD regimen, previously, in our current frontline approach, which is dasatinib and hyper-CVAD, as long as the patient has had an adequate performance status and relatively good organ function, there are no age restrictions from our perspective in terms of administering this therapy. Again, this does come with very intensive supportive care. The patients do require a protective environment or some form of protection during the induction phase because they have a high induction mortality, otherwise, over 30%, in the absence of this intervention.

I think that, at this point, when we analyze the data, in elderly ALL in general, regardless of the Philadelphia-positive disease or not, we are unfortunately stuck in
a rut of the long-term disease-free survival that is less than 30% on average, regardless of the modality whether you use intensive chemotherapy or less intensive chemotherapy. And for some reason, the difference in biology of these patients needs to be examined further in terms of other targeted approaches.

**Dr. Schiffer:** Okay. You mentioned the fact that, in contrast, for example, to chronic phase CML, you find mutations at the time of diagnosis, *BCR-ABL* mutations at the time of diagnosis of ALL and also that the second-generation TKIs, and I guess, in this case, particularly dasatinib, will have activity against many of those that would be resistant to imatinib.

Wandering into off-label land, which TKI should be preferred? Because you do only have one crack, and I wonder whether we will ever have randomized trials to address this question?

**Dr. Thomas:** Right. I think that is a very valid point, in fact, which is the optimal TKI, and that depends on what your objective is. I think, at this point, imatinib is still considered a standard approach in terms of addition to chemotherapy. There has been sufficient data suggesting that it is optimal treatment.

However, as the patients relapse and develop *ABL* mutations, what becomes more relevant is the selection pressure, perhaps, that you may be inducing very resistant mutations that will not respond to your third- or fourth-generation inhibitors, and one of those is the T315I.

Unfortunately, the use of dasatinib has not ameliorated the identification of T315I disease at relapse. If you look at nilotinib, it actually has the lowest mutation rate of all the second-generation TKIs that are available at this point. Because of these salvaged data, which have not looked as promising as that of dasatinib, it has not been pursued. But you have to remember, when you use it in the frontline setting, it may be superior to that with imatinib.

I think one of the issues with delivery of dasatinib in patients who cannot tolerate it, there is a higher incidence of myelosuppression and pleural effusion. I think nilotinib is an alternative that should be explored further.

The other agents are not far along in terms of their development other than maybe bosutinib in terms of being combined with chemotherapy at this point.

**Dr. Schiffer:** A question that comes up all the time is, post a successful allogeneic transplant, do you continue the TKI, whichever one you chose to use, and for how long.

**Dr. Douer:** I am not sure and cannot give a -- I, intuitively, would continue. There are no data to say for how long. You can use the PCR to direct you, but I am quite sure that after transplantation most patients will be PCR-negative. It is a very effective treatment. So I do not know if that will help us to direct.
What I do in my own practice is I continue it and I give it up to a year, if the patient tolerates it. If there are problems with tolerance, I would follow the PCR, and then resume it if it becomes positive. And I do not think there is any standard.

**Dr. Schiffer:** No. But arguably, once the PCR becomes negative, it may be too late. What do you all think?

**Dr. Hunger:** Well, I can certainly tell you what we do. I would not claim that we know what the right thing to do is. In our Children’s Oncology Group trial, after allogeneic transplant, patients receive 6 months of imatinib starting at the time of blood count recovery and resolution of any acute toxicities, and then are stopped.

The patients who received chemotherapy plus imatinib, once the maintenance chemotherapy was completed, did not receive further imatinib. Neither study has, of yet, shown a spike in recurrences after the cessation of therapy. But I think more follow-up is needed. I think it is a very challenging question, and I think we may have different risk-benefit ratios, also, in a 8-year-old than a 65-year-old in terms of long-term use of a TKI.

**Dr. Silverman:** I think also, I agree in terms of our practice is also to use imatinib posttransplant; though, I do not think any of us can claim we have data to demonstrate how much, for how long, and whether this benefits. It just feels like the right thing to do.

I worry a little bit, though, we do this as well, about the screening, using your PCR as screening as to who to use it or when to come back in with it because, unlike the case of CML (chronic myelogenous leukemia), I am not convinced that screening in ALL will necessarily pick up an incipient relapse that -- certainly we have had many cases that go from PCR-negative and come in with full-blown acute leukemia --

**Dr. Hunger:** In a short period of time --

**Dr. Silverman:** -- in a very short period of time, in which a screening would not pick them up, which is very different than the case of CML where screening clearly has a predictive role.

**Current and Future Treatment Options for Adult ALL**

**Slide 42.**

**Dr. Schiffer:** I think we should now move on to our second topic, which is current and future treatment options for ALL in adults, a difficult topic, which we gave to Dan Douer.

**Slide 43.**
Dr. Dan Douer: Thank you, Charlie. These are my disclosures.

Slide 44.

The treatment of ALL in adults is complex and not standardized, as you can see in this slide.

We know that, as opposed to AML, all patients need to get a long duration of maintenance and CNS (central nervous system) prophylaxis. But there are multiple regimens that are being used by different investigators and different physicians. There is really no one regimen that is preferred by the majority of people.

You can divide all the regimens, in a general sense, into two groups, one which I would call the BFM (Berlin-Frankfurt-Munster)-based regimens, which is not a regimen but more of a concept or a theme that has been derived from pediatric protocols and has always got an induction of 2 phases with the full drugs in the phase I, and the 3 -- or sometimes more drugs in phase II that you can see on the slides. Then, there is a complex consolidation with multiple drugs and different cycles.

The unique thing about this is -- first, is asparaginase, either in induction or in consolidation, and more recently in both parts of the treatment, and also there is the concept of this delayed re-induction: these two parts of the inductions are repeated that, in pediatrics, have been shown to be of value. So this is the BFM regimen or theme.

The second -- this is a regimen that has been developed by MD Anderson, and Debbie has studied it a lot and it has not been used in children, is a simpler one and easier to remember and has got a Part A of the four drugs that you can see on the slide, and a Part B, which is high-dose methotrexate and high-dose ara-C. These drugs alternate four times for a total of 8 cycles. I think this regimen is more myelosuppressive, but it does not have asparaginase. It is one of the major differences, in addition to the other drugs that are completely different than the BFM regimens.

Also, it has -- as opposed to the BFM regimens, it has not been studied in multi-institutional trials on ALL on the data. Most of the published data are from MD Anderson.

Slide 45.

In this slide, you can see a list of several of the studies. These are the earlier studies that were done of different regimens. You can see there is some improvement in the
complete remission rate over the years. But the disease-free survival remains quite stable at about 35%.

**Slide 46.**

These are, in this slide, more recent trials. Now they are using asparaginase both for induction and consolidation, and most of them are based on the BFM, again, improving the complete remission rate to 90%. So I think now we can really get everybody into remission, but the disease-free survival still stays poor at about 35%.

At the end, is the hyper-CVAD regimen that, according to the published data, seems to have the same disease-free survival. Now it is very difficult to compare these studies. None of them have been studied in any randomized fashion. The different patient characteristics, the percentage of Philadelphia-positive patients varies, and even the upper age limit is different. For example, the CALGB (Cancer and Leukemia Group B) studies include patients over 60, and the MD Anderson studies include patients over 60. I think, Debbie, you have an ASH presentation where you look at patients that are younger, and they have a higher outcome.

So it is very difficult to compare these studies with each other. But overall, when you look at these data, there is a lot of room for improvement in the treatment of ALL, which has not been done over the years.

**Slide 47.**

Here are some strategies that I just want to mention how we can try and improve it. Should we transplant every Philadelphia-negative patient who has a donor? Should we learn from the pediatricians how to do it? They get better responses, and some data, as Lew will tell us, might be related to the different treatment, although it is not the only reason.

There are certainly -- as Debbie mentioned, there are special subtypes, the Philadelphia-positive, and maybe we should look into new drugs.

**Slide 48.**

This is just to follow up on the previous talk, Philadelphia-positive in the past, was a bad outcome. We have improved outcome.

**Slide 49.**

Then, another subtype was -- a cytogenetic subtype is the MYC translocation of
Burkitt’s leukemia, the 814 translocation and with newer regimens that include high-dose methotrexate and high-dose Cytoxan®, which hyper-CVAD would be a similar one. You can get much better outcomes of disease-free survival, more than 75%. I think recent data, not only with the hyper-CVAD but with other regimens, suggests that Rituxan® is effective in this disease, which most -- all patients are CD20 positive.

So I think in subtypes of patients, like the Philadelphia chromosome that you presented earlier, Debbie, and in the mature B-cell Burkitt’s, by changing regimens, we are improving, but what about the other patients?

**Slide 50.**

This is the question of bone marrow transplantation, and here is the recommendation of the International Registry, which suggests doing allogeneic transplantation in high-risk patients, not only Philadelphia-positive, but based on higher age and higher white cell count. This is based on some randomized trials where the only benefit was seen in those patients with high risk who underwent allogeneic transplantation as opposed to standard chemotherapy and autologous transplantation. So autologous transplantation is not recommended.

**Slide 51.**

But here is the MRC ECOG trial that Debbie showed you the regimen earlier, which shows, in the Philadelphia-negative patients, that those who did not have a donor -- this is an intent-to-treat analysis -- had a survival of 45%, which is similar to what we will see in a population of Philadelphia-negative patients. But those who had a donor had a better outcome of 53%. So there seems to be a better outcome.

I should mention later that I think the chemotherapy regimen was not as intensive as it is in many other protocols. One other conclusion from this study is that the worst results were also in patients who had autologous transplantation.

**Slide 52.**

The interesting finding in this study is that those who did the best actually were those who were the low-risk patients, rather than those in the high-risk patients. The difference was because of the higher mortality in higher risk patients probably because they included patients over 35 years of age because this is a high risk. So it is very difficult to draw conclusions from this study since it is different from the other studies, and I think we need to discuss this topic of transplantation, but that is one thought.

**Slide 53.**
The second approach is that most adult regimens, as I mentioned, derive from pediatric protocols, but they are less intensive, and physicians, or adult physicians, do not adhere to the protocols either by dose or timing than the pediatricians. Also, there are lower doses and shorter duration of asparaginase treatment because there is a concern of toxicity. In fact, a lot of physicians stop the treatment whenever they see the first sign of toxicity and do not continue it.

So the question -- can we learn from the pediatricians and use pediatric approaches that are more intensive and also produce longer asparagine depletion because the concept -- or the key concept of asparagine treatment is the duration -- or the ability to obtain asparagine depletion in the serum.

Slide 54.

This is a study from adults showing that if you could get or achieve asparagine depletion, the outcome is better than those who were not able to achieve, and then there are also some data from children. So this is the basis for including asparaginase in adult treatments in longer duration of time.

Slide 55.

If you look at pediatric studies, the idea of sustained asparagine depletion was developed at Dana-Farber by Dr. Sallan and colleagues who continue to do these studies. In each one of these studies, it was shown that when you give a prolonged duration of asparagine with the idea of depleting asparagine for a long duration of time, the outcome is better than those who received less asparagine. There are five studies that you can see listed, and the references are at the bottom.

Slide 56.

What do we do with adults? Well, you can see here in those who actually use it, in the induction, it is similar to what we use in children, and I do not think the problem is inducing the remission. In ALL, we get the 90% complete remission rate. But when you look at the consolidation, either it is not used, even in the BFM regimen, or it is used in a very short duration of time, one or two cycles only, as opposed to many, many weeks of administration in children. I would just highlight it again; the MRC ECOG trial in which they gave three doses of *E. coli* asparaginase in postremission, the lowest amount of asparaginase that I think has been given in every trial.

Slide 57.

So the question is, can pediatric approaches be given in adults? Is it tolerated? Is it
feasible? This is the largest trial that has been presented recently in ASCO (American Society of Clinical Oncology) from the French group. They used a pediatric approach in which they increased the nonmyelosuppressive agents, and particularly the *E. coli* asparaginase, by 16-fold. They achieved event-free survivals, which are higher than what we have seen in the past and are similar to what one would see in the MRC ECOG trial with transplantation -- obviously, these are not randomized trials -- and are also better than the previous trials using adult regimens.

This is the largest trial, which shows that it is feasible to use pediatric approaches. Interestingly, in their study, there was no difference between patients who were transplanted and not transplanted if they used this intensive approach with a lot of asparaginase.

**Slide 58.**

The second study is from the Dana-Farber Cancer Institute taking the exact pediatric approach that Dr. Silverman I think you developed, and using it in adults and showing, again, an improvement in the outcome. Their follow-up is short, only a median follow-up of 2 years. But the preliminary data are encouraging, with an event-free survival of 72%. I think we need more time to see how this curve will settle down. But even if it settles down to 60% or 55%, I think this would be an improvement considering that this also has some Philadelphia-positive patients in it.

**Slide 59.**

The first study -- and I will present is a little more in detail -- is from our own institution in which we adopted pediatric CCG protocol that was described 10 years ago by Dr. Markman. We gave 6 doses of the long-acting pegylated asparaginase intravenously, in our case, in different phases of the treatment. In fact, it is 8 cycles of chemotherapy. It is a BFM model.

**Slide 60.**

We had 39 patients. The median age was 33. We limited it to the age of 57, so it is not older adults. We could see a complete remission rate of 95%. The interesting thing was that all of the patients that entered the remission achieved it after the first cycle. We did not need to use 2 cycles, and that has an implication of the outcome.

**Slide 61.**

We found that it is feasible. The toxicity -- first allergic reaction, we did not see. Pancreatitis, which I think is an inherent problem of asparaginase, you cannot avoid it, you have to accept it like you accept neutropenic fevers, was 13% to 15%, very little venous thrombosis. The main side effects are laboratory increase in liver
enzymes and bilirubin that the main problem is it could delay the next cycle of chemotherapy, and hyperglycemia we also see. They are all reversible.

Slide 62.

We wanted to see how many patients can tolerate it. This is a study that is ongoing. And 15 patients did not continue, but only 7 of them because of treatment-related problems. The rest went to transplant, so we did not continue with the treatment.

I should mention that Philadelphia-positive patients were included. There were 9 patients. And since a year and a half ago, we added imatinib to these patients, and we sent them to transplant.

Slide 63.

This is the event-free survival. I must mention the follow-up is very short. But in the Philadelphia-negative patients, 72%, I think this will drop eventually. But even if it drops to a level of 60%, it is good. And in all patients, it is 67%, so this does include the Philadelphia-positive patients.

I should also mention that it is not shown that the relapse rate is 23%, with all relapses occurring early. We did not see late relapses.

Slide 64.

The final slide is the -- can we use new drugs. We talked about imatinib, adding rituximab. I think MD Anderson has shown that especially in CD-positive non-Burkitt types of ALL but certainly in the Burkitt’s type, it has improved. And then, other antibodies like alemtuzumab and new drugs that target Notch-1 or the MLL drugs -- mutation could be of use.

Slide 65.

In summary, and we can continue that in the discussion, the questions that I pose for the future of treatment of Philadelphia-negative ALL is intensive pediatric approach versus allogeneic transplantation in those who have a donor. The second question is the issue of prolonged and perhaps sustained, not only prolonged, asparagine depletions versus non-asparaginase in a completely different regimen, for example, in hyper-CVAD, in multicenter trials because this has never been done. And then, I think we will talk about it by Stephen, the last talk, the role of minimal residual disease. Thank you very much.
Slide 66.

**Dr. Schiffer:** Thank you very much, Dan. So let me get practical. In contrast to pediatric ALL, the treatment of adult ALL is scattered across the entire spectrum of medical oncology and hematology. Only a fraction of patients are referred to specialty centers. And the reality is a high fraction of those patients cannot be referred -- geography, finances, or whatever.

So you are a physician in this circumstance. You cannot refer your patient. What recommendation do you have as to a particular regimen and how do you advise these doctors to treat these patients?

**Dr. Douer:** Well, first of all, I think it is very hard to answer this question because there is no one regimen that is better than the other. I think we have lost many years in the studies that were done, and we have not advanced. I think we, first of all, need to do new studies and try and find what could be a better study that we can recommend to the community to use.

I think it is a little bit of personal preference. The hyper-CVAD, for example, is an easier regimen to do. Although, I think it is more toxic, and you can remember it. That is one of the problems with the other regimens, and I think you might have more hospitalizations.

Practically, the BFM protocols, if you choose one of those, is one of the CALGB trials. I think they include perhaps a little more asparaginase. I think eventually, once these studies of the pediatric approaches do show that there is a better outcome without transplantation, I think one of those should be adopted.

At this point, what would I do today? It is very difficult.

**Dr. Schiffer:** Absolutely. You move out of Los Angeles to the middle of the country.

**Dr. Douer:** That is the problem.

**Dr. Silverman:** You know, it is hard. But I mean, I think in terms of feasibility of administering a pediatric regimen, not at a large academic center -- this is what pediatric oncologists anywhere do. This is our bread and butter. And whether or not you practice pediatric oncology in a large urban center or not --

**Dr. Hunger:** It is a change. That is all you do.

**Dr. Silverman:** So it is a matter --

**Dr. Hunger:** -- here, you have a bunch of physicians who are busy with many, many other tumors, and these are very time-consuming and difficult regimens.
**Dr. Silverman:** It is time consuming and a matter of familiarity. But if it is a superior outcome, then, you know, even though it is a small fraction of what is being seen, it may be worth the investment of the resources of just learning and becoming familiar.

**Dr. Douer:** If you get a better outcome by treating in places that see a lot of the patients -- it is like bone marrow transplant. You do not do it everywhere in the community; you refer them.

**Dr. Schiffer:** Okay, I am beginning with some premises. You do not have a clinical trial, and you cannot refer them, which is the unfortunate reality for the majority of these patients. I will tell you, I tell doctors, when I am called, you know, Michigan is 11 hours from top to bottom. So we have a lot of patients from the Upper Peninsula who cannot make the trip to Ann Arbor or Detroit.

But they should learn one regimen and learn to do it as well as they can because my impression is that there is not much of a difference in the bottom line amongst these regimens. And often, we do talk about hyper-CVAD because, even though the methotrexate is -- ara-C is quite toxic, doctors are more accustomed to it. It is sort of like AML. You get them in there, and you do it. You know where the patient is, and you have more control with them. But it is just an important practical question.

Let me move on a little bit. You did not make the distinction between T- and B-ALL, which is sort of the big way we divide patients up in adult ALL because, with the exception of the Philadelphia-positive and the Burkitt’s type, we do not have the breakdowns that the pediatricians do in terms of hyperdiploid that tell AML translocation and things like that to sort of guide us as to higher intensity regimens and lower intensity regimens.

I am very frustrated about where to go and how to do trials in adult ALL in order to be a little less empiric. Maybe you have the advantage of having a trial for each sort of subgroup. What can we learn from you in that regard?

**Dr. Hunger:** Well, I think one of the interesting things is that there are more or less the same number of children under 18 with ALL as adults over 18 with ALL. So the total absolute number of cases is quite similar. So that means that Lewis and I, as pediatric oncologists, I think as you pointed out, 25% to 30% of the patients we treat have ALL. So we get kind of good at it. It is something we do all the time.

**Dr. Schiffer:** Your staff gets very good at it.

**Dr. Hunger:** Your staff gets good at it. Our nurses get good at it. Our teams are used to the same questions all the time. And it also has given us the opportunity to break down patients into different subgroups. Now we, within the Children’s Oncology Group, have been accused by some of going too far with that. But what we have found, for instance, is we can identify a lower risk group of patients that have over a 90% cure rate with relatively nonintensive chemotherapy, all outpatient based, little toxicity.
I think your question of T-cell ALL, I think there are important reasons to recognize T-cell ALL as different. First, in childhood, we learn the hard way that if we treat T-cell ALL with less-intensive regimens, those patients do not do well. However, if you treat them with an intensive regimen, such as the one Dan described, they do just as well as the B-lineage Ph-negative patients.

I do think that there are agents that are appropriate for different subsets. Obviously, the monoclonal antibodies we were discussing are just directed against B-lineage leukemia. In pediatrics, we are very interested in nelarabine, and we have a trial testing nelarabine in frontline T-cell ALL. Notch mutations are present in more than 50% of T-cell ALL patients and inhibitors are out there and being developed. Lewis has been involved in those trials. So I think the reason to recognize different subsets is hopefully to tailor therapy to those subsets.

**Dr. Silverman:** I think two things. I think, one, to get back to your question about studying these different subsets, one thing that I think we have done in pediatrics, as Steve pointed out, is very large cooperative groups. If you are dealing with the same absolute number of patients, then these small subsets demand that you have to test different treatments based on biologically distinctive subsets in multiple institutions. And I think that is number one and really moving ahead.

I think another approach, and one that we are trying very hard to do at Dana-Farber, and certainly other groups are taking it on as well, is to look at age-unrestricted trials to really look at underlying biology as what you are studying and really -- without the distinction of at 18, you are on one trial, and over 18, you are on another trial. But in fact, if you have T-cell ALL with a Notch mutation, perhaps you should participate in a similar trial, whether or not you are 15 or 25. I think we are going to learn a lot with age-unrestricted biologically based clinical trials.

**Dr. Thomas:** I just want to make one comment. I think that I agree with most of what has been said in terms of the sentiment, but I disagree with you in that physicians can only learn one regimen. I think the application of the regimen should be tailored to what is best for the patient. There is clearly emerging data, as we will hear, that the younger groups of adults benefit from a more intensive pediatric regimen than they do from a conventional ALL regimen.

So the fact that a physician only knows how to give the conventional ALL regimen is really not justification for giving that to a patient who would benefit from a more intensive regimen.

It is difficult, too -- as personal experience using the hyper-CVAD regimen, as that is indicated, is somewhat more facilitated, well, in terms of administering it. The more intensive pediatric regimens are a doable thing. And with education, you can actually incorporate those into your practice. So I think, again, we need to get away from the notion that physicians cannot administer these regimens.

**Dr. Schiffer:** I did not mean to imply that. But I think this is probably an important
area for patient advocacy, as well, where patients can push and educate physicians into how to administer certain other regimens.

**Dr. Douer:** I think there is one problem -- I agree with the point of it is always good in medicine to learn one regimen and use it well -- if you are using the right regimen. The problem I see is that a lot of physicians treat 1 ALL a year or maybe 1 in 2 years, and they never have the time or the opportunity to learn 1 regimen. They might see it one time. I think that is the problem. Maybe one position will be that overall they never have the opportunity to learn it.

So I think that education would be to send them to major centers that see perhaps more than 10 patients a year on clinical trials and might advance the field.

**Dr. Schiffer:** It is hard to disagree with that. The problem is that that is not always practical. And I think, when we are advising physicians, we have to acknowledge that at times.

**Treatment of Adolescents and Young Adults With ALL**

**Slide 67.**

**Dr. Schiffer:** That was a spirited discussion and a good introduction to our next topic, which Lewis Silverman will be presenting. This will cover the treatment of adolescents and young adults with ALL, which really represents an interface at the moment between adult and pediatric hematologists and oncologists.

**Slide 68.**

**Dr. Silverman:** Thanks very much. I have no disclosures.

**Slide 69.**

Childhood ALL is, as was alluded to earlier, the most common malignancy observed in children. And with current multiagent therapy, event-free survival rates are relatively favorable. We are able to cure approximately 80% of the children who are diagnosed with ALL. We have long known that age is a very important determinant of outcome in childhood ALL with really the best outcomes seen in children who are 1 to 10 years old. Adolescents and young adults, and typically in pediatric trials that is really 10 to 18 or 10 to 21-year olds, appear to have inferior outcomes.

**Slide 70.**

These data are from the German-based PFM group summarizing outcomes on clinical
trials they ran from 1986 to 1999, which really demonstrate this point well, showing you that the best outcomes are achieved by those children aged 1 to 10 years old. The worst outcomes are seen in infants with ALL and intermediate outcomes with event-free survival rates about 50% to 60% seen in those groups of patients who are 10 to 18 years old.

Slide 71.

The question that we have long asked are why do adolescents have inferior outcomes compared with those children who are 1 to 10 years old? Really there are 3 possible contributing factors to the inferior outcomes of adolescents. The first is differences in underlying biology that we see by age. The second is a higher frequency of treatment-related toxicities in older children and adolescents, and finally, issues we have touched on earlier that I am going to summarize a little bit more, are differences in therapy. That is really getting to the heart of therapies that are based for adults with ALL versus pediatric regimens.

Slide 72.

A little bit about differences in underlying biology. This slide is from our own experience at Dana-Farber in treating children between 1 and 18 years old, in which we looked at differences in presenting characteristics. What this slide shows you is that really we saw no differences, significant differences, in the percentage of patients who were male or female, based on age, nor really any differences in the presenting leukocyte count. But there was a marked difference in the incidence of the T-cell phenotype, T-cell phenotype being much more common in adolescents. As you can see from the slide, going up with age, more common in the 15 to 18 year old than it was in the 10 to 15 year olds.

Slide 73.

These data, which are again from the BFM group, show you some differences in the underlying biology of the disease looking at various cytogenetic abnormalities and response to therapy. What you can see on the top half of the slide is that there is a much higher incidence of favorable cytogenetic abnormalities in younger children, so that children who are 1 to 10 years old have a much higher incidence of both the TEL-AML1 infusion and high hyperdiploidy compared with those who are 10 to 15 or 15 to 18 years old. Interestingly, while TEL-AML1 appears to decrease over adolescence, the incidence of high hyperdiploidy in this series, at least, was equivalent in the 10 to 15 and the 15 to 18 year olds. Also shown in the bottom half of the slide, in the last two rows, are the incidence of unfavorable presenting features and early response to therapy. The Philadelphia chromosome, which we have heard a lot about in this panel discussion, is much more common in children who are older than 10 years old than it is in those who are less than 10 years old, as displayed on this slide. Although as you can see, the incidence in those over 10
years old was still only 4% or 5% in this series, which is much lower than what we see in adults with ALL.

Also they looked at early response measures, in this case, looking at bone marrow morphologic response, midinduction at day 15, and can show that those patients who are between 10 and 18 years old had a much higher incidence of a slow early response characterized by an M3 marrow at day 15 compared with children who were 1 to 10 years old.

Just by the nature of presenting features, and the clues we get by early response to therapy, it does appear that adolescents do present with higher risk disease, and this may in part contribute to the inferior outcomes we see in that patient age group.

Slide 74.

Another possible contributing factor that I think we are only beginning to understand is whether or not adolescents are at higher risk for treatment-related toxicities and whether these morbidities impact their response to therapy. I am going to talk about data existing on two chemotherapy agents, the first asparaginase, and the second corticosteroids.

Slide 75.

In our own experience at Dana-Farber, where we use asparaginase intensively, we give 30 weeks of asparaginase during the consolidation phase, trying to maintain asparagine depletion for those entire 30 weeks. We do see some differences in the incidence of asparaginase-related complications by age. As demonstrated on this slide, we saw absolutely no difference in the rate of allergy by age. That seemed to be constant in the 10% to 15% range in the children we see. But we did see an increase in the rate of pancreatitis, 3% in children who were 1 to 10 years old, 9% in those who were 10 to 15, and 6% in those who were 15 to 18, an interesting seeming peak in the younger adolescent that we did not see in increasing with age in the 15 to 18 year old.

Thrombosis also seemed to have that same possible peak in the younger adolescent compared with the older adolescent. Thrombosis was very uncommon in those 1 to 10 years old, occurring in 2% of patients. It occurred in 14% of those who were 10 to 15 years old, and 10% in those who were 15 to 18 years old.

Slide 76.

These data come from the Children’s Cancer Group, and display a major complication of corticosteroid therapy, which is osteonecrosis. Osteonecrosis is a disabling bony complication which can lead to permanent disability, and is something that seems to be very much related to the age of the patient. As displayed
on this slide, the incidence of osteonecrosis observed on this Children’s Cancer Group trial was extremely low in children who were less than 10 years old. It was observed in fewer than 1% of the patients, but the cumulative incidence was markedly increased in adolescents, and did not seem to increase with age. So it was much higher in the 10 to 15 year olds, and even higher in those who were older than 16 on this trial.

Slide 77.

Finally, we get to the issues of treatment -- treatment, of course, being a crucial determinant of outcome, and there has been a lot of studies coming out in the last few years trying to examine differences between pediatric and adult regimens for the older adolescent and young adult population, and this really comes out of the fact that older adolescents, those who are 15 to 21 years old, may be treated on either of those regimens, depending on which type of oncologist they are referred to.

There are emerging data from multiple groups that indicate that there are more favorable outcomes for these older adolescents if they are treated with pediatric regimens.

Slide 78.

This is our own experience at Dana-Farber in treating this older adolescent age group, again our regimen includes 30 weeks of asparaginase during the consolidation phase, and also very frequent pulses with vincristine and corticosteroid during the 2 years of treatment. As you can see on this slide, we have relatively favorable outcomes for even our oldest adolescents, those children who are 15 to 18 years old on our trials, event-free survival rate that approaches 80%.

Slide 79.

One of the first published comparisons of a group of older adolescents who were treated either on a pediatric or adult regimen was done by the French group, and in the next couple slides, I will review data that they reported. In this study, what they did was they looked at patients who were aged 15 to 20 years, and compared those who were treated on a pediatric trial, the FRALLE (French Group on Therapy for Adult Acute Lymphoblastic Leukemia) trial, with those who were treated on an adult regimen. They showed that there really was not much difference in the presenting characteristics of the patients that they were treating, so that it appeared that these patients had similar underlying biology, and it was simply a matter of where they were referred to be treated.

Slide 80.
What they demonstrated in a pretty dramatic fashion was that patients who were aged 15 to 20 years had a much better outcome if they were treated on a pediatric regimen compared with the adult regimen. On this slide, you can see both the overall survival and event-free survival were significantly better for those patients who were treated on the pediatric FRALLE trial.

**Slide 81.**

There have been multiple studies published since the publication of that trial a few years ago, all of which have replicated the same result. On this table, I summarized some of those studies that come from the US group, from Dutch, from Swedish, from the United Kingdom, all of which demonstrated improved event-free survival for those patients aged 15 to 21, somewhere in that age group, who were treated on a pediatric compared with an adult regimen.

**Slide 82.**

What is it about pediatric regimens that might lead to a more favorable outcome for the older adolescent population? Well, people have looked at what are the components of treatment, and one of the things that really comes out in all of these comparisons is that there are higher doses of certain agents. We mentioned a little bit here that the pediatric regimens are more intensive. In fact, I would argue that they are not necessarily more intensive; they are more dose-intensive in certain drugs. And in fact, the drugs that they are more dose-intensive with are the nonmyelosuppressive drugs listed here: prednisone, vincristine, and asparaginase, as you can see. This is taken from the French trial, on the pediatric regimen, there were much higher cumulative doses of prednisone, vincristine, and asparaginase than were given on the adult trial administered at the same time.

Another thing that people have tried to capture, and I think is much harder to study, is compliance with the regimen. As was alluded to, many people feel that pediatricians, because we use this much more often, are very regimented in making sure that patients comply with the complex dose schedule and guidelines of our regimens. In the French trial, what they tried to look at was the interval between the achievement of complete remission and the start of the next chemotherapy course as a proxy of compliance to protocol, because really the protocols in both cases required that as soon as you achieve complete remission, you moved onto the next phase of treatment.

On the pediatric trial, the median between the achievement of complete remission and the start of the next phase of treatment was 2 days, and only 15% of patients had a delay of greater than 7 days. On the adult trial, the median between achievement of complete remission and beginning the next phase of treatment was 7 days. And this difference was significant.
Slide 83.

The question that has come up, and we have already discussed a little bit in this panel discussion, is could these relatively favorable results for adolescents treated with pediatric ALL regimens be extended to young adults with ALL?

Slide 84.

We have talked about, and Dan presented a number of interesting and intriguing data from a number of trials. I am going to discuss one more trial that was recently published, which comes from Spain, in which they took 81 patients who were aged between 15 and 30 years and were treated all on a pediatric-based protocol.

These patients all had standard risk features at diagnosis, meaning that they all had white counts less than or equal to 30,000 and they all did not have the Philadelphia chromosome or other adverse cytogenetic abnormalities such as \textit{MLL} gene rearrangements. Again, their treatment was a pediatric-based protocol. And I can add, getting back to the question of whether or not adult-based oncologists can learn pediatric regimens, that all of these patients were treated by adult oncologists.

Slide 85.

In this trial, what they could demonstrate was (1) it was feasible for these patients who were aged 15 to 30 to receive this chemotherapy, and (2) they seemed to have a relatively favorable outcome. So they observed a 98% complete remission rate with this pediatric regimen delivered to older adolescents and young adults, and the 6-year event-free survival by age, was 60% for those who were 15 to 18 years old, and 63% in those who were aged between 19 and 30 years. So really, they observed no difference in event-free survival, and again these event-free survival rates are relatively favorable compared with event-free survival reported for other adult-based regimens.

Also importantly, the therapy was reasonably well tolerated. They were not seeing significant complications from this pediatric regimen in this young adult population. And importantly, they really did not see any age-related differences in treatment-related toxicities. So patients who were between 15 and 18 years old really had the same profile of toxicities and the same severity of toxicities as those who were 19 to 30 years old.

Slide 86.

In summary, in thinking about adolescent and young adult ALL, I think it is important to consider that patients within this age group have biologically higher risk disease. They have a lower incidence of favorable cytogenetic abnormalities, the TEL-AML1 fusion, and high hyperdiploidy. They have a slightly higher incidence of
the Philadelphia chromosome, and a much higher incidence of T-cell phenotype. They also appear to be at some increased risk for treatment-related complications. These include an increased risk of pancreatitis and thrombosis with asparaginase, and with osteonecrosis with corticosteroids. But despite these differences, it appears that they have better outcomes on pediatric ALL regimens, and delivering pediatric ALL regimens to older adolescents and young adults does appear to be feasible. And as we have already discussed, pediatric regimens are currently being piloted in adults with ALL. Thanks very much.

Slide 87.

Dr. Schiffer: Thank you very much. Let me just ask you for some practical points. We have heard from multiple people that the induction results are approximately the same because you are in the hospital, you get your drugs, and everyone is pretty good at that. Subsequently, the differences are gross, and it looks, when you look at many of those curves, that some of the differences begin to occur early, and continue through maintenance. What are there some tricks of the trade that even those of us who do leukemia for a living do not know about from the pediatric perspective?

Dr. Silverman: You know, I do not know if I have an easy answer to that. The regimens we use are complex, but I do not think they are undoable to be followed. I think that there is a lot of outpatient-based therapy in our regimens. And outpatient-based therapy is harder to control, because when a patient is in the hospital, you know what they are getting; and when they are at home, you are really reliant on patient compliance to make sure that the therapy you intend to be administered is actually administered. I think that is an important point as one thinks about expanding pediatric regimens throughout the age groups, is really coming up with strategies to ensure compliance, to help people at home take these regimens as they are prescribed. I think that is really the most important part of this, is really sticking to the recipe that we have come up with.

Dr. Schiffer: Mothers.

Dr. Silverman: Well, mothers certainly do help.

Dr. Douer: Spouses.

Dr. Schiffer: Spouses.

Dr. Hunger: I think one point I would add to what Lewis said is one of the differences in the comparisons that have been made in similar-age patients between patients treated on pediatric and adult trials is the early CNS therapy. When you look at the CCG (Children’s Cancer Group) and CALGB comparison, which showed an over 30-point event-free survival advantage for the pediatric trial, there were 10, more than a tenfold increase in CNS relapses on the adult trial. That particular adult trial had delayed central nervous system prophylaxis. In fact, patients did not even receive a lumbar puncture at the time of initial diagnosis, so they did not know who
was CNS-positive or not. It seems to me, for reasons that I do not quite understand, to be honest with you, that there, at least in the past, has been a reluctance to give early CNS-directed therapy, or even to perform a lumbar puncture in a thrombocytopenic adult. I think that that is a key, relatively simple intervention that could improve outcome, is determine who is CNS-positive at diagnosis, and treat all patients with CNS prophylaxis beginning from day 1 of therapy.

**Dr. Schiffer:** We did not do that in the COTB study. What do you do?

**Dr. Thomas:** With the hyper-CVAD regimen, actually the CNS therapy started on the second day of induction chemotherapy. So they received intensive intrathecal chemotherapy concurrently. If they have CNS disease, we actually intensify the intrathecal chemotherapy a little bit more so than actually they do in the pediatric group where they give weekly intrathecal methotrexate if they have CNS disease. We actually give it twice weekly until they clear. Also the hyper-CVAD regimen has high-dose methotrexate and high-dose cytarabine in there, which offers additional CNS protection.

**Dr. Schiffer:** But not until the second month.

**Dr. Thomas:** Correct.

**Dr. Schiffer:** And, Steve--.

**Dr. Thomas:** Right. But I think that is a very valid point. I think you cannot treat one compartment of the disease and ignore the other, because even if the patients go into complete remission and do not have CNS disease at diagnosis, they still have the propensity to develop CNS disease there, which can serve as a reservoir for subsequent disease recurrence. So I actually agree with that point. I think that is a very significant factor in terms of the difference between pediatric and oncology intervention.

**Dr. Silverman:** I think the other important point that comes from that comparison in the CALGB trial, all the adults actually received cranial radiation. So it is not even that definitive or intensive CNS-directed therapy later can make up for the fact that you are not doing it early on. That really struck me as I reviewed that trial, that it is really the early initiation of CNS-directed therapy, which may be a very important feature.

**Dr. Douer:** In our study, that I presented, we started intrathecal on day 7, and give two induction, so earlier. The other thing that I will mention, we do not see osteonecrosis so much in adults. I do not know if that is your experience. Is it because you use more dexamethasone rather than -- ? I have not seen it so much.

**Dr. Silverman:** I do not know, certainly there are issues related to steroid preparation in pediatric patients, and perhaps a higher risk of osteonecrosis with dexamethasone compared with prednisone, but I do not think that is really the answer to it, because our experience in administering our pediatric regimen in adults
with ALL, which we have been doing now since 2001, is that we really do not see much in the way of osteonecrosis in adults. So I think it may be as much a patient-based issue as it is the therapy-based issue. I think that is an important point as well, that there has been a long fear that adults will be unable to tolerate these intensive pediatric regimens, and some of that is based on how teenagers do, but in fact, some of the side effects of teenagers may have something to do with being a teenager, and that in fact adults do not seem to experience the same steroid-related morbidities that we are seeing in the growing adolescent.

**Dr. Schiffer:** Let me ask a question about maintenance, because about, I do not know, well more than half of your time is spent receiving that. And one of the things I learned from pediatricians was to push the maintenance harder, that is, not to be satisfied with, because it is almost the pharmacodynamic measurement. You know, do not get nervous at a neutrophil count of 1500, or things of that nature. I noticed that in reviewing many of the adult trials, that people would cut back their doses at probably higher than optimal neutrophil counts. Do you have some thoughts about that?

**Dr. Hunger:** Well, I think maintenance is the big black box of pediatric ALL therapy, and perhaps adult ALL therapy also. Why do you need it? How long do you need it for? It does seem clear that very high-risk patients probably can get away with significantly less maintenance than lower risk patients can. But I do think that certainly compliance is an issue, and compliance cuts both on the patient side of compliance: Does the patient take the prescribed medications? And on the physician side of compliance: Does the physician adjust the medications as directed by the protocol? We typically look for a tighter range of myelosuppression, which is simply a surrogate of the efficacy of antimetabolite therapy. So we adjust medications to keep the absolute neutrophil count between 750 and 1500. Other centers go lower. The St. Jude trials, I do not know what Boston does, but the St. Jude trials do not drop doses unless the ANC drops below 300. So I think certainly 1500 is much less aggressive than we are in pediatrics, in adjustments.

**Dr. Schiffer:** I have certainly changed, and I routinely will go down to 750 without hardly noticing it. It means you have to see the patients obviously to monitor. There is a lot of talk about asparaginase and intensive asparaginase. Tricks with asparaginase? For example, pancreatitis. Can you administer more asparaginase after you have an episode of pancreatitis versus amylasitis?

**Dr. Silverman:** That is a great question, and we struggle with that a lot, because we are so asparaginase intensive in our regimen, and have actually tried to look at that. First off, we tried to differentiate between amylasitis and symptomatic pancreatitis, and we do screen patients for amylase levels before administering asparaginase. And if we find a high amylase level in an asymptomatic patient, we will hold the dose, but we do not discontinue asparaginase. I have to tell you (1) that is a pretty uncommon finding, and (2) all those patients that we have rechallenged, they seem to do quite well. Patients who have clinical pancreatitis characterized by abdominal pain and symptoms along with their high amylase or lipase levels, if someone has a severe case of pancreatitis, which we have definitions in the protocol, but I think we
all have a clinical sense of what is a really bad case and what someone who has a couple of days of mild abdominal pain and gets better, for severe pancreatitis, we do not rechallenge patients. For mild cases, we have rechallenged patients. We looked back at how those patients did who we rechallenged. About half of them develop a second episode of pancreatitis, and about half of them do not. Of the ones who do, we were still able to get in a median of 8 weeks more of asparaginase into them. I think it is a balancing act, and I think in many ways, if a patient has had any episode of pancreatitis, in some ways you need to balance, they are at very high risk for getting more pancreatitis, even if that first episode was mild with asparaginase. But you might be able to eke out a few more doses if you think it is important enough. And in those cases, I think there is some clinical decision making that can be made.

**Dr. Douer:** I can tell you our experience in that, we do not stop it if it is high amylase. We continue. But if the patient has pancreatitis clinical, we do not give subsequent doses. But one trick we have found that if you admit the patient very early, the first symptoms of abdominal pain, and put them NPO and treat them very aggressively with IV, they tend -- and it is not based on a lot of patients, but that is our feeling -- they tend not to progress into the severe pancreatitis that you can -- that requires surgery or hemorrhagic. So I think early recognition might be helpful, not preventing pancreatitis, but preventing severe forms of pancreatitis. That is what you are worried about.

**Dr. Schiffer:** Okay, thank you very much. I will point out that this discussion took us up to the age of 30. We still have between 30 and 60 to deal with, both in terms of understanding whether they can actually tolerate these types of regimens, and of course the likelihood that the biology is going to be changing also. So there are still a lot of jobs to do.

**The Prognostic Implications of Minimal Residual Disease in Acute Lymphoblastic Leukemia/Discussion/Conclusion**

**Slide 88.**

**Dr. Schiffer:** Our last presentation by Steve Hunger will discuss the prognostic implications of minimal residual disease. Certainly in this regard, the pediatricians are way, way ahead of us in trying to understand how this might govern further therapy, indeed in adults who would love to have to deal with this problem of minimal disease.

**Dr. Stephen Hunger:** Thank you very much. I am going to talk now about the prognostic implications about minimal residual disease in ALL.

**Slide 89.**

I have no disclosures to make.
Slide 90.

As we have referred to earlier, there have been tremendous improvements in the outcome of children with ALL over time. This slide is one from the Children’s Cancer Group that shows the outcome from the late 1960s to the late 1990s with significant improvements steadily during that time. Other groups, the Dana-Farber, St. Jude, the European groups can show more or less the same slides.

Slide 91.

We have looked more recently to see if these improvements in outcome have continued, and whether any improvements that occur are limited to different groups or occurring across the board. This slide shows an analysis we did recently of over 21,000 patients enrolled in Children’s Cancer Group trials between 1990 and 2005. We divided that interval into three different eras of approximately equal length, each of which accrued a little bit over 7000 patients.

As you can see here, we saw a stepwise improvement over time with the 5-year overall survival increasing from almost 84% between 1990 and 1994 to over 90% in the most recent 5-year era between 2000 and 2005.

Slide 92.

This slide shows that that improvement occurred across the board. So in every subgroup we looked at, we saw significant improvement in overall survival. Here we show age subgroups, including those over 16 years of age. We show increases in B-lineage, increases in T-lineage, and increases in those we call standard or high risk. And overall, there was a 42% decrease in the risk of death between 1990 and 1994, and 2000 to 2005, and that was seen across the board with between a 25% and a 50% decrease in the risk of relapse in every group of patients.

Slide 93.

This is certainly very encouraging, and from this we concluded obviously that there has been a substantial reduction in the number of deaths that occurred since 1990, and these reductions have occurred in all patient subsets. Remember when we start to examine the absolute number of deaths, and where they occur, what this tells us is that to try to further improve outcome, we have to focus on both very high-risk patients, such as those we talked about earlier with Philadelphia chromosome-positive leukemia, or other cytogenetic abnormalities, and also patient subsets that overall have a very good prognosis, because 35% to 40% of the deaths still occur in patients that have what we call standard risk features, so age between 1 and 10 years of age, and an initial white blood count less than 50,000. We cannot simply
congratulate ourselves on this significantly good outcome of these patients. We have to continue to focus our efforts to try to cure more patients in this group.

Slide 94.

What are some of the mechanisms by which we might approach it? Well, certainly one of the most powerful prognostic features that exists is the early response to therapy in ALL. I think we all know that there is a very poor outcome for patients who fail to enter complete remission after 4 or 8 weeks of chemotherapy. However, this is really a very limited clinical utility, because in most trials over 95% of patients enter complete remission, and in the pediatric trials, the rates generally are in the range of 98% to 99%. So identifying patients that do not enter complete remission is really not going to help you improve the overall cure rate of children with ALL.

One of the things that has been observed for quite a long time is that the degree and rate of clearance of lymphoblasts during induction is a powerful predictor of outcome. I think the second point that is very important is that the Children’s Cancer Group has shown in past therapies that if you take patients who have a poor early response and are predicted to have a bad outcome, if you intensify their therapy, you can improve their outcome significantly. We can use early response to try to identify patients who are at higher risk of recurrence and introduce different therapies to that patient.

You can measure early response in several ways. The first, and certainly the cheapest, is that developed by the BFM group, which is to look at the response to a prednisone prophase. Patients receive 7 days of prednisone and a single dose of intrathecal methotrexate, and you look at the number of peripheral blasts after a week, and you see that those who have more than 1000 blasts per microliter have a dramatically worse outcome than those with a lower blast count.

The other analysis that the Children’s Cancer Group used for a number of years is the bone marrow morphology during induction. Simply enumerating the percentage of blasts remaining at day 7 or day 14 of induction also is highly predictive of outcome. More recently, most groups have moved to what are called minimal residual disease analyses.

Slide 95.

Minimal residual disease. What is it, and how do we measure it? Well, first, we have the observation that the morphologic assessment is a crude but accurate and reproducible way to identify patients who have either very good outcomes or very poor outcomes. MRD is the presence of cells following chemotherapy that are below the limits of morphologic detection. So typically by morphology, you can detect
blasts in the range of about 5%, perhaps 1% if you are a very good morphologist. Minimal residual disease techniques typically can achieve a sensitivity that can detect one leukemia cell in 10,000 to 100,000 normal cells. So you can now detect disease at the range of 0.01% or 0.001%. The hypothesis was made by a number of groups that more sensitive measures of early response should be a more accurate way to identify groups for risk-directed therapy.

Slide 96.

What techniques can one use to assess minimal residual disease? Well, what I am going to spend most of my time talking about today is the detection of leukemia-associated phenotypes via flow cytometry. This is applicable in almost all cases. It is fast and relatively inexpensive. It is somewhat less sensitive than molecular methods, but it is not clear that that limited sensitivity has significant clinical relevance.

The second technique that has been used very widely is PCR amplification of antigen receptor loci, derived from immunoglobulin gene rearrangements or T-cell receptor rearrangements. In large studies, this has been applicable in about 80% of cases, perhaps 90% with more current technology, so one limitation of this approach is that not all patients can be analyzed. It is laborious and expensive. The costs today are roughly tenfold higher than flow cytometry, but it is very sensitive.

I think one of the important things is that parallel studies of flow cytometry and PCR performed on the same samples at the same institution have shown very similar results. So I think we are measuring the same phenomenon, although the techniques and values may vary.

Another mechanism that certainly can be used is PCR amplification of translocation-derived fusion transcripts. This is limited to specific defined patient subgroups that have a particular translocation. It may be very valuable in those groups, such as Philadelphia chromosome-positive ALL, but it is not widely applicable, and cannot be used in all patients.

Slide 97.

This slide shows an example of flow cytometric detection of leukemia cells. In the top slide we see a normal pattern of antigen expression, and then in the bottom slide we see a diagnostic ALL sample with the leukemia cells shown as green dots. You can see that they appear in different regions and space in this slide.

Slide 98.

Then at the end of induction, we see at the top, we see the diagnostic slide from the same patient; and then at the bottom, the day-28 slide where we see that there are
still green dots existing, and this patient had quantitated 0.039% minimal residual disease at end induction. These techniques can be done very rapidly, and can be done in a centralized manner.

**Slide 99.**

I would like to show you some of the data from one of our recent trials in the Children’s Oncology Group. This is the COG P9900 series, studies that were conducted between 2000 and 2005, and part of these studies included minimal residual disease analyses to see how predictive they were of outcome, and whether they could be implemented in the context of multi-institutional trials.

Patients were treated at more than 100 centers throughout the United States and Canada. They had bone marrow collected at the end of induction, and later in therapy as well, and also peripheral blood collected at day 8 at their local institution. More than 2500 patients were enrolled in these trials, and then these samples were shipped to a single reference laboratory directed by Dr. Michael Borowitz at Johns Hopkins Hospital. Now first of all, the analysis was clearly feasible. These data were available for more than 98% of patients within 24 hours of sample receipt. This established that this centralized real-time detection of minimal residual disease was feasible in the context of a cooperative group trial.

It is important to emphasize that in this trial, because we were simply determining the feasibility of this approach, the MRD (minimal residual disease) results were kept blinded, and no changes in therapy were made, based on these results, and the results were not conveyed to treating physicians.

**Slide 100.**

This slide looks at the influence of MRD determined at end induction by flow cytometry in this clinical trial. What you can see here is we have looked at the 5-year event-free survival of over 2000 patients who we have divided into 3 groups. In the top line are those patients who are negative with a sensitivity of 0.01% at end induction. These patients have a 5-year event-free survival of 88%. In the bottom curve, we see patients who had MRD positive at greater than 0.1% at end induction. These patients had only a 43% 5-year event-free survival. And the middle curve shows an intermediate level of MRD. Clearly the MRD present in the bone marrow at end induction is highly predictive of outcome.

**Slide 101.**

It is interesting to wonder what you are measuring when you measure MRD. When we look at induction, the patients received either 3 or 4 drugs for 4 weeks of therapy. There are a number of drugs that get introduced later into ALL therapy that
these patients have never seen, so they did not receive any cyclophosphamide, any 6-mercaptopurine, any methotrexate, any ara-C; however, response to therapy is highly predictive of outcome, and it predicts both early and late relapses.

What this slide does is look at the influence of day 29 MRD levels on relapse. On the left hand panel, we see what happens in the first 3 years. And within the first 3 years, about 30% of patients who are MRD-positive will relapse within that time, whereas only about 7% of patients who are MRD-negative will relapse within that time.

However, then if you look in the right-hand portion of this slide, we look at what happens after 3 years. We look at all the patients who are still in remission at 3 years, and the MRD level at the time of the end of induction therapy was still highly predictive of outcome. Of those who are MRD-positive at end induction, about 30% relapse in the next 2 years, whereas those who are MRD-negative at the end of induction, only about 5% relapse in the next 2 years. We are clearly measuring with early response kind of a general sensitivity to chemotherapy, not a sensitivity to specific agents.

**Slide 102.**

Interestingly, MRD is very predictive, as I have shown you, of bone marrow relapse, but it is not predictive of extramedullary relapse. This slide shows this in very nice detail. On the left hand portion of the slide, we look at the rates of bone marrow relapse among patients who are MRD-positive versus negative, and you see that the patients who are MRD-positive at end induction have a much higher rate of bone marrow relapse than those who are MRD-negative. On the right hand portion of the slide, if you look at the rate of central nervous system or other extramedullary relapse, the risk is more or less identical between the two groups. So I think this is an important message to us, that MRD levels at end induction are very predictive of bone marrow relapse, but do not tell us about extramedullary relapses.

**Slide 103.**

Another thing we did on this trial is we looked at peripheral blood at day 8. If you recall the prior slide I showed you, while the patients who are MRD-negative in bone marrow at day 29 did quite well, about half of the relapses occurred among those patients. How might you find patients who are at a very low risk of relapse? One way would be to look earlier. So here we are looking at peripheral blood MRD at day 8 of induction, and we see a rank ordering of the outcome of patients with the patients who are MRD-negative doing much better than those who are MRD-positive. The more MRD you have in the blood at day 8, the worse the outcome is.

Now if you look at the patients who are MRD-negative in the peripheral blood by day 8, only 16% of events occur in that group. So you are starting to see that you can identify groups at very low risk of relapse by looking at those with the fastest
response to therapy.

Slide 104.

This shows a multivariate analysis of these data, and it shows that the most powerful prognostic finding in this study was the day 29 bone marrow MRD studies. Other things of prognostic significance included NCI (National Cancer Institute) risk group and cytogenetic features. Interestingly, the test that we have previously used is the gold standard for early response, the bone marrow morphology during induction, no longer had prognostic significance in this multivariate analysis. We now think that MRD is the best marker of early response, and are moving toward abandoning bone marrow morphology as a measure of response.

Slide 105.

The conclusions of this study are that the day 29 and day 8 MRD levels are highly predictive of bone marrow but not central nervous system relapse. We feel that the best cutoff for identifying patients at an increased risk of relapse is a bone marrow level of greater than 0.01% at end induction. Using this, we can eliminate day 8 and day 15 bone marrow morphologic response, and that the bone marrow MRD at end induction predicts both early and late relapse.

One question that comes from that is, can we look at MRD response at later time points, and can that help us to predict patients of different risks of relapse, and perhaps use that to select different therapies for different patients?

Slide 106.

There are less data on time points after the end of induction, but we wanted to look at what data are available. Now in the study I just showed you, we also collected bone marrow samples later in therapy. It varied per trial, and it was between week 22 and week 30 of therapy. When you look at this, you see overall about 5% of patients are still MRD-positive at this time, using flow cytometry of the bone marrow.

One might anticipate that these patients would have a very, very low chance of cure, because this really is near the start of maintenance therapy, where they have received most of their intensive therapy.

Slide 107.
This slide, I think, is surprising for several reasons. First off, what it does is it looks at the patients who are MRD-positive at end induction, and then looks at whether they cleared their minimal residual disease level between then and week 22 to week 30. If they cleared the MRD by that time, they do better than if they still had MRD at that time. But one of the things that is more remarkable to me is that still about a third of patients who are MRD-positive late in therapy were cured by continuing the same chemotherapy.

It does tell us that we do not completely understand therapy, and I think it also tells us that maintenance therapy is an important component. Relatively few patients were still strongly MRD-positive at this late time point in therapy.

Slide 108.

The BFM group has also taken a look at a more intermediate time in therapy, which I think is very instructive, and probably is a more valuable point in time. So they have looked at the end of induction, which they term time point 1, and they have looked at the end of the consolidation or protocol 1B block, that they call time point 2. In a pilot study done in 1991, they analyzed a relatively small number of patients, about 100 overall, and grouped them into three risk groups. In the so-called MRD high-risk patients, who were those who had MRD that was at greater than 0.1% at both the end induction and time point 2, so week 12 or 13 of therapy. They have recently published long-term follow-up of these data, and they showed that with small numbers, only 15 patients in this MRD high-risk group, the 10-year event-free survival was only 16%. So if that holds up, that would certainly tell you that analyzing MRD at that point in time could identify a group of patients in whom further continuation of the same chemotherapy is unlikely to be effective.

Slide 109.

In the more recent BFM study, the BFM 2000 study -- and this was presented recently at the SIOP (International Society of Paediatric Oncology) meeting in 2008 -- they now have analyzed over 2500 patients, and put them into different risk groups. In these so-called MRD high-risk groups, again, is the same definition, those who are positive at a level of greater than 0.1% at both the end induction and week 12 of therapy, and overall about 8% of patients fall into this group.

Slide 110.

When you look at the outcome of that group, those patients had a somewhat better long-term survival, but still quite unsatisfactory with the 4-year event-free survival of only 35%.

Interestingly, what they did in that study is they, following determination of MRD at this second time point, they gave three blocks of additional chemotherapy. They then
checked MRD levels again. So if the patients became MRD-negative at this second or third time point, and then went on and had a stem cell transplant, they had a 4-year event-free survival of 78%. Showing patients that get a slow response to therapy, but eventually cure their level of disease, measurable in the bone marrow, do very well if they receive a stem cell transplant.

However, if they remained MRD-positive now, and this is about 20, 24 weeks into therapy, the outcome was much less favorable, with stem cell transplant 43% event-free survival, with chemotherapy 17% event-free survival.

**Slide 111.**

The conclusions that I would make from this is that end induction MRD levels are highly prognostic of outcome, and can be used to assign postinduction treatment intensity. There is an inverse relationship between level, increasing levels of MRD, and decreasing event-free survival. Earlier measures of MRD such as that obtained in the peripheral blood at day 8 of therapy may help to identify ultra-good-risk patients. We believe from our studies that detection of MRD via flow cytometry has logistical advantages for large-scale clinical trials. In the current clinical Children’s Oncology Group trials, we use this for all patients to adjust postinduction treatment intensity. We enroll over 2000 patients a year in these trials from over 200 institutions, and are able to turn around these results within 24 hours, and over 98% of patients have informative results.

I think it is also likely that MRD later, perhaps at week 12 to 13 of therapy, may help to refine the prognosis and identify patients in whom novel intervention should be tested.

**Slide 112.**

Thank you very much.

**Slide 113.**

**Dr. Schiffer:** Thank you. You have raised a number of really intriguing issues. First, just a comment about the ALL slide, the one that shows improvement over the years. One of the things that is intriguing -- and I think it was Archie Bly who I recall mentioning it -- is that much of that improvement, if not almost all of it, occurred without the discovery of new drugs, and with better understanding of how to use them. To my mind, without much understanding of the biology, that it antedated all of the fantastic things that we have learned about the biology of ALL.

Amongst the questions that are raised by the MRD, and let me pose a couple of them to you, these were all done in a central laboratory. We now get reports sometimes from our pathologists that detect the leukemia cell by flow without standardization
as to methodology percentage, etc. It is obviously standardized in your hands. How can that be made more readily available in a reliable way?

**Dr. Hunger:** I think that that is an important issue. Our laboratories that do this testing have gone to great pains to standardize the assays between two different laboratories, and we have shown, in fact, with 2000 patients a year, we show almost identical percentages of MRD-positive patients in the two different laboratories, which really argues that they are measuring things well.

Unfortunately, I do not think that that extends to the analyses done routinely in the majority of otherwise very competent flow cytometry laboratories. So I am very leery to take MRD value from laboratory X and use that to intervene on patient therapy. There are some very good labs out there. There also are some that are perhaps not as adept at this type of measurement. We probably have not done as good a job as we should in the United States about moving towards standardization. One of the things that our European colleagues did with flow cytometry is with molecular determination of minimal residual disease, is they put enormous effort into a collaborative effort throughout a network of laboratories into standardizing the assays, exchanging reagents, and proving that you could do this in multiple laboratories with molecular techniques. The Europeans have actually been slower to use flow cytometry for minimal residual disease, but currently they have efforts to do the same sort of standardization with flow cytometry across a number of laboratories. I think that this can be done, but I do not believe it has yet been done, and I am personally leery about using MRD from labs that I do not know well.

**Dr. Schiffer:** I guess we do not know very much about its applicability to adults obviously.

**Dr. Hunger:** We do not, but certainly there are data there, and Lewis can speak. I know the Dana-Farber has been doing, and they have done a number of analyses on MRD. There is no reason to think that it should be any different in adults, and none of the data I have seen from groups suggest that it is any different --

**Dr. Silverman:** Right. I think there are more limited number of studies in adults with ALL. It appears that adults with ALL have a higher proportion of patients with high-end induction MRD than we see in the pediatric setting, but I think the overall trends that high MRD seems to portend a poor outcome appears to be true, even in these limited studies in adult ALL.

**Dr. Schiffer:** And I guess in adults, the flip side of the question is whether being negative --

**Dr. Silverman:** Is better.

**Dr. Schiffer:** -- it will hold up in the long run. Of course, the $64,000 question -- that is an old phrase -- is what to do when you find it, and we have heard -- we have had talk about that transplant trial and maybe we can get some thoughts about what you do should you have a credible assay, and you find it.
Dr. Thomas: You are referring to the MRC, the ECOG trial?

Dr. Schiffer: In terms of the largest transplant trial, but what do you do when you find...?

Dr. Thomas: MRD?

Dr. Schiffer: Yes, because in adults, we think we -- almost this intensive as we possibly can be. We may not be, but I mean, that is the intent of our regimen. So what can we do?

Dr. Thomas: Well, I mean, MRC trial that actually also looking at minimal residual disease, and they found that to be significantly prognostic for relapse-free survival. In that setting, the potential issues had to do with the intensity of the chemotherapy administration prior to allogeneic stem cell transplant. It may be that perhaps if they had a more intensive regimen prior to the transplant, the differences in the standard-risk group would not be as obvious because any time you intensify and treat a less-intensive treatment with the transplant, you are going to get a better outcome. In that particular intervention, the minimal residual disease positivity was relatively high, and those patients underwent stem cell transplant, and they had a better outcome. I think that there are a few factors that may play a role in terms of interpreting that data.

Dr. Douer: I think there are some studies and results that show some predictability of positive and negative MRD on prognosis similar to children. The question is what to do with it. I think first it tells us that whatever chemotherapy we are giving, that it is not so effective, and that means changing the modality to a graft-versus-leukemia approach, which is immunotherapy, and thus transplantation makes sense. I am not sure that we did finish exploring the chemotherapy. I think in adults we still have a ways to go, especially with the pediatric approaches; and maybe with these approaches, we will have less patients that will have positive MRDs, and there will be less need to go to transplantation. But if you end up with a positive MRD usual best chemotherapy agents, it tells us you are becoming resistant to it, depending question of what time. That would make sense to move to transplant. The other problem, I think, in general in ALL, we do not yet have in adults very good prognostic factors. We are using age and kind of a median of 35 to middle, which is very arbitrary, white cell of 30,000. We are beginning just to look at chromosomes. We are beginning to look at that, and I think MRD may end up to be even in adults possibly the most important predictive factor which will be worthwhile in a future study of transplantation to use this as a model to study transplantation.

Dr. Silverman: I think that is an important point, going back to Steve’s first slide of improving outcomes over the last 2 decades. He had the last decade and a half, but if you go back further, and your comment that we did not really have many new drugs, one of the major things that was going on in pediatric ALL research was the identification of prognostic factors and risk stratification, and really the application of more intensive regimens to patients at higher risk of relapse. To start, we had age
and white count as our proxies, and over the years we have become more adept at identifying underlying biological subtypes of ALL. I think MRD is yet one more example of our being able to more sensitively identify patients at higher risk of relapse, and whether or not we can find conventional or novel chemotherapeutic agents for those patients, or whether stem cell transplant is the answer, I do not think anyone knows. But I think what it allows us is to really identify a subgroup of patients in whom we know our conventional chemotherapy is unsuccessful. That is the first step to really improving the cure rate.

**Dr. Schiffer:** What is COG doing when you detect it in the current trial?

**Dr. Hunger:** We are doing a couple of things. I think the first thing is that we have shown in previous trials that if we apply our most effective therapy to patients who appear to be at low risk of relapse, but have a poor early response, they do much better. Any patient who is MRD-positive at end induction, then is shunted to more intensive chemotherapy, but it is really a standard chemotherapy regimen, if you will.

I think, in the future, we plan to use high levels of MRD to allocate patients to novel therapy strategies, and I do think the European data suggest that bone marrow transplantation might be appropriate in patients who have high levels of MRD later in therapy. What I did not highlight out of their data is if you have positive MRD at end induction, but then you clear it by week 12 or 13, those patients actually did quite well. I do not think the end-induction MRD levels should be used to allocate patients to stem cell transplantation. It might be the later levels. The other thing that is very clear from these and other data is that taking patients to transplant who are MRD-positive at a time of transplant, is going to cure only a very small minority of those patients.

One of the problems with prognostic factors is they do not really do us any good if we just develop a very fancy way to identify patients who are not going to do well. We want to identify patients who we can help by changing their therapy.

**Slide 114.**

**Dr. Schiffer:** Thanks very much. These have been really interesting, and I think fun presentations and discussions, and I have learned a great deal. Before closing, I would like to just show a slide that addresses some questions that I think remain unanswered, and I hoped you would find intriguing.

The first is we have discussed a good deal about minimal residual disease, but really we had not resolved the issue of what to do after you find it, particularly in people who have already been treated intensively. As an adult oncologist, I would certainly look forward to the time when I can actually have these data to try to use them in my patients.

Another point that we alluded to, and it was shown in some of Lew’s slides, is there
are profound biologic and cytogenetic differences between childhood and adult ALL. A good example is in the non-Philadelphia B-lineage diseases. Why does that happen? It is likely that the adult ALLs do not derive from mutations and disease that occurred in utero, but I think we have very little insight as to why this difference occurs, and, of course, this may also influence to some extent the results of therapy.

The whole issue of transplantation in B-lineage ALL, again, particularly for adults, remains very confusing, and certainly patterns of care have begun to be changed and influenced a little bit by that very prominent presentation and paper, which is a meritorious study, but has a number of issues that one can quibble with. The last question that I would like to leave you with is one that really intrigues me about many cancers, ALL and AML in particular, and that is you guys have told us how to cure patients, and how to cure a high fraction of patients. But that is not the same thing as understanding why patients are cured. Why does the disease go away? Explanations, a simple explanation is you just killed the last cell by smacking it repeatedly with chemotherapy. That may be somewhat naïve. In AML, we wonder sometimes whether you can differentiate the leukemia and actually have clonal remissions. Another possibility is that somehow immune surveillance becomes reactivated, the same immune surveillance that disappeared and allowed the cancer to grow somehow with all the crude stuff we do to people, comes back. But I think it is a simple question, but with profound implications, if you can figure out the answer. I end a lot of my lectures with that question, and with no answers.

Slide 115.

But in any event, in closing, I would like to thank all of you for your attention, and I hope that you found what we presented today will be useful to you in your practice. I would like to thank all my colleagues for terrific presentations, and discussions, and again thank you all for joining us.