Hello, and welcome. I'm Dr. Chetasi Talati, I'm the chair for this activity. Before we begin, I would like to start by recognizing a panel of experts who I have had the pleasure of working with on this exciting initiative. Today, I'm joined by Dr. Erba and Dr. Kurtin, and we are going to be discussing how to navigate the changing landscape in acute myeloid leukemia, and what considerations are needed when we are talking about treatment administration in the outpatient versus inpatient setting.

The Changing Landscape of AML

- Rapid expansion of new options to treat AML across the spectrum of the disease
- AML diagnostic criteria
  - Secondary AML
- Induction therapy: outpatient care delivery model
  - Definition and criteria
  - Safety and feasibility
- Reasons to consider outpatient as an option
  - Cost, quality, patient preference, COVID-19 impact

As you may be aware, the treatment armamentarium for acute myeloid leukemia has expanded rapidly over the last three to four years with many new treatments, as well as the new indications. Along with that, the diagnostic criteria for acute myeloid leukemia was revised by WHO in 2016, which we will touch upon as well. Traditionally, the induction chemotherapy has been associated with inpatient hospital stay for about a month. However, with newer therapies, which are out there, the definition of induction has been somewhat challenged, and importantly, the safety and feasibility of such treatments in an outpatient setting has been explored, which we will discuss.

The reasons to consider outpatient therapy for our acute myeloid leukemia patient includes quality of life for these patients. Remember, induction chemotherapy requires a month-long hospital stay traditionally, so can we shorten that for our patients and also account for patient's preferences in terms of do they want to stay inpatient versus outpatient? Are there options? How do we do that? How do we make that happen? Also, currently with the COVID-19 pandemic, this question impacts both physicians and patients in terms of deciding outpatient versus inpatient administration.

Now, I will turn it over to Dr. Kurtin to go over the next few slides.

The Changing Treatment Landscape

Sandra E. Kurtin, PhD, ANP-C, AOCN®
Assistant Professor of Clinical Medicine
Adjunct Clinical Assistant Professor of Nursing
The University of Arizona Cancer Center
Tucson, Arizona

Dr. Sandra Kurtin: Thank you so much. Talking about the changing treatment landscape in acute myeloid leukemia, there have been many exciting developments, particularly over the last four years.

Defining the Criteria for AML and the Current and Emerging Landscape

- AML diagnosis: ≥20% circulating or bone marrow myeloid blasts *OR* the presence of specific cytogenetic abnormalities regardless of blast percentage
- Multiple sub-classifications

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Arber, et al. *Blood.* 2016.

One of the pivotal things that happened is the World Health Organization (WHO) really reclassified the diagnostic criteria and categorization of acute myeloid leukemia in the update that was published-- the 2016 version, which was published closer to 2018. For a long time we've known that a blast count of greater than 20% was consistent with a diagnosis of acute leukemia. Within this new categorization, it has become much more specifically driven by cytogenetic classification, and in some cases, molecular classification. There are two particular categories that we'll talk more about in the middle of the list here, which is AML with myelodysplasia related changes and therapy related myeloid neoplasms.

Secondary Acute Myeloid Leukemia (sAML)

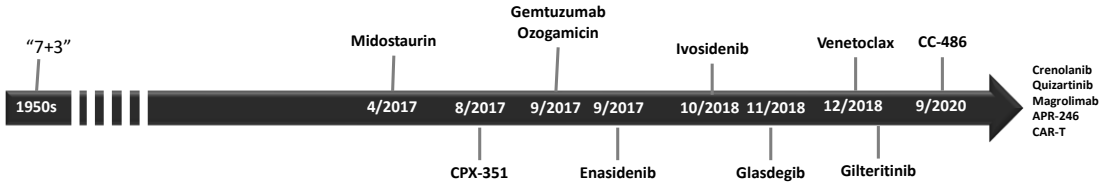
Definition: Secondary acute myeloid leukemia (sAML) refers to a leukemic process either:

(A) Evolving from prior myelodysplasia (MDS), myeloproliferative disorder (MPN), or aplastic anemia with or without treatment*; OR*

(B) Occurring after previous exposure to radiation or chemotherapy exposure for another cancer

Let's talk a little bit more about this newer categorization of secondary AML. This includes two very important subgroups, and it's really important to look at these when you're trying to decide how best to treat these patients. One is AML with myelodysplastic related changes. These are folks that have an antecedent myeloid malignancy, in most cases MDS, and in some cases MPN or myeloproliferative neoplasms or maybe even a crossover of those two. Then a subtype, more rare, but aplastic anemia with or without treatment. These are patients who may not have been treated for that prior myeloid malignancy but have those characteristics based on the cytogenetic profile and morphology primarily. The next group is something we're seeing much more of as people are being treated over longer periods of time for other malignancies. These are treatment related AMLs. This may be due to radiation for instance, to the pelvis in a patient with prostate cancer or exposure to other chemotherapeutic agents and the onset of these varies according to the prior treatment. It may be as soon as three years after they've completed that treatment or in some cases as long as 10 years.

AML: Changing Treatment Landscape



- Supportive care
  - Transfusion support
  - Tumor lysis management
  - Antimicrobial support: treatment and prophylaxis
- Allogeneic stem cell transplant and graft-versus-host disease management
  - Conditioning regimens
  - GVHD management

This is a very exciting slide to me. I wasn't around in 1950 doing this work, but soon after that. We see that much of the change has happened in the last four years. Prior to that we really had 7+3 cytarabine and daunorubicin. Since then, we've now looked at actionable targets. Midostaurin with FLT3, we have CPX-351, which is the liposomal formulation. We're going to hear more about that of cytarabine and daunorubicin, gemtuzumab, the CD33 antibody, enasidenib, our IDH2-targeted agent, ivosidenib, our IDH1-targeted agent, and then several other FLT3 inhibitors, glasdegib, gilteritinib. Venetoclax, a BCL2 inhibitor, much newer to the treatment paradigm. CC-486, which is an oral formulation of a hypomethylating agent azacitidine. Then you see down at the end of the arrow, here's some newer and exciting things coming, some additional FLT3 inhibitors, also a CD47 monoclonal antibody and a CAR T as well as a drug now really specifically targeting TP53, which we know carries an adverse prognostic significance.

I'll turn it over to Dr. Erba.

Current Therapy Regimens

Harry P. Erba, MD, PhD
Professor of Medicine
Director, Leukemia Program
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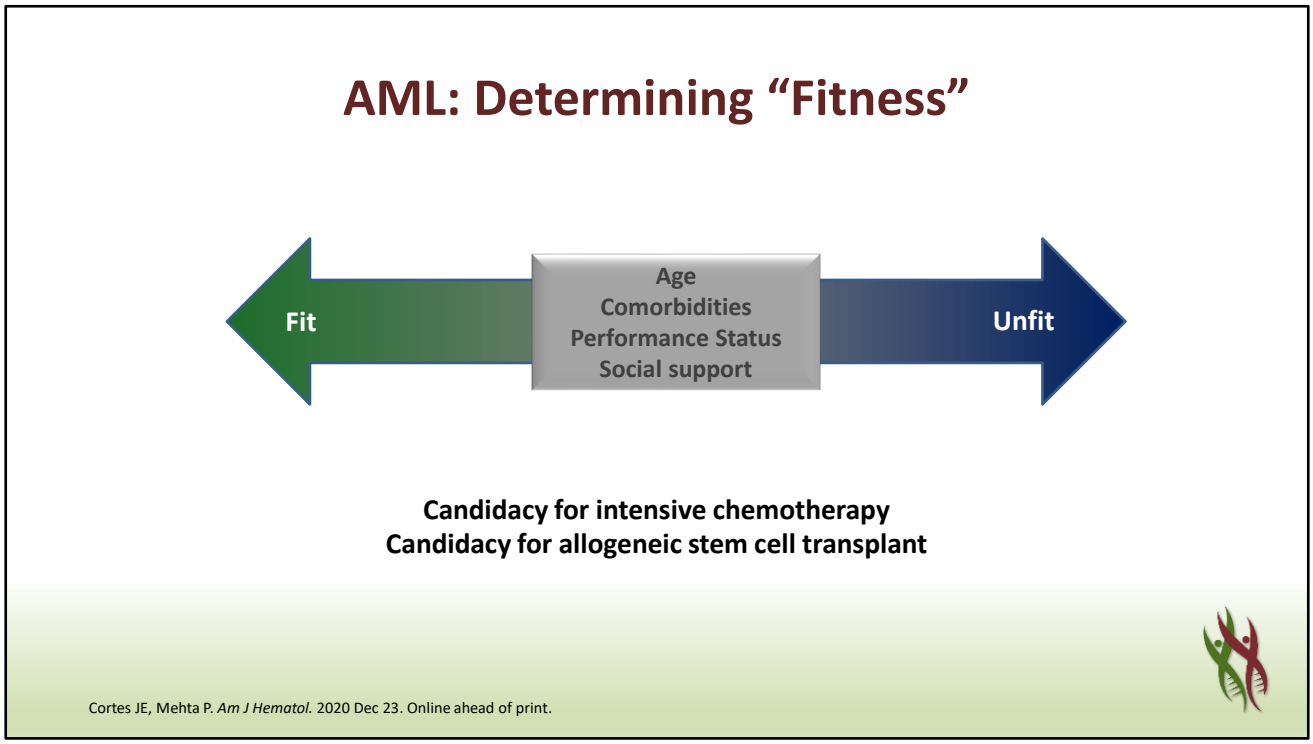
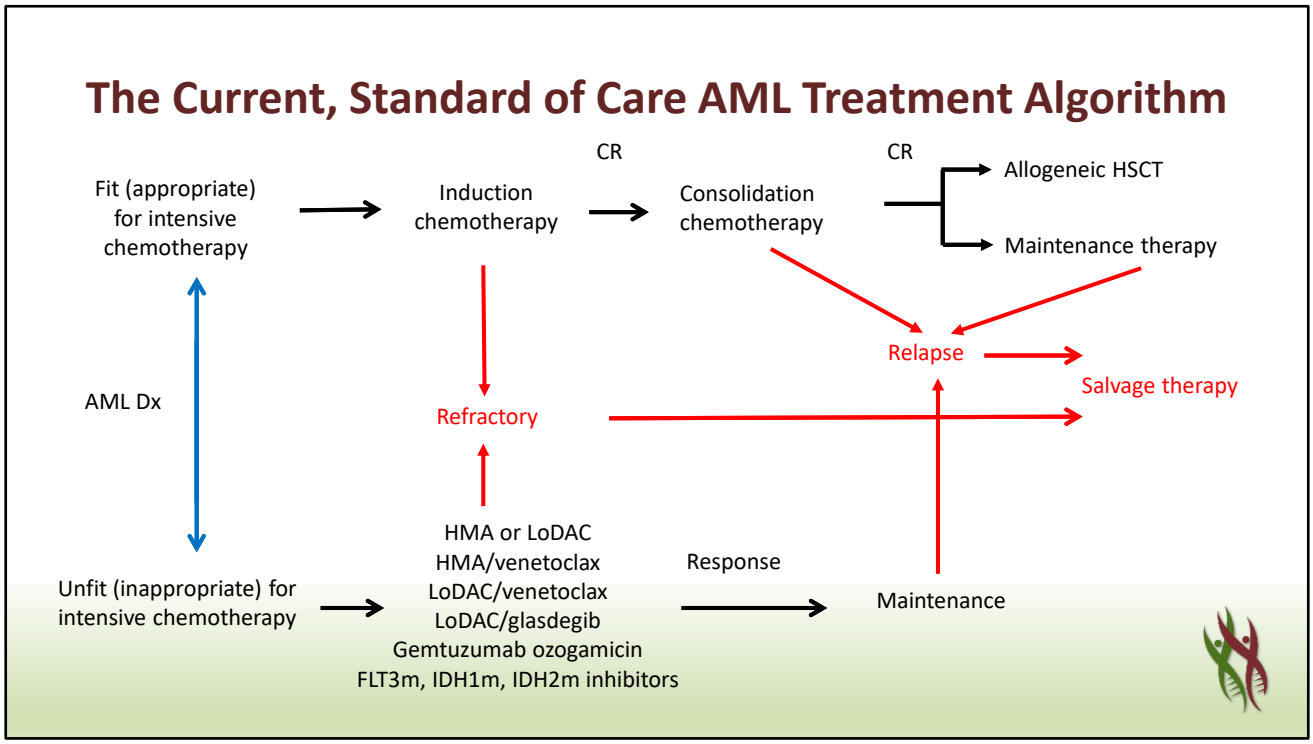
Durham, North Carolina

Dr. Harry Erba: Thanks Sandy. What I'm going to go through are the current therapeutic regimens. Some of the decision-making that needs to be done in choosing between these.



Now, for decades, we have been looking at fitness of our patients to determine what type of therapy they would receive. This comes from clinical trials that have shown that certain characteristics of the patient are associated with increased chance of treatment-related mortality within 30 or 60 days of intensive induction chemotherapy. Many models have been developed. They include things such as, advancing age, poor performance status, comorbidities. Also, we need to look at things that aren't on this list, such as frailty indices for our patients, a get-up-and-go assay for some of our older patients, cognitive function, physical functioning. All very important in determining fitness for intensive chemotherapy. Then in terms of social support, this is critically important as we start to think about outpatient therapy. We'll talk more about that later. Now, the trouble with this fit versus unfit is that there is no one definition that helps us clearly define patients that are fit for intensive chemotherapy or unfit. As time has gone on, we've also learned that it's not just the patient's biology, but the leukemia biology that is really important in this decision-making between intensive and non-intensive therapies and ultimately, candidacy for allogeneic stem cell transplantation. Many of us have gone away from using the word just 'fitness,' which is clearly part of the decision to 'appropriateness' for intensive chemotherapy, which may include things like cytogenetics and mutational burden, specifically the types of mutations. For example, without any randomized trial data to guide us, many of us are less excited about giving a very fit patient with a therapy-related AML or an AML with a P53 mutation and complex karyotype intensive chemotherapy.

Navigating the Changing Landscape in AML: Key Considerations in Treatment Delivery



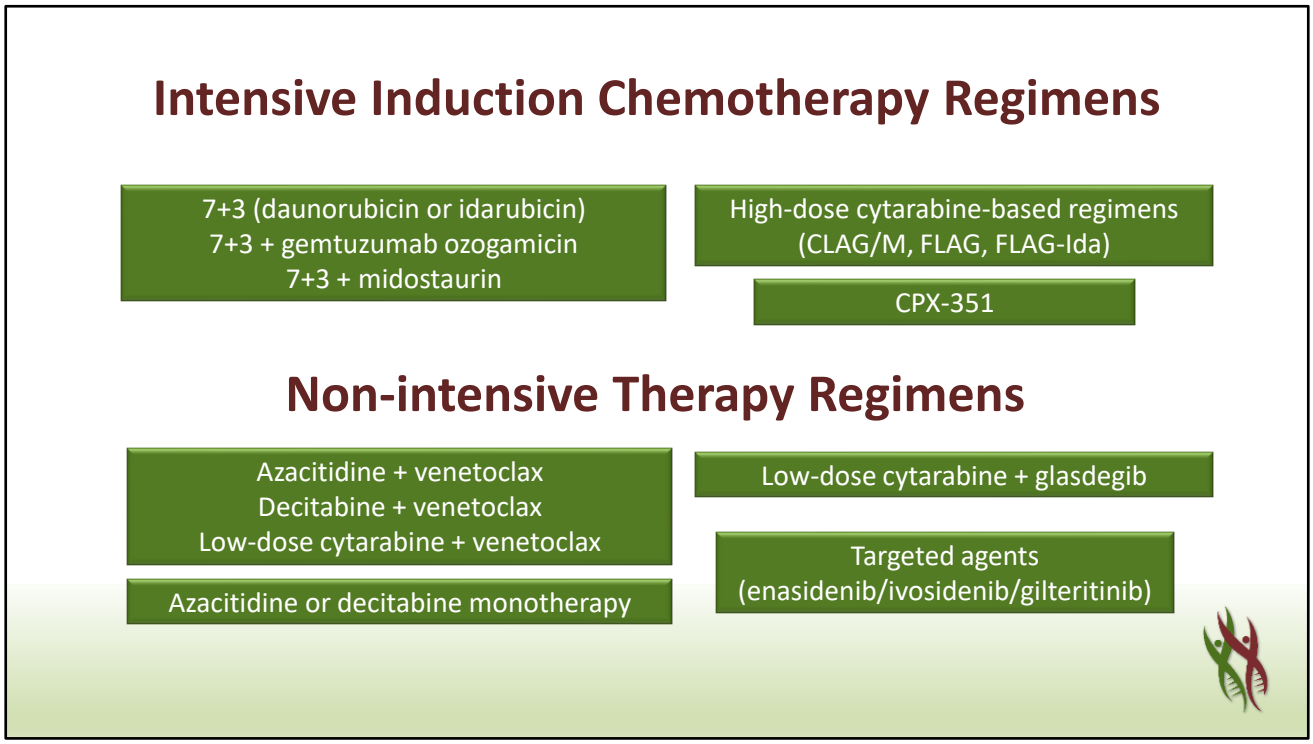
What I'm trying to show you here is our current standard of care for AML therapy. As I said, at the time of diagnosis, we try to make some kind of assessment of fitness or unfitness for intensive chemotherapy. Really, we're talking about appropriateness. I'm going to show you different therapeutic interventions for intensive chemotherapy that can be undertaken. The general algorithm is to achieve a complete remission of the disease quickly, within one or two cycles of chemotherapy, then give post-remission therapy consolidation, often with something like 5+2 or intermediate- or high-dose cytarabine. Along that way, make a determination if a patient is eligible for allogeneic stem cell transplant, which arguably has associated with it the lowest risk of relapse for patients in first remission, or now available maintenance therapies.

Now, part of this decision was so difficult in the past because if the patient was felt to be unfit, that was a big decision to be made because all we really had for these patients is listed at the top of that column at the bottom. That was HMA, decitabine, azacitidine or low-dose cytarabine. Shortly after that, gemtuzumab ozogamicin based on the approval, again, the second approval of gemtuzumab for this population of patients. However, the response rates are incredibly low, 20% to 25% CR rates. They may take quite a bit of time to achieve. They are still associated with the complications of active leukemia, such as neutropenic infections and requiring transfusions.

Now, what I'm going to talk about on the next slide is how this has dramatically changed. Quite frankly, it's beginning to blur this line between fitness and appropriateness even more. Unfortunately though, when we use and one of these

regimens that are considered less intensive, in each and every case, response needs to be maintained with continued maintenance.

Navigating the Changing Landscape in AML: Key Considerations in Treatment Delivery



Here's some of the options that we have. Quite classically, we've been using 7+3 since the initial publication by Yates and colleagues in the 1970s, a combination of seven days of cytarabine and three days of daunorubicin or another anthracycline such as idarubicin or mitoxantrone. For patients with core binding factor leukemias, I think there's really ample evidence now, especially from a meta-analysis that the addition of the anti-CD33 antibody gemtuzumab ozogamicin to 7+3 really improves outcomes, not just response rates. In fact, more importantly, improves overall survival. Based on the results of the international RATIFY trial led by Richard Stone, we know that the addition of the type I first-generation FLT3 inhibitor midostaurin to 7+3 followed by consolidation led to an improvement in overall survival for patients with AML, with FLT3 ITD or TKD mutations.

However, some have employed and chosen to employ high-dose cytarabine-based regimens, as initial intensive therapy, randomized trials between those regimens and 7+3 have not clearly shown any benefit. Nonetheless, the response rates are high and some of these studies show very deep remissions. Specifically, we're going to talk about patients with AML with myelodysplasia related changes in therapy-related AML, where the liposomal formulation of daunorubicin cytarabine CPX-351 has been shown to improve the survival of patients compared to 7+3.

Under non-intensive therapies, the world has changed. In my practice over 30 years, never have I seen such a dramatic shift in treatment paradigm as we saw in November of 2018, when the FDA approved various combinations of the BCL2 inhibitor venetoclax with azacitidine, decitabine, and low-dose cytarabine. Now, based on the results of the VIALE-A trial, we know that Aza-venetoclax is associated with a survival benefit over azacitidine. Now we can offer to our older patients who may not be fit for intensive chemotherapy, a regimen that doesn't waste their time. It has very high response rates in the 70% range and median survival of 15 months. Then specifically, we have targeted agents that can be used, especially in older patients unfit for chemotherapy, the IDH2 and IDH1 inhibitors, enasidenib and ivosidenib respectively. Outside of the label, gilteritinib has single-agent activity in relapsed/refractory disease is not yet approved in the previously untreated patients.

Safety and Feasibility in Moving Chemotherapy to the Outpatient Setting

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Dr. Talati: Thank you very much both for that excellent overview.

Now, let's dive into the logistics in terms of safety and feasibility of moving treatment to the outpatient setting.

Pilot Study to Explore Safety and Feasibility of Intensive Outpatient Initial or Salvage Induction Chemotherapy Administration for Adults with AML/High-risk MDS

- Eligibility criteria[1]:
  - No significant organ dysfunction and a treatment-related mortality (TRM) score <5%-10% (28-day TRM)
  - Regimens: IAP, GCLAM, D-GCLAM, GCLAC, D-MEC
  - All patients were without active infection and had to have normal chest imaging, adequate cardiac function/ no active cardiac issues, TRM score of <9.21, peripheral blast count <10x10^9/L, fibrinogen level >100 mg/dL
  - TRM score calculator[2]

- Total 17 patients (n=8 with initial induction; n=7 with salvage induction)[1]
  - Daily follow-ups
- 14 patients completed induction outpatient (82.4%)
- 3 patients required inpatient admission (n=2 for neutropenic fever; 1 for mucositis)
- 0 deaths within 14 days of treatment initiation

1. Mabrey FL, et al. *Blood Adv.* 2020;4(4):611-616.2. Walter RB, et al. *J Clin Oncol.* 2011;29(33):4417-4424.

I'm going to go through a couple of studies, which are extremely small, but I think are relevant when we are talking about, can we do this safely in an outpatient setting? This small study was actually published in 2020 in *Blood Advances*. The most recent study that's out there. This is a small pilot study comprising of total 17 patients that illustrates the feasibility of outpatient chemotherapy without compromising safety. Patients included on the study received intensive chemotherapy. Regimens are listed here under the second bullet point. Patients could not have any organ dysfunction, and they had to have a low treatment mortality score. The treatment-related mortality score, the TRM score, was actually the calculation that was used, was devised by the University of Washington in Seattle, Ronald Walter, and the paper that was published, which is cited here. They had to have TRM score between 5% to 10% or less than 5%. The lower the better. These patients could not have significant organ dysfunction. They could not have active infection, they had to have normal chest imaging, adequate cardiac function, and not with active DIC and not proliferative disease, which was extremely important when they were deciding whether this patient is eligible to receive chemotherapy as an outpatient.

Out of the 17 patients which were enrolled on the study, 14 patients were able to complete the induction on an outpatient basis. Three patients required inpatient hospitalization. Two had febrile neutropenia, and one had severe mucositis that required inpatient management. Importantly, there were zero deaths seen within the 14 days of treatment initiation.

The caveat here is that the majority of the complications with intensive chemotherapy, we would expect them to occur around week 2, week 3, so 14 days you can argue may be too early to assess the mortality, usually 30 days versus 60 days. However, this is the data that's been published.

The Inpatient/Outpatient (IPOP) Program for CPX-351

- IPOP: Involves close monitoring of patients who receive traditionally inpatient chemotherapy as outpatients
- Exclusion criteria: increased risk for tumor lysis including WBC >50K, increased creatinine/uric acid, active cardiopulmonary symptoms, ECOG >2, no caregiver or unable to reside within 60 minutes of the treating facility
- Daily monitoring with CBC, CMP, uric acid, and phosphorous with planned admission to the hospital on day 6

- Total 22 patients treated with CPX-351
  - n = 14 via IPOP
  - n = 8 via inpatient induction
- Results:
  - 1 of 14 outpatients (7%) admitted on day 2 of induction due to hypotension and a fall
  - 13 outpatients (93%) tolerated outpatient CPX-351 and hospitalized on day 6 as planned for continued care
  - 1 patient on CPX-351 via traditional inpatient approach died prior to day 30
  - Mean hospitalization duration 28.3 (IPOP) and 30.5 days (inpatient delivery)

Outpatient delivery of liposomal daunorubicin and cytarabine in selected patients appeared to be both feasible and safe, significantly reducing the length of hospitalization for induction chemotherapy

This study is specifically for CPX-351, the liposomal formulation of daunorubicin and cytarabine. That is currently approved for patients with acute myeloid leukemia with myelodysplasia related changes and therapy-related AML. This is a hybrid model. This is out of Moffitt Cancer Center. Tim Kubal had led this program. This is the inpatient/outpatient program called IPOP. This was designed to closely monitor the patients who were intended to receive traditionally inpatient chemotherapy as an outpatient. This program had daily monitoring with CBC, CMP, check the uric acid, phosphorus, magnesium levels with planned admission on day 6 of the therapy initiation. The first five days, patients could remain outpatient. Remember the way CPX is given is a 90-minute infusion on day 1, 3, and 5. Unlike 7+3 where cytarabine is supposed to be continuous infusion for 24 hours over 7 days. CPX, the way it's given, allows for this regimen to be given as an outpatient, but these patients on day 6 would have to be admitted to the inpatient hospital setting. Now, on this study, we compare two subgroups; 22 patients were enrolled, 14 patients were treated via this IPOP hybrid setting, and 8 patients received CPX inpatient from the get-go, from day 1.

Out of the 14 patients via IPOP, 1 patient required admission on day 2 because of hypotension and fall for further management; 13 patients remained outpatient for the entire duration of the administration. Total five days of CPX, and then they were admitted on day six to manage further complications from the chemotherapy. One patient that had received CPX-351 as a traditional inpatient setting died prior to day 30. That patient was on a traditional inpatient setting.

Now, mean hospitalization duration was slightly shorter for patients that were treated via IPOP, 28 days versus 30.5 days. Again, the conclusion of this study, as they had determined was that outpatient delivery of the CPX-351 in selected patient population was safe, feasible, and the hospital duration could potentially be shortened for these patients. Remember, like previous studies, there were strict criteria on who can actually receive this type of therapy on an outpatient basis. Very important, if they did not have any caregiver support, or they were living beyond 60 minutes of the treating facility, they could not receive this on an outpatient. They had to be admitted on day 1.

Lower Intensity Treatment: Outpatient Approach

- Lower intensity treatments are mainly administered in an outpatient setting
- In VIALE-A:
  - All patients were hospitalized on or before day 1 of cycle 1 for venetoclax ramp-up and discharged 24 hours after reaching the final dose of venetoclax/placebo
- TLS during the ramp-up period was noted in 3 patients (1%) in the azacitidine-venetoclax group
  - All 3 patients had transient biochemical changes that resolved with uricosuric agents and calcium supplements without interruption of azacitidine-venetoclax
- Targeted agents: outpatient basis

Azacitidine + Venetoclax
Decitabine + Venetoclax
Low-dose Cytarabine + Venetoclax

Low-dose Cytarabine + Glasdegib

Targeted Agents
(Enasidenib/Ivosidenib/Gilteritinib)

DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

Now, talking about the lower-intensity treatments, as you heard from Dr. Erba and Dr. Kurtin earlier, now we have more options, including HMA-venetoclax, which is a game-changer in the treatment of acute myeloid leukemia in our older adults. Now, typically these treatments can be administered on an outpatient basis. Now, in the VIALE-A study, the VIALE-A study is the study that confirmed the benefit of azacitidine-venetoclax compared to azacitidine monotherapy in newly diagnosed acute myeloid leukemia patients who are ineligible to receive intensive chemotherapy. All patients were hospitalized on or day before the start of the cycle, start of the venetoclax ramp up, and they were discharged 24 hours after the final dose of venetoclax or placebo was reached.. This was mainly done because of the tumor lysis syndrome that we have seen in our patients with CLL when they get treated with venetoclax. However, in the study, only 1%, only three patients actually had experienced TLS in the Aza-venetoclax group. All three patients had transient biochemical changes that resolved with uricosuric agents and calcium supplements without interruption of Aza-venetoclax.

Overall, what we learned is that, number one, TLS risk is extremely low. Therefore, if the physician believes that the patient can be treated as an outpatient, we can cytoreduce these patients adequately before initiation of such treatment on an outpatient basis, you can potentially start this therapy as an outpatient. That was the consensus from our panel discussion as well. Also talking about the targeted agents, again, these are enasidenib, ivosidenib, or gilteritinib, so any of the IDH1, IDH2 inhibitors, or FLT3 inhibitor.

These therapies can commence on an outpatient basis for most of our patients as long as we are able to cytoreduce them with hydroxyurea prior to initiation of such treatment to lower the risk of TLS for these patients.

Outpatient AML Therapy is Feasible

Outpatient management of selected AML patients appears safe, careful planning is required in order to provide the necessary support, education and rapid management of serious complications that may occur

Overall, outpatient management of selected acute myeloid leukemia patients appear safe. However, careful planning is required in order to provide the necessary support, education, and rapid management of serious complications if they occur.

Case Studies

Then we are going to go over two case studies. I will ask Dr. Erba and Dr. Kurtin for their opinion on how they would manage these patients.

Case Study #1: A 72-year-old Male Diagnosed with Previously Untreated AML-MRC

Bone marrow aspirate and biopsy with hypercellular marrow (90%) with 75% myeloblasts in the background of significant dysplasia.
Cytogenetics: 46,XY, del(7q)[20]
NGS myeloid panel: pending
FLT3-ITD and FLT3-TKD mutations via PCR were not detected.

CBC: WBC 23,000 with 30% circulating myeloblasts, Hb 8.0 and platelets 37,000.
CMP: creatinine level of 1.0 mg/dl and normal LFTs.
2D echocardiogram: EF 60%.
Uric acid: 8.8 mg/dl; calcium: 8.9 mg/dl; phosphorus: 5.1 mg/dl; LDH: 698 IU/l.
DIC panel: mildly elevated PTT/PT, INR 1.2, Fibrinogen 198

ECOG: 1

Comorbidities: Gout maintained on allopurinol 300 mg daily, asthma, and coronary atherosclerosis for which he takes aspirin 81 mg daily.
He is an accountant and an avid runner.
Never smoker. Lives at home with his wife.

Case study number one. This is a case, a typical patient that you would see in your clinic. A 72-year-old male with newly diagnosed acute myeloid leukemia with AML with MRC myelodysplasia related changes. He had CBC that was abnormal, which led to a bone marrow biopsy. Bone marrow biopsy showed hypercellular marrow, 90% cellularity with 75% myeloblasts and a background of significant dysplasia. Cytogenetics revealed presence of deletion 7 in all 20 metaphases. NGS mutation panel wasn't back as it takes approximately one to two weeks at a majority of the centers. FLT3, ITD, and TKD mutations, which were tested via PCR method, were negative, not detected. CBC, his WBC was elevated at 23,000 with 30% circulating myeloblasts. Hemoglobin was low at 8. Platelets were 37,000, low, his CMP creatinine was normal at 1.0, and normal liver function test. He had adequate cardiac function with ejection fraction of 60%. His uric acid was 8.8. LDH was mildly elevated, and his DIC panel was fairly okay for having acute myeloid leukemia. Overall, his ECOG performance status was pretty good. One, comorbidities, he had gout for which he was taking allopurinol daily, asthma, CAD, for which he was taking aspirin, 81 milligrams daily, which we have stopped now. He is otherwise perfectly healthy. He runs every day, exercises, never smoked, lives at home, he has good support system.

Now, for this patient, would you consider this patient fit for intensive chemotherapy or lower intensity treatment? I'll ask this question to Dr. Kurtin.

Dr. Kurtin: I would consider him fit. Obviously, if he's running regularly, that is good. He does have some comorbidities. It sounds like they are not altering his performance status. I think to Dr. Erba's earlier point, it's the appropriateness of treatment and really directing what is the more intensive regimen. At his age of 72, allogeneic stem cell transplant may be less of a consideration, although in some centers, it would still be considered.

Dr. Talati: Thank you. Now, what would be your therapy of choice if you are considering intensive chemotherapy for this patient?

Dr. Kurtin: Well, if he has antecedent myeloid malignancies, I think that, and obviously, his platelets, he's starting out with a low platelet count, which is going to make this a little bit more tricky. I would want to know are there megakaryocytes in the marrow? Is this because his marrow is full of leukemia? In some cases, it would be appropriate to use a slightly more intensive, something like the liposomal daunorubicin and cytarabine to really clean out the marrow and hopefully restore normal hematopoiesis. It would be a conversation with the patient and his wife in terms of their goals and lifestyle.

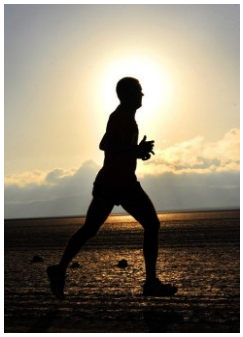
Dr. Talati: After having that discussion, the patient opted to proceed with CPX-351, the liposomal formulation of cytarabine and daunorubicin. Now, Dr. Erba, would you consider this patient appropriate for outpatient administration of CPX-351?

Dr. Erba: I think he would be potentially appropriate for outpatient administration of CPX-351 for a variety of reasons. I will say very quickly about this case, it does bring up a number of very important points. He has myelodysplasia related changes. By two criteria, the dysplasia possibly and should be in two lines with over 50% of progenitors. That's often hard to distinguish for the pathologist and especially if there's so many myeloblasts in the background. The thing that clearly makes this myelodysplasia related changes is the fact that he has a de novo AML with an MDS defining cytogenetic change deletion 7q. Actually, it makes the point of why I get FISH analyses very early on, it helps me make a decision, because I can sit with this patient and talk about curative options and the only curative option is ultimately to get him to an allogeneic stem cell transplant, which he sounds like he would be a good candidate for. The questions I would specifically ask him is, does the caregiver live with him? Is he going to be reliable and do what he is told? Does he live close to our center and come in on days 1, 3, and 5 for therapy? I actually would give this patient CPX-351 as an outpatient, monitoring for worsening of tumor lysis and monitoring for worsening of potential DIC, given that his fibrinogen is in the low part of the normal range.

Dr. Talati: Thank you. Yes, extremely important.

Outpatient induction with CPX-351 was initiated.

On day 1, this patient was asymptomatic pre-CPX-351 administration, but he had early signs of TLS. Therefore, rasburicase 6 mg and normal saline 1L were administered intravenously in the infusion center, and allopurinol was continued at 300 mg twice daily.



On day 2, the patient remained asymptomatic, and his uric acid levels had decreased (7.0 mg/dl); his other laboratory results remained in the normal range (creatinine: 1.0 mg/dl; calcium: 8.4 mg/dl; phosphorus: 4.8 mg/dl; LDH: 587 IU/l).
The patient remained asymptomatic, and his laboratory results remained stable on days 4 and 5 and he completed chemotherapy administration in the outpatient setting.

On day 6, this patient was admitted for nadir and count recovery for approximately 30 days.

He lives with his wife, he lives within an hour. He fits all the criteria that we have discussed with the CPX study with the IPOP regimen. Overall, he did initiate CPX as an outpatient. To your point, on day 1, he was asymptomatic, as typically majority of our patients are when we start chemotherapy, and he developed early signs of TLS. Therefore, he was given rasburicase and normal saline, again as an outpatient in the infusion center, and allopurinol was continued. However, the dose was doubled to 300 twice daily. He was taking 300 once daily for his gout management. Now, on day 2, again, he was asymptomatic. His uric acid levels had decreased after the rasburicase, and his other lab parameters remained in the normal range in terms of the TLS monitoring, the creatinine and other electrolytes. Overall, he completed his day 3 and 5. He was admitted on day 6 for completion of the induction process for approximately 30 days. He was able to remain outpatient for the duration of the chemotherapy administration for about five days or so.

Dr. Erba: I know that's the way your Moffitt study was done, but in the community, it may be very difficult to readmit a patient just because of blood counts. There has to be an issue, a cause for the admission. If this patient was really that reliable and can come to the center for a chance to be evaluated by us and transfusion support, I've actually taken care of these patients as an outpatient continuously on oral antibiotics and antifungal and antibacterial and antiviral with transfusion support, and then admit them for cause if they have a complication. I think it's possible to do that with liposomal daunorubicin/cytarabine because in my experience you seem to get less mucositis than we would get with the daunorubicin/cytarabine given in this 7+3 regimen. It's something that could be considered as well.

Case Study #2: A 77-year-old Female Admitted for Neutropenic Fever with Pneumonia

She had a history of non-small cell lung cancer treated approximately 5 years ago with surgical resection followed by adjuvant carboplatin, paclitaxel and radiation therapy. She recently underwent a PET/CT approximately 1 month prior that did not reveal any evidence of disease and continued remission.

Her CBC: WBC 3.2 × 10^9/l; ANC: 0.36 × 10^9/l; platelet count: 32 × 10^9/l; hemoglobin: 6.8 g/dl.
Bone marrow biopsy and aspirate: Hypercellular marrow (80%) with 40% myeloblasts.
Cytogenetics resulted with complex karyotype. NGS resulted with presence of IDH2, RUNX1, ASXL1 and TET2 mutations. TP53 mutation was not detected. FLT3-ITD and FLT3-TKD mutations were not detected.

Diagnosis: Therapy related acute myeloid leukemia.

ECOG PS: 1

PMH: Hypertension, hyperlipidemia, coronary atherosclerosis s/p PCI approximately 1 year ago, prior history of non-small cell lung cancer s/p resection and adjuvant carboplatin, paclitaxel and radiation therapy that completed 5 years ago with recent restaging scans 1 month ago are suggestive of continued remission.

Social Hx: Former smoker and quit 6 years ago. Lives alone at home; however, has two daughters who are her caregivers. Retired librarian.

Now the second case study that I want to discuss. This is a case of a 77-year-old female who actually was found to have acute myeloid leukemia when she was admitted to the hospital with pneumonia. Going back, going through her story, she had a history of non-small-cell lung cancer, which was treated approximately five years ago. Surgical resection followed by adjuvant carboplatin, paclitaxel, and chemotherapy or radiation therapy. She underwent PET-CT just recently, which showed no evidence of disease and continued remission. Overall, when she was admitted to the hospital with this fever and was found to have pneumonia, her CBC revealed WBC of 3.2; mildly low neutrophil count, which was low at 360, ANC of 360; platelet count that was low, so 32,000; and anemic at 6.8. She had a bone marrow biopsy done. At that time, bone marrow biopsy resulted with hypercellular marrow with 40% myeloblasts, again, confirming acute myeloid leukemia. Cytogenetics resulted with complex karyotype. NGS came back. As we would for these patients with therapy-related acute myeloid leukemia, we want to look for a TP53 mutation as Dr. Erba and Dr. Kurtin had pointed out earlier because that would impact your overall treatment plan. It would impact your prognostic discussion with the patients. NGS came back and a patient had presence of IDH2 mutation, RUNX1, ASXL1, and TET2. TP53 mutation was not detected in her case. FLT3-ITD and TKD were not detected. Overall, diagnosis of therapy-related acute myeloid leukemia was made. She had good performance status. Past medical history: hypertension, hyperlipidemia, CAD, status post PCI, that was approximately a year ago. As we discussed, prior history of non-small-cell lung cancer treated with surgical resection, adjuvant chemoradiation, in remission based on the PET-CT that was done about one month ago. She is a former smoker, quit six years ago. She lives at home and has two daughters who live close by and who are her caregivers. She's a retired librarian.

Now the question comes, how would you treat this patient? At 77 years old, do you consider this patient for intensive chemotherapy or lower-intensity approach? Maybe this time I'll start out with Dr. Erba.

Dr. Erba: Well, I think I find this patient not only unfit for intensive chemotherapy but potentially inappropriate for intensive chemotherapy fitting both criteria and actually being a great candidate for less intensive therapy. The reason I say that, not to be ageist, but by the time you're getting to 77 years old, you are really, very unlikely to be considered a candidate for allogeneic stem cell transplantation. Outcomes with intensive chemotherapy are much less. I've always been impressed how the body remembers prior chemotherapy, no matter how long ago it is. Therapy-related AML is complicated by, in my opinion, the excess morbidity we see often with intensive chemotherapy. Let's remember, she's had radiation to her chest, and so pneumonia is going to be a major issue during her therapy. For all of those reasons, I don't think she's fit for intensive chemotherapy. In terms of why I think she's a great candidate for less intensive, she fits the labeled indication for HMA/venetoclax, being over 75. The second is, in a subset analysis of patients, patients with an IDH1 or IDH2 mutation have one of the highest response rates to the Aza-venetoclax combination of close to 80%, with a median survival of two years as presented by our colleague Dan Pollyea at ASH in 2020. Finally, I would not use enasidenib in this patient. It would be an off-label use for a previously untreated patient, and most of the studies that have looked at single-agent or HMA with single-agent enasidenib or ivosidenib, have shown lower response rates in the context of a RUNX1 concomitant mutation.

Dr. Talati: Thank you much for all those insights, and I completely agree. I think Aza-Ven, especially with IDH2 mutation, makes perfect sense here. She got started on Aza-venetoclax on an outpatient basis. Now, question for Dr. Kurtin. Would you treat this patient on an outpatient with Aza-Ven, or is your practice to admit this patient for the venetoclax ramp up?

Dr. Kurtin: We don't admit patients routinely for venetoclax. I think, particularly in these treatment-related AMLs, you see them presenting with low counts. You don't have high white counts. They tend to have some level of pancytopenia. It really becomes more about finding out about these two daughters. How far away do they live from the patient? Are they working full time? Do they have the flexibility to get her back and forth for what's likely to be frequent transfusion support for a period of time while we're waiting to see about a response? We would do it as an outpatient but have a very careful conversation ahead of time about our goals of care, about what's required in the early weeks and months of treatment in terms of intensive supportive care to be able to do that safely.

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- Given her low ANC (0.36 × 10^9/l), **antimicrobial prophylaxis** with voriconazole, ciprofloxacin and acyclovir was initiated
- Due to drug-drug interactions with ciprofloxacin and voriconazole, the dose of venetoclax was reduced by 75%
- Throughout the course of treatment, this patient was seen twice-weekly at a center near her home in the community for **transfusion support**
- She had a bone marrow biopsy performed on day 22: Hypocellular marrow (10%) with <5% myeloblasts
- Therefore, further venetoclax was held and cycle 2 was delayed by approximately 1 week to allow for count recovery. Upon appropriate ANC and platelet recovery, her cycle #2 resumed with azacitidine and venetoclax with modified schedule of 21 days of venetoclax per cycle
- She attained CR after two cycles with normalization of CBC parameters. She continues on the same treatment at this time

Dr. Talati: Thank you. We will touch upon that too, what supportive care she actually received.

She got started on azacitidine days 1 through 7 in combination with venetoclax with appropriate ramp-up schedule. She was not admitted to the hospital because, as we discussed, it is safe to do so on an outpatient basis. Now, in terms of supportive measures, as you brought up, given her low white count and low neutrophil count, specifically ANC of 360, antimicrobial prophylaxis with antifungal, antibacterial, and antiviral was initiated. Also, with venetoclax, very important, you need to have a pharmacist on the team who helps you dose-modify venetoclax. With voriconazole, it is required that venetoclax dosing needs to be reduced by 75%, and therefore, appropriately from 400, her dose was supposed to be 100 milligrams of venetoclax. Drug-drug interactions are very important. They need to be considered. You always need a pharmacist to go through all the medications that you are going to prescribe and what needs to be modified accordingly. Throughout the course of treatment, as you pointed out, she was seen twice-weekly at the center near her home in the community for transfusion support. Approximately twice-weekly is what we recommend, usually with the first cycle, and then second cycle, depending on how she's responding to things. Part of the trial protocol, this patient had a bone marrow biopsy that was performed around day 22 and you are mainly doing this for two purposes. One, to assess whether there has been any response to Aza-Ven, and secondly, is to assess their degree of myelosuppression from the combination. This patient had a bone marrow biopsy done on day 22 that resulted with hypercellular marrow. Cellularity was noted to be 10% with less than 5% myeloblasts.

When you see a hypocellular marrow with clearance of blasts here, usually what we do is, depending on peripheral blood count, we tend to delay by a week or so to allow for counts to recover. Her further venetoclax was held at this time, and cycle 2 was delayed by approximately one week to allow for appropriate count recovery. Upon ANC and platelet recovery, again, that is not something that's set in stone. Usually, our threshold is ANC at least try and get it more than 500. Higher, the better. Platelets closer to more than 50,000 or so. Adequate count recovery, and her cycle 2 was restarted with azacitidine and venetoclax. You modify the schedule of venetoclax. Again, not set in stone, but usually we lower the number of days to 21 days, in that case, to reduce the duration of cytopenias with the second cycle, especially when we have the blast clearance that we see in the marrow on day 22.

Again, all these guidelines are not set in stone, but this is typically what gets done at an academic institution. This is mainly for the safety of the patients so that they can remain outpatient and to prevent further complications with febrile neutropenia or bleeding complications. As you would expect, this patient attained complete remission after about two cycles with normalization of CBC parameters. We had already seen blast clearance, but by cycle number two her counts came up to CR parameters where platelets were more than 100,000 and neutrophil count was more than 1,000 along with blast clearance in the marrow. She continues on the same treatment at this time.

Eligibility for Outpatient Induction Therapy: Intensive Approach

7+3 (daunorubicin or idarubicin)
7+3 + gemtuzumab ozogamicin
7+3 + midostaurin

High-dose cytarabine-based regimens (CLAG/M, FLAG, FLAG-Ida)

CPX-351

- Considerations:
  - Clinical status
  - Choice of the chemotherapy regimen
  - WBC at initial diagnosis (proliferative vs nonproliferative) and risk of TLS
  - Ability to initiate hydroxyurea for cytoreduction safely as outpatient
  - Chronic kidney disease or acute kidney injury which may make it difficult to monitor for TLS
  - Febrile neutropenia
  - Social support/logistics

Overall, just going through the summary here. Eligibility for outpatient induction chemotherapy, intensive chemotherapy regimens that we discussed, what you need to consider. You need to consider the clinical status of the patient. How are they walking into your clinic? When you are looking at them, do they look fit enough? There are get-up-and go tests, as Dr. Erba pointed out. That's one test. What is the performance status of the patient before AML, and how are they looking now? What is your choice of chemotherapy regimen? We talked about 7+3. Cytarabine is usually continuous. IV infusion, is it feasible to do that in an outpatient setting? You need pumps. Does your infusion center have those capabilities? Typically not. Therefore, a lot of times, whenever it's 7+3 backbone, those patients do get admitted on day 1 to start the chemotherapy in the hospital versus the CPX-351? We have some data supporting complete outpatient versus partial outpatient approach. It is a 90-minute infusion as we discussed on day 1, 3, and 5, and therefore, it is feasible and possible to do that as long as you have the support staff at your center to do so. What is the white count at initial diagnosis? Is the disease proliferative? If the white count is 50,000/60,000, etc., this patient, when you start them on chemotherapy, they are going to experience tumor lysis syndrome. For further management with IV fluids, possibly rasburicase, etc., it may require inpatient admission from the beginning.

Also, are you able to start hydroxyurea as an outpatient? Are you able to manage them twice weekly, see their labs, follow them through, etc.? All of these things need to be considered when you are making a decision. If they already have CKD, it's going to make it difficult to monitor for TLS. You are seeing them for the first time.

Creatinine is 1.5. Now you don't know if this is TLS-related, you don't have a baseline, or is this model for a CKD picture? Again, when it's difficult to make that determination, patients actually get admitted. Febrile neutropenia gets admission. We talked about that. Social support, very important. Is the patient able to come outpatient to your center every day to get labs done, to get physicals done? Do they have a support system to do so? Do they have family who's going to drive them over? You don't want a patient with platelets of two to drive to the treatment center, so things like that. That's for intensive chemotherapy.

Eligibility for Outpatient Consolidation Chemotherapy

- Outpatient administration is standard
  - Proximity to the treatment center
  - Reliable caregiver/transportation
  - Stable comorbidities
  - Treatment center capacity/hours of operation
    - Limitations include infusion center timings to accommodate certain regimens
- Management:
  - Prophylactic antimicrobials
  - Frequent labs adjusted to treatment plan and patient needs
  - Visits for transfusion support
  - G-CSF support
  - Education about febrile neutropenia and other potential complications

For consolidation chemotherapy, I would go out on a limb and say that outpatient consolidation chemotherapy is pretty standard. However, it's usually the feasibility from the infusion center perspective because a lot of the consolidation treatments require every 10- to 12-hour administration on day 1, 3, and 5. Now there is data to support day 1, 2, and 3. Is your infusion center able to accommodate that? Once they finish the chemotherapy administration, typically, you can get them on an outpatient twice-weekly basis for transfusion support, appropriate antimicrobial and growth factor supports with pegfilgrastim or filgrastim.

Eligibility for Outpatient Induction Therapy: Nonintensive Approach

Hypomethylating agent monotherapy
Hypomethylating agent + venetoclax

Low-dose cytarabine + venetoclax
Low-dose cytarabine + glasdegib

Targeted agents: enasidenib, ivosidenib, gilteritinib

- Considerations:
  - Clinical status
  - WBC at initial diagnosis (proliferative vs nonproliferative) and ability to initiate hydroxyurea for cytoreduction safely as outpatient and risk of TLS
  - Chronic kidney disease or acute kidney injury which may make it difficult to monitor for TLS as an outpatient
  - Social support/logistics

Now for the non-intensive chemotherapy approach or non-intensive approach, doesn't have to be chemotherapy. Hypomethylating agent-based therapy with venetoclax or targeted agents in relapsed/refractory setting. Again, consider the clinical status if there is febrile neutropenia in the picture, patient gets an admission for management of that. Initial WBC count, is the disease proliferative? If the white count is for FLT3-mutated AML, for example, if the white count is 50,000/60,000 from the start, you need to adequately cytoreduce this patient before you initiate gilteritinib. Even with Aza-Ven, if you're starting out with proliferative disease, it requires that we want the patient to be adequately cytoreduced with hydroxyurea as low as possible, drag the white count down. My preference is usually less than 10, but on the study, VIALE-A study, patients needed to be as at least less than 25,000 before they start this regimen. Can you do that safely on an outpatient basis? Again, outpatient is to determine TLS when you are putting them on hydroxyurea.

Again, same thing with the CKD and if it muddies the picture in terms of how to monitor this patient for TLS when you are actually doing the ramp-up of venetoclax, etc. Social support, extremely important. Is the patient reliable? Can he or she come to your clinic three times, two times a week for transfusion support, for monitoring of TLS, etc?

Logistical Requirements for the Treating Center

- Before the initiation of therapy, pharmacists, APPs, and registered nurses arrange calendar development, medication review and patient education, including a comprehensive discussion of potential side effects
- APPs closely monitor patients' tolerance of therapy and look for side effects and/or signs of toxicity under physician supervision
- Supportive care is a vital
- Capacity to accommodate all infusions (outpatient infusion pumps)

Now, what are the logistical requirements for the treatment center? As you just heard from the whole conversation, the treatment center has to be capable. You need a lot of support in terms of pharmacy. Pharmacists need to be on your team. It's a multidisciplinary approach. You need a multidisciplinary team. You need APPs, advanced practice providers, who are going to see these patients every single day to do a physical, get labs checked, replace electrolytes as needed, assess whether it is still safe on a daily basis for them to remain on an outpatient when they are getting intensive chemotherapy. Also, for Aza-venetoclax, when they get seen twice a week, is there enough support at your center to see them twice a week? Because, again, it requires a lot of effort on the treating physicians' part as well. Also, education. Supportive care is vital. These patients require transfusions. About 80% to 90% of our patients are transfusion-dependent, especially when we are starting out. If not, with the therapy, they will become transfusion-dependent, especially with the first couple cycles until they are in remission. Do you have enough support to provide in terms of transfusions, red blood cells and platelet transfusion? Also, can your infusion center accommodate the infusions? We talked about high-dose cytarabine for consolidation. Is the schedule appropriate for your infusion center? Can you do that on an outpatient basis?

Patient Education

- Provide detailed treatment/visit calendar
- Medication review
- Comprehensive discussion of potential side effects
- Educate patients and caregivers on how to recognize
  and report signs/symptoms of serious complications
- Education on importance of keeping all appointments and prompt reporting of any symptoms

In terms of patient education, we talked about the calendar. Review the medications, drug-drug interaction, especially with a lot of the newer therapies. You need the pharmacist on your team to review the medications to make sure that you are not causing toxicities with certain agents here. Comprehensive discussion of potential side effects, febrile neutropenia, how to monitor that, differentiation syndrome with gilteritinib and IDH inhibitors, which is different than the differentiation syndrome we are used to with APL treatments, so what to tell the patient when they go home and they are taking these agents at home. Also educate the caregivers because they are the ones who are going to be managing and seeing and overseeing the overall treatment plan. It's a lot for a patient to learn all these things at once, so you need the caregiver's help to make them realize what are you looking for so they have a way when this happens, how do you contact your physician? Again, compliance is extremely important. Compliance with appointments as well as compliance with the therapies. Again, all of this education, it becomes very important when we are talking about outpatient therapies.

Management During Outpatient Treatment Administration

Transfusion and Hydration Support

- Anemia
- Thrombocytopenia
- Hydration during chemotherapy administration
- Inpatient admission for DIC

Tumor Lysis Monitoring

- All patients should be prescribed allopurinol prophylaxis
- Hydrate with intravenous fluids daily and avoid excessive intake of potassium-rich foods and drinks.
- Close lab monitoring for signs of impending TLS
- Rasburicase in case of moderate or severe hyperuricemia (uric acid >8.5 mg/dL) and meets ≥2 of the following criteria:
  - ✓ LDH >2x ULN, Bulky disease, WBC count >25,000/uL, pre-existing renal insufficiency or ≥ 3 urate crystals on urinalysis
- Monitor and treat hyperkalemia, hyperphosphatemia and hypocalcemia as indicated

Implementation of Prophylactic Antimicrobials

- Prophylactic antimicrobials are strongly recommended for AML patients who are neutropenic (absolute neutrophil count $<0.5 \times 10^9$/L)
- Antibacterial and antifungal prophylaxis is recommended for patients with expected ANC $<0.1 \times 10^9$/l for >7 days
- Herpes simplex virus–seropositive patients undergoing allogeneic HCT or induction chemotherapy for AML should receive antiviral prophylaxis with a nucleoside analog
- Appropriate choice of antimicrobial taking into account drug-drug interactions should be made

Overall, there are three pillars to successful outpatient treatment administration. Transfusion and hydration support. Anemia, thrombocytopenia, keeping up with certain thresholds, hydration during the chemotherapy administration. When they have or when you identify that patient has an ongoing DIC, admit the patient. Monitoring for such things. Tumor lysis monitoring. Everybody should be prescribed allopurinol prophylaxis for TLS. When do you give rasburicase? Every center has the criteria, but these are the typical criteria that we use. Bulky disease in terms of very proliferative disease. You're starting out with a high uric acid, high LDH, etc., those patients, they should receive rasburicase to prevent TLS. If the TLS does occur, there should be a way your hospital or your center should have ability to give them rasburicase and monitor the electrolytes subsequently. Close monitoring of TLS, extremely important, and implementation of prophylactic antimicrobials. These patients should have antibacterial, antiviral, and antifungal. Every center has their choice of antifungal posaconazole, voriconazole. Depending on the treatment regimen, some may choose fluconazole. What is the standard for your treatment center? Usually, it's an azole. Typically, it's posaconazole or voriconazole. All of these patients should receive HSV prophylaxis with acyclovir, so antiviral prophylaxis when neutrophil counts are low, when you are expecting them to remain low for a certain duration of chemotherapy such as patients undergoing bone marrow transplant or when they are receiving intensive chemotherapy or HMA-venetoclax when counts haven't recovered. Also, antibacterial. Usually, it's a prophylaxis, levofloxacin, which also-- ciprofloxacin is because it also has pseudomonal coverage. Each center has their choice, so getting your infectious disease team on board and defining the guidelines, defining what should be the standard at your center. Antimicrobial prophylaxis, extremely important, whether it's intensive chemo or non-intensive approach here.

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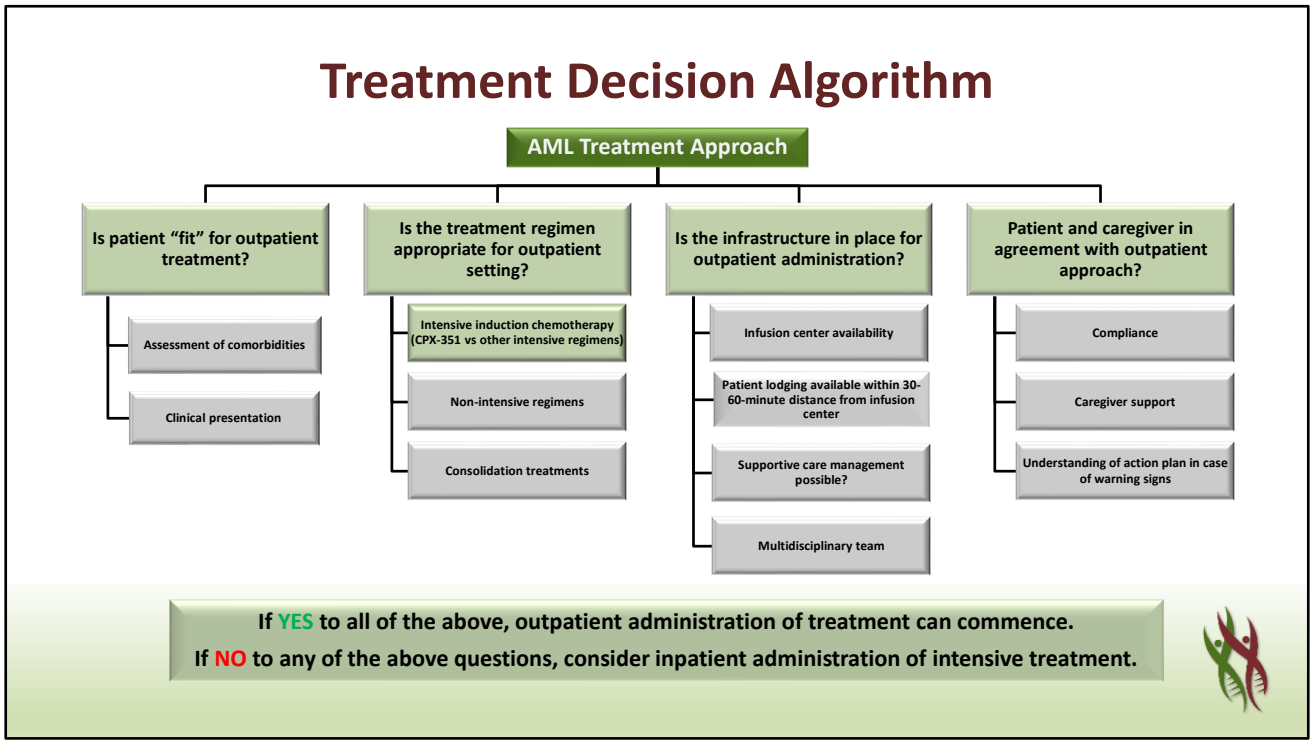

With that, this is the overall general treatment decision algorithm, things you should be thinking about. If you answer 'yes' to a majority of these questions, you can do this outpatient. You can administer the therapy outpatient. Number one, is the patient fit, or to Dr. Erba's point, appropriate for outpatient therapy? Is the patient appropriate for intensive chemotherapy, or because of the biology of AML, such as TP53 mutation, are they more appropriate for lower-intensity approach? Is the patient fit for outpatient treatment? You assess the comorbidities and their overall clinical presentation as well as the disease biology. Is the treatment regimen appropriate for outpatient setting? The 7+3 continuous infusion of cytarabine may not be feasible for everybody to do it as an outpatient, unless you have that feasibility in terms of having the continuous infusion pumps, ability to switch them daily. Majority of the centers don't; 7+3 typically will remain inpatient from day 1, but CPX is something to think about. Can you do this on an outpatient basis? There is some data to back that up. You can do that as an outpatient in its full entirety, or you can do this hybrid program where you administer a week outpatient day 1, 3, and 5 and put them in hospital on day 6, but again, to Dr. Erba's point, that hospitalization may not be covered, so you may need to think about, can you follow them outpatient for its full entirety and admit them in case of complications?

Non-intensive regimens, specifically HMA-venetoclax, you can potentially do that outpatient. Remember, cytoreduce as much as possible, consolidation treatment, as long as your infusion center is able to accommodate Q10, Q12 hour infusions, you can do that outpatient with twice-weekly visits subsequently to manage for. Give them transfusions for growth factor support, making sure they are doing okay from the mucositis and other standpoint. Is there appropriate infrastructure in place at your center? So infusion center availability. Patient lodging, if they are living two hours away, it may not be feasible for them to come here every single day. Can we have a social worker involved? Can we see if there is lodging available close by? Can we support somewhat in that sense if patient's strong desire to remain outpatient? Supportive care management. Is it possible at your center with twice-weekly visits and whatnot with the transfusions? Are you able to give them blood transfusion at that frequency? Do you have a multidisciplinary team? Is there a pharmacist, advanced practice providers, nursing staff? Is everybody aware about how to do this? Education, is your team capable of doing this? Is the patient and caregiver in agreement with the outpatient approach? Some patients may say, "You know what, this is something that I cannot do as an outpatient. I would prefer to be admitted," because there is a lot, or they may say, "I don't have my daughter who lives in another state." Especially with the COVID-19 and whatnot, people are not able to visit as much. Taking into consideration patient's perspective. Can we do this safely in an outpatient setting?

If you can answer yes to all of these questions, potentially, you can do this on an outpatient. If it's not feasible, if there is a ‘no’ to any of these questions, I would say, strongly consider inpatient administration for these therapies.

Concluding Remarks

- Outpatient management of AML appears safe in selected patients, in selected centers, and only with necessary support and careful planning
- Low-intensity regimens can be administered safely in the outpatient setting in majority of patients
  - HMA + venetoclax, targeted therapies (ivosidenib, enasidenib, gilteritinib), HMA, LDAC + glasdegib, LDAC + venetoclax
- High intensity induction regimens should be administered on an inpatient basis however can be administered on the outpatient basis in carefully selected patients.
  - Induction regimens: CPX-351, 7+3 based regimens, high-dose cytarabine containing regimens
  - Consolidation regimens can be administered as an outpatient therapy
- Patient and treatment center eligibility assessment for outpatient setting
- Partnership with an academic institution for a comprehensive review of the case to devise an appropriate treatment plan
- Emphasis should be placed on clinical trials when considering therapy for AML

Walter RB, et al. *Leuk Res*. 2016;45: 53-58.

In summary, outpatient management of AML appears safe in selected patients in selected centers and only with necessary support and careful planning. Lower-intensity regimens can be administered safely in an outpatient setting, such as HMA-venetoclax, that's becoming more and more routine since its approval. All of these patients, do you really need to admit them for that ramp up period? With a TLS risk of about 1%, I would argue you can do that safely as an outpatient as long as you have means to manage and monitor the TLS. With targeted therapies, make sure you're cytoreducing your patients before you start such therapies and educate the patient what to look out for when they are taking these drugs at home, and have appropriate follow-ups. I like to see my patients more frequently after every cycle initially. If they understand what's going on, then we can have the visits spaced out a little bit more depending on the needs for transfusions as well. High-intensity induction regimens should be administered on an inpatient basis. However, it can be administered on an outpatient basis in carefully selected patients with some regimens such as CPX-351.

Now, patient and treatment center eligibility assessment prior to the start of any treatment. Can they do this outpatient? Have you provided enough education? Is the patient and the caregiver on board with this? Also, I would highly highlight that partnering with an academic institution to review the case to understand, is the treatment plan appropriate for this patient and is it safe to do so on an outpatient basis initially when you are starting out, especially? Because I would see them as a partner, and that way, let's say two months later if there is a complication or something that arises, you have that backup.

I'll just ask Dr. Erba and Dr. Kurtin for last few remarks if they have any other thoughts on this before we end.

Dr. Erba: Thank you, Dr. Talati. That was a wonderful summary. I don't really have much to add. I think the caveat here is really to go back to those studies and note that even at major centers like Moffitt, for one of the studies with CPX-351 and the study from Seattle with the group from Applebaum and Pam Becker and Roland Walters that did outpatient intensive chemotherapy. These numbers are very small, even at major academic centers. These are patients who are highly, highly selected for outpatient administration, and I think taking to heart all of the things that you've summarized so well, Dr. Talati, is very important.

Dr. Talati: Thank you.

Dr. Kurtin: I would just add that this is very much a team sport, and it takes everyone, the entire multidisciplinary team to do this successfully. To your point, the accessibility and then really, it requires maybe not just one caregiver but a caregiver team to be able to safely manage this patient in the outpatient setting. Then also, the whole collaboration with the inpatient team for those transitions and care that are often inevitable in this population.

Dr. Talati: With that, thank you, everybody, for your attention.