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Expert Answers to Common Questions on Response Matters:

Transforming the Standard of Care in CML by Mastering Response-Guided Treatment

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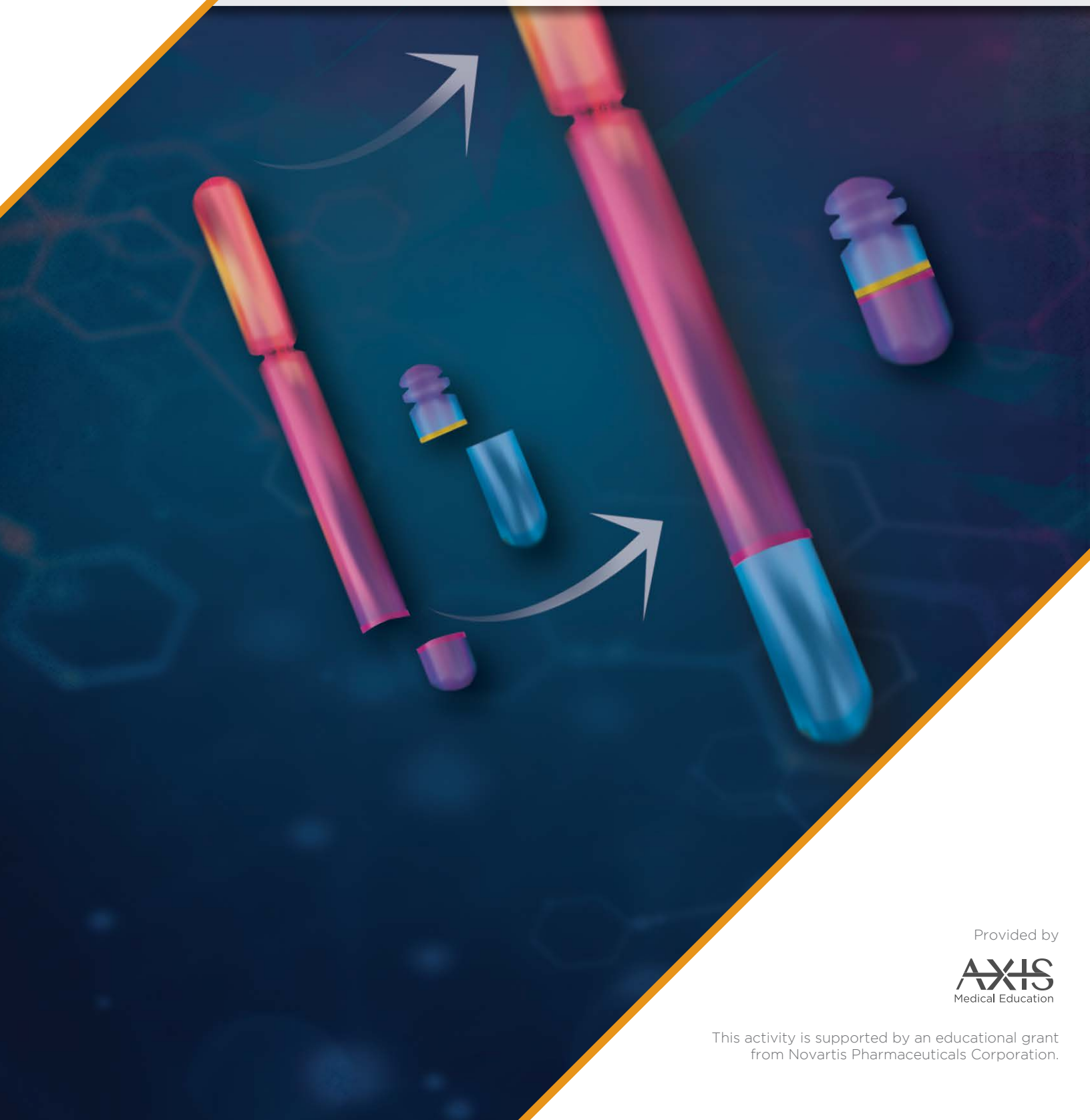

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Expert Answers to Common Questions on Response Matters: Transforming the Standard of Care in CML by Mastering Response-Guided Treatment

Michael Mauro, MD

Michael Mauro, MD: Well, hello, and welcome, I'm Dr. Michael Mauro. I'm Director of the CML, or Chronic Myeloid Leukemia Program at Memorial Sloane-Kettering Cancer Center in New York, and today I'll be answering questions that were asked by clinicians during the recent educational series on the standard of care in CML.

So, our questions today will focus on four main topics: testing methods, treatment options for CML, resistance and nonadherence, and comorbidities and adverse events. So, let's begin.

The first topic for today's discussion is current and emerging detection methods.

So, many questions here, but let's answer a few. And the first might be: Should clinicians routinely check for the T315I mutation for newly diagnosed PH-positive CML before prescribing TKI therapy.

Clinical Pearl

- Routinely checking for T315I mutation is generally not needed for newly diagnosed PH-positive CML prior to prescribing a TKI therapy.
  - T315I detection may be shrouded by a very high-level *BCR-ABL* or a wild-type *BCR-ABL*

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The answer to this is generally, no, because chronic-phase CML is – that kind of testing is going to be shrouded by a very high-level BCR-ABL, and you may have an overwhelming wild-type BCR-ABL, and you may not be able to detect a small clone. We don't necessarily frequently see mutations when this has been done. As a footnote, higher risk, sort of – definitely advanced phase, or what we now by the WHO criteria define as very high-risk chronic phase CML which has characteristics of blast phase disease.

Patients with clonal evolution and maybe lymphoid blast clones by evidence, by flow cytometry, those types of patients we may want to do more extensive testing because T315I mutation may be more prevalent, for example, in blast phase disease, lymphoid blast phase disease, and certainly requires different treatment. It is only sensitive to ponatinib and asciminib therapy with regards to TKIs. So there we go.

Cardiac Evaluation

- 50% of newly diagnosed CML patients have significant comorbidities
  - Assess them for comorbidities
  - Understand their status
  - Treat the comorbidities accordingly

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- Another question: Are patients having baseline cardiac evaluation completed prior to beginning treatment for CML?

Again, another very good question, and I would say in general that, you know, your typical CML patient is likely to have comorbidities. Some studies looking at thousands of patients have shown that typical newly diagnosed CML has – 50% of patients have significant comorbidities. So, we definitely need to assess them and understand their status, and make sure they're optimally treated. And it clearly impacts treatment decision.

Know Your Tools: Comparing TKIs

Issue	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib
Dosing	QD/BID, with food	BID, without food (2h)	QD, w/ or w/o food	QD, with food	QD, w/ or w/o food	QD or BID, w/o food; dosing varies (T315I or not)
Long term safety	Most extensive	Extensive; Emerging toxicity	Extensive; Emerging toxicity	Extensive, No emerging toxicity	More limited but increasing; Emerging toxicity	Emerging; long phase I data (8y)
Heme toxicity	Intermediate	Least	Most severe; ASA-like effect; Lymphocytosis	Comparable to dasatinb in 2nd, 3rd line; Comparable to nilotinib in 1st line	Thrombocytopenia ASA-like effect	Thrombocytopenia Neutropenia
Non-Heme toxicity	Edema, GI effects (diarrhea, nausea), Muscle cramps, ↓Phos	↑Lipase, ↑Bili, ↑Chol, ↑Glu, Fatigue, Musculo-skeletal symptoms, Black box: QT prolongation	Headache (early/transient) Pleural / pericardial effusions	Diarrhea; Transaminitis	↑Lipase, Pancreatitis, Rash, Hypertension, Black box: vascular occlusion, heart failure, and hepatotoxicity	↑Lipase, Pancreatitis, Hypertension, Hypersensitivity reaction, Possible cardiovascular adverse events
Potential special concerns	Early question re: CHF, late renal effects	Vascular events (ICVE, IHD, PAD)	PAH (pulmonary arterial hypertension)	Mild renal effects	Vascular events (ICVE, IHD, PAD, VTE)	Longer follow-up needed re: cardiovascular AEs

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- Some of the second generation TKIs for example, such as nilotinib, have more risk, more metabolic disease risk, advancing diabetes or elevated blood sugar, shift in cholesterol, and actually triggering vascular disease. So, I wouldn't say it's required for every patient, but certainly good general internal medicine standard of care should be applied, and your typical patient may be 50 or 60 years of age, or beyond, although some are younger, and many of these patients have not having been checked in by their primary care physician need to, and many need cardio-oncology or cardiovascular medicine specialty care. We'll get to that a little bit later in some other questions. So, my general answer is, yes. They need some baseline evaluation. They don't need specific testing that's complicated or expensive, but we certainly need to understand the comorbidities and, in certain cases, know them in great detail.

Okay. So, let's switch gears and talk about treatment options. Also, many questions here, and one was: Is anything in the pipeline for transplant or for those who fail ponatinib?

So, transplantation just on a word, is still a relevant treatment for CML. It's often cast aside. But I want to just use this opportunity to remind us all that in a patient with low risk of transplant-related morbidity and mortality who has highly resistant CML who remains in chronic phase, it's an opportunity because CML is highly treatable with transplant, and the complications are somewhat lower and it's quite amenable to the graft versus leukemia effect. So, transplantation needs to be considered in patients who are say, on third-, fourth-line therapy who aren't meeting milestones and particularly those of younger age in whom good donors can be identified.

The Spectrum of *BCR-ABL* Inhibitors

	1st Generation TKI	2nd Generation TKI	3rd Generation TKI	Allosteric TKI
Approved (FDA/EMA)	Imatinib	Bosutinib Dasatinib Nilotinib	Ponatinib	Asciminib
Ex-US Licensed/Approved	Flumatinib	Radotinib	Olverembatinib	
In development			Vodobatinib Vamotinib (PF-114) ENLV-001	TERN-701 TGRX-678

FDA, U.S. Food and Drug Administration; EMA; European Medicines Agency; TKI, tyrosine kinase inhibitor.

- But let's shift – because this was about treatment options – and discuss what would be relevant in the non-transplant setting. So, we now have multiple TKIs approved. We have imatinib as a first-generation, nilotinib, dasatinib, and bosutinib as our second-generation inhibitors, ponatinib as a de facto third generation inhibitor, and asciminib now as a novel agent, a myristoyl pocket inhibitor, or stamp inhibitor. So, those really give us a fairly broad array of options. However, intolerance and resistance still develop to multiple lines of therapy.

  So, we continue to develop new TKIs in CML and we have to remember MET transplant, and those would be the take-home messages for that question.

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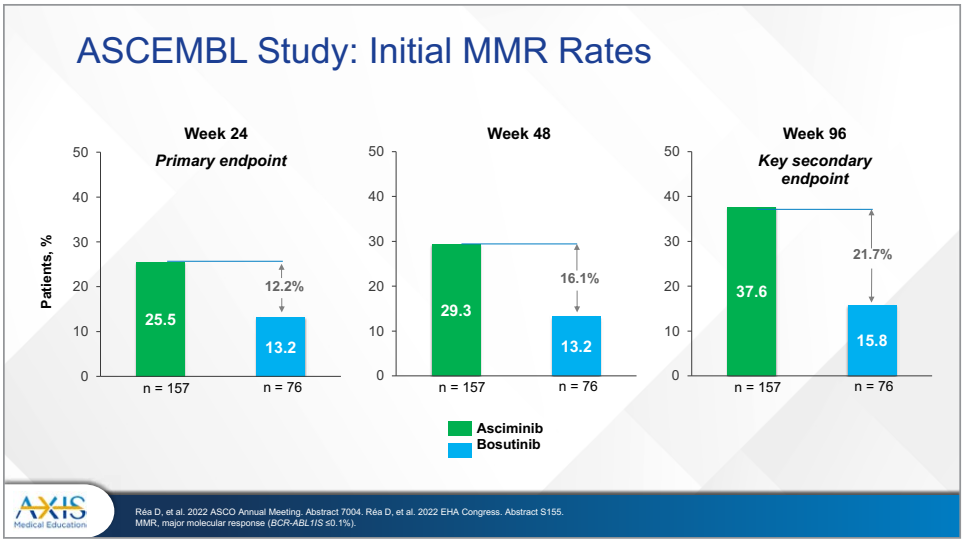
- Another question in this area was: Why would a physician prescribe first-line bosutinib for high-risk chronic phase CML over dasatinib or nilotinib? I thought this would be a good opportunity to highlight the fact that bosutinib is actually a very good drug. It's quite safe. If you look at comparative safety data from its early phase 1, 2, and 3 trials it was favorable. It doesn't have a particularly severe adverse event profile. It does have specific adverse events such as gastrointestinal and hepatic complications, transaminase elevation, early onset of diarrhea that needs to be actively managed. And there were some suggestions, not guidelines in the label, but perhaps the option to ramp up the dose potentially. But bosutinib as a second-generation inhibitor, you know, had clear data that it was better than imatinib in randomized trials and is recommended by guidelines for high-risk disease or higher-risk disease. And for the – you know, for the right patient, if those early adverse events can be avoided or overcome, it may be a very safe and very well tolerated drug. So, I would not shy away from thinking of bosutinib as a front line, or definitely as a very confident alternative in early therapy.



We know that comparative data compared to asciminib in the third line it was a bit harder to tolerate and was less efficacious. Asciminib really was the preferred agent in third line setting in the ASCEMBL trial. So, I think, you know, it's place is evolving but it certainly has a role still.

Another question in the same category: What is the role of the oncology pharmacist in discussing CML treatment options with patients before and during treatment?

Well, I'm lucky, I'm at Memorial Sloan-Kettering and we have a very active oncology pharmacy group and I'll say that if you have access to oncology pharmacy talent, or you have at least ability to reach out to them, the key questions you would see as their role would be to review concomitant medications and drug interactions, which are often many and often very important. One notable one would be proton pump inhibitors, or ACE-2 blockers and their interactions with, for example, dasatinib. The other important area that they can often be knowledgeable in is in nontraditional, or nonprescribed supplements and nontraditional medications. There are a number that have significant interactions and potential negative impacts and you know, it's a world where many patients are seeking alternative therapeutics or alternative means to improve symptoms or manage symptoms. So I think, CBD is another great example. That has a significant interaction with TKIs, and we have to avoid that. So there's there's definitely work to be done in that area and the oncology pharmacist can be quite a crucial team member.

Okay, third area. Let's move on to the next topic, which is resistance and nonadherence. What are the foremost challenges for patients who are resistant or intolerant to TKIs?

I would say probably I would look at that question itself and say that that is a common cooccurrence. We often see resistance and intolerance that are hard to separate. And if you think about it, they really are somewhat inseparable. A patient, if they're intolerant to therapy, is maybe less adherent, less able to take a therapeutic dose and that often begets some degree of resistance or even loss of response. We know that from important studies about adherence, which was another question in this section, that if patients miss more than three doses a month, they are likely to potentially face diminishing rates of deep remission and stability of deep remission.

NCCN Response Milestones

BCR-ABL1 (IS)	3 mo	6 mo	12 mo
>10%	Possible TKI resistance	TKI-resistant disease	
>1% - 10%	TKI-sensitive disease		Possible TKI resistance
>0.1 - 1%	TKI-sensitive disease		TKI-sensitive disease
≤0.1%	TKI-sensitive disease		

Color	Concern	Clinical Considerations	Recommendations
	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI and evaluate for allogeneic HCT
	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI or continue same TKI (other than imatinib) and consider evaluation for allogeneic HCT
	TKI-sensitive disease	• If treatment goal is long-term survival: ≤1% optimal • If treatment goal is TFR: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient
	TKI-sensitive disease	• Monitor response and side effects	Continue same TKI

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Shah NP, et al. NCCN Guidelines. Chronic Myeloid Leukemia. V1.2024.
CCyR, complete cytogenetic response; HCT, hematopoietic cell transplantation; IS, International Scale; TKI, tyrosine kinase. inhibitor.

So, managing the intolerance or the adverse events, is the primary challenge I think, in addition to recognizing resistance and properly categorizing resistance. And I think our task is to make sure we do not miss milestones, we monitor patients on time. There have been some studies which have unfortunately showed us that even in research settings, molecular testing isn't always performed, cytogenetic testing is not performed, and patients need this feedback and guidelines are not that complicated to follow.

Housekeeping for CML Patients

- Address, discuss, and manage adverse events
- Monitor for adherence
- Complete testing in a timely fashion

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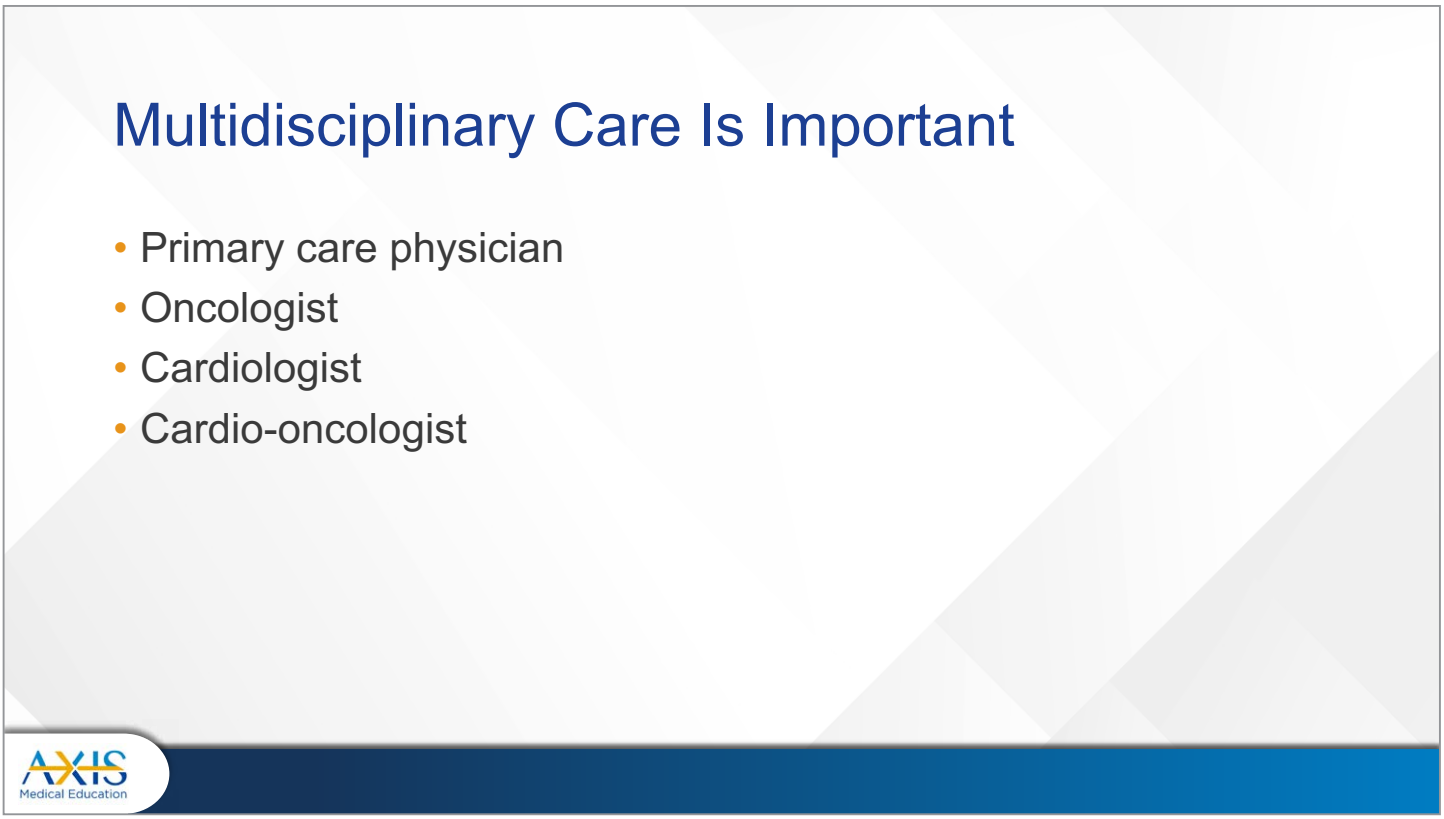
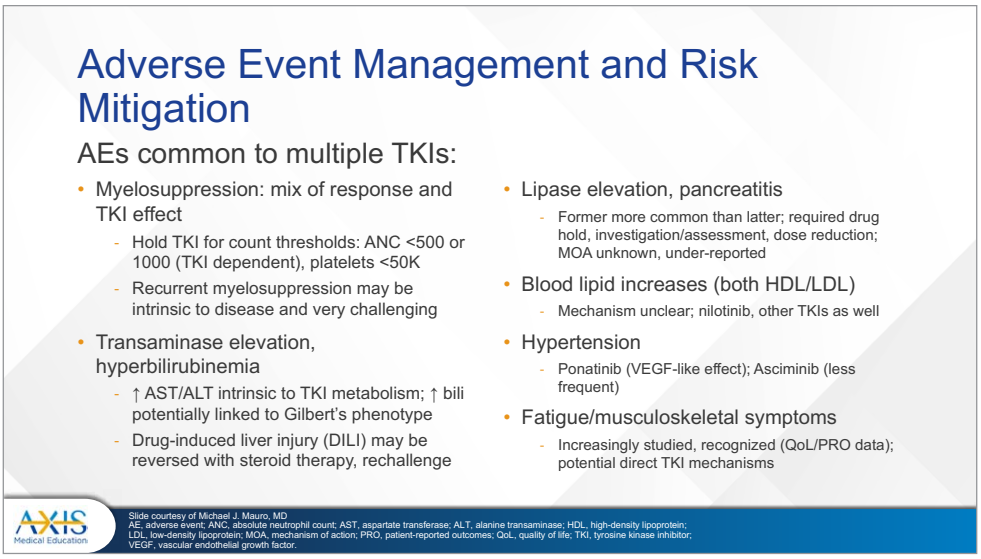
The CML patient is not the difficult one in the practice, they're the one that we have to be – we have a lot of housekeeping, we have to make sure that they're adverse events are being addressed and discussed and managed, that they're adherent to therapy at a high rate and that their testing is done at a timely fashion and reviewed, and managed.

Okay, so the final topic would be comorbidities and adverse events which we just sort of opened up that Pandora's box. But a few questions here, one was: Who is responsible for managing blood lipid increases and hypertension related to treatment with TKIs? Primary care, cardiology, oncology?

I think that's a discussion. You know, there is clearly an emerging specialty of cardio-oncology in the US and abroad, which can really be important. They are very precise in their ability to craft a monitoring plan for a patient who has cardiovascular disease, make sure their disease outside of CML is fully assessed. And let me just say that it's not that we have a separate agenda for the CML patient who has heart disease or cardiovascular disease, or they need X, Y, or Z, you just need the best cardiovascular care that a patient would have irrespective of their CML. And that's sometimes a challenge because they're always in the oncologist's office and it's often the thought that, well, aren't you doing everything? Aren't you checking my blood and you're seeing me, and can't you just prescribe my blood pressure and my thyroid?



And I really shy away from that in my own practice, and we need multidisciplinary care for the patient with CML. They need a good primary care physician to quarterback, they need oncology to, of course, cover all the bases related to their CML care. Many need cardiovascular medicine specialists or cardio-oncologists and so, I didn't really answer the question to say who should be managing what. But I think it's best in the hands of those that do that best. And in many patients that may be the cardiologist, and we certainly can't cut out the primary care physician, they really need to be part of the equation. I would shy away from having the oncologist doing everything unless you feel comfortable, and that is your practice or your standard.



Okay. Another question in this area: What steps or resources do I have in place – or do we have in place for assessment of patient indication regarding drug interactions and side effects, knowing that patients have a lot of, you know, other providers, other prescriptions, and other things that they might be taking?

Back to my point before about the oncology pharmacist. That may not be your practice or your ability, so some simple things might be just to either through nursing or physician, or even just teams in the office, just to make sure you know what things people are taking and not just prescriptions. Say, what are you ingesting on a daily basis that's not food? Are you taking supplements other prescriptions? Have you been prescribed anything new? If you are prescribed something new, give us a call so we can advise. You know, certain antibiotics for example can prolong the QT interval and that might be an issue for a patient who is on nilotinib for example, which can have some QT prolonging effects. Just an example.

So I don't have any particular steps or resources but I'm advising people to make sure that they have a heads up on the fact that the CML patient is running a marathon, they have years of therapy, three years minimum, often five plus, more. Sometimes, very long duration of therapy, so we have to keep track and monitor their regimen and manage all these issues all at the same time.

Okay. One additional question in this space: What are my thoughts on initiating lower doses of TKI or deescalating the dose to manage toxicity?

I think this is an emerging space so, stay tuned. We've seen trials, for example touting the benefits of lower dose dasatinib. We've seen trials lowering the dose of nilotinib and seen preserved response and ability to, sustain deep remission and even go into treatment-free remission.

But I would caution that we need to stay within the boundaries. I would start a patient on a full therapeutic dose, I would be willing to lower the dose based on guidelines and adverse events.

I think it's a little bit premature for us to be automatically using lower doses without randomized clinical trials or FDA label change but I think we have to know about dose reductions and consider them. And the other area that's robust for potential future research is rather than the cold turkey approach of treatment-free remission, many patients ask about de-escalation prior to discontinuation. There was a nice study from the UK called the DESTINY trial which looked at that and showed that there may be some merits there. So, I think we have to work on that question, too.

Okay. So, with that we'll end today's session. And I wanted to thank our audience for listening in, for your attention, and good day to all.

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