

Chronic myeloid leukemia: an overview of data from American Society of Hematology 2014

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ABSTRACT

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Key words: chronic myeloid leukemia.

Leucemia mieloide crónica: revisión de los datos de la Sociedad Americana de Hematología 2014

RESUMEN

Esta revisión es un servicio para la comunidad interesada en la leucemia granulocítica crónica, los comentarios son la expresión personal del autor. Esta información es una revisión de los numerosos estudios aceptados y presentados de la última reunión anual de la Sociedad Americana de Hematología (diciembre de 2014). Se aceptan comentarios al respecto, buenos o malos, la información citada es fácil de encontrar y sin costo.

Palabras clave: leucemia mieloide crónica.

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INTRODUCTION

This short review should be read together with two on line resources:

1. The original ASH abstracts are referred to in square brackets e.g. [123]. The following link will take you to those abstracts on line: <https://ash.confex.com/ash/2014/webprogram/start.html>. Look for topics 631 (mostly biology) and 632 (mostly clinical) and you'll find the vast majority of the CML abstracts.
2. A pdf document that contains the abstracts of all 30 oral presentations and a listing of 127 posters can be downloaded here: [https://www.dropbox.com/s/vwbs-j1cc3444e7y/ASH 2014 CML report.pdf?dl=0](https://www.dropbox.com/s/vwbs-j1cc3444e7y/ASH%202014%20CML%20report.pdf?dl=0)

Highlights

There seemed to be five CML themes at ASH 2014:

- Updates on clinical trials including cardiovascular risk.
- Stopping treatment and factors associated with recurrence.
- New technologies, particularly next generation sequencing and digital PCR.
- Some useful long term observations from registries.
- Lots of new data on CML in children – more than I recall seeing at any previous meeting.

Updates on clinical trials

There were lots of updates on clinical trials and there are comparative data between imatinib and nilotinib (ENESTnd, imatinib vs nilotinib, [4541]) and dasatinib (Dasision, imatinib vs dasatinib,

similar to SPIRIT 2 but with 1 yr rather than 5 yr endpoint) [154]. There were reports on a dasatinib phase II front line study [4565], 7 year follow up of one of the original dasatinib studies [520], bosutinib [4559] and the French SPIRIT trial (I400 vs I600 vs I+IFN) [1793] as well as imatinib vs ponatinib (EPIC [519]). There were a number of abstracts about ponatinib [518, 4552, 4558] including front line use [519, 4535] and an update on the PACE trial [3135]. This drug (as well as nilotinib) has struggled for the last year because of concerns over cardiovascular events but it is possibly the most effective TKI and the key to getting it right might be dose [4546, 3153]. We'll be evaluating the selective use of dose-optimised ponatinib in the NRCI SPIRIT 3¹ trial in patients who are not responding optimally to first line treatment.

I was delighted to be able to present the NRCI SPIRIT 2 study for the first time [517]. This is the largest dasatinib trial (n=814) to date. MR3 (major molecular response) rate at one year is 58.4% with dasatinib and 43.1% with imatinib (p<0.001) but there is no difference in progression or survival.

This is a common theme with other studies. To date all the 2nd generation compared to imatinib studies have shown higher molecular response rates but no difference in overall survival. The 5 TKIs all have increasingly well defined side effect profiles: dasatinib –pleural effusion (22% in SPIRIT 2) but no cardiovascular signal (see below); nilotinib and ponatinib –cardiovascular events; bosutinib –GI toxicity common but no apparent cardiovascular problems.

Imatinib therefore remains a very reasonable option for first line therapy especially as it will come off patent in 2015/16 in many countries. Indeed it already is off patent in Canada for example

¹ www.spirit-cml.org

where competition from at least two competitors (Teva and Apotex) is driving the price down. This is a welcome development for struggling health services that I think will lead to more rather than less imatinib use across the world. A useful informal list of generics is maintained by the CML Advocates patient group.² In many countries, including Mexico, the introduction of generic imatinib coincides with the withdrawal of the GIPAP programme,³ which has provided imatinib free of charge to those with limited finances. Paradoxically therefore the reduced price of generics might lead to less rather than more access for patients to imatinib. It's not clear how this will play out in various health systems around the world but it will be a major factor in determining how we treat CML over the next few years.

So what's the point of the newer TKIs? They clearly have a role *a)* in patients not responding well to imatinib; *b)* in patients for whom deep response and stopping treatment is important. So it's not 'one size fits all' and the key issue therefore is how to figure out which patients need the more potent (and expensive) drugs and when to intervene. It's increasingly apparent that there is a balance to be struck between efficacy and toxicity, especially cardiovascular toxicity.

Using early PCR values to predict response remains topical [4561] with some suggesting that response after only 1 month on treatment is predictive [816]. We've heard about the importance of 'less than 10% at 3 months' for some time now but it's emerging that perhaps the slope of the early response is more useful [156, 816, 3148]. So going from 90% to 11% in the first 3 months might be 'better' than going from say 13% to 9%. Most such analyses have been applied to imatinib but the same seems

to hold true for dasatinib [1795]. Prognosis may be determined not just by early response to treatment but perhaps by TGF- α and IL6 levels [1788], as well as polymorphisms in BIM (BCL2L11) [1797]. We're gradually getting better at identifying patients for whom a change of therapy might be a good idea. Sequencing might help further (see later).

There were updates on various aspects of cardiovascular risk and TKIs: it's still not well understood. CV risk seems to mainly be a concern with nilotinib and ponatinib and there's some reassuring evidence that there is not such a concern if patients don't have prior CV risk factors [1811]. Mouse and human data on mechanism with nilotinib were presented [1800]. Development of insulin resistance in some patients on nilotinib might be important [1813] and more light is being shed on potential mechanism of CV events with ponatinib [1783] but I think it's fair to say this whole area is still poorly understood. Dasatinib (and bosutinib) appears to carry less CV risk [4534] – helpful to know when selecting the right treatment for individual patients. The *SCORE* chart can identify patients on nilotinib at risk [4545] and homocysteine levels might be important [3136]. Useful case series/registry data also contribute to our understanding [3234, 3147]. In then UK we'll be using the QRISK2⁴ score to evaluate cardiovascular risk in SPIRIT 3.

Here's an interesting observation: many CML patients will end up on a statin and there's some data (albeit retrospective and with no PK) that patients on statins have higher MMR rates [1804]. That might be due to CYP3A4 interactions pushing imatinib levels up but who knows, maybe statins have an anti-leukaemic effect but the story is not yet convincing to my mind.

² <http://www.cmladvocates.net/generics>

³ <http://www.themaxfoundation.org/gipap/Default.aspx>

⁴ www.qrisk.org

Stopping treatment and factors associated with recurrence

Stopping continues to be very topical. The EuroSKI study was presented for the first time [151]. This is similar to the original STIM study and by October of this year, 648 patients had been registered and 200 were evaluable after 6 months. Patients had to have been on a TKI for at least 3 years and been in MR4 for at least a year. So far the 18-month KM probability of relapse-free survival is 55% (95% CI 47%-61%) which is higher than the original STIM study. In contrast the ISAV study [813] seemed to show a lower rate of durable *complete* molecular remission. 112 patients were enrolled in this study: Only 15% maintained CMR, 48% relapsed although the remaining 37% didn't go above MR3 and some stayed at that low level for quite some time. There was a higher rate of relapse amongst young patients - not known why.

Results from other imatinib stopping studies are coming through: ENESTnext [1796], SENSOR [1815], Gimema study [4532], Korean studies [1816, 3155, 4553] and rates of successful stopping vary. There was an update from the French stopping 2nd generation TKI study –the only one of it's kind so far and with still a relatively small number of patients, n=52 [811]. Kaplan Meier probability of treatment-free survival in MMR (CMR data not presented) at 24 months is 57.4% (95%CI 43.9-70.9). There was an interesting abstract about patients' attitudes toward stopping in Hungary [4547]. Most, but not all, are keen.

There were a few abstracts looking at factors associated with molecular relapse following stopping. It's still not very clear but there are suggestions that it might be related to: polymorphisms in BIM (BCL2L11) [1797]; low number and impaired function of NK cells [812]; age and results of dPCR [813] (more later...). Some, but not all, studies suggest that duration of prior TKI therapy is also important.

As more studies report it's becoming clearer that, following stopping, some patients can relapse quite late, say after a few years, so ongoing monitoring remains important. Reassuringly in all of these studies no patients have gone into blast crisis and patients regain molecular response if therapy is restarted. The INTERIM study is a bit different and is looking at *intermittent* imatinib in elderly patients: giving less seems to be OK in older patients [1794].

There seem to be two emerging schools of thought: there are those (including most TKI companies) who believe that stopping is the highest priority and deep molecular responses important as a route to 'cure' (however you might wish to define that). Others accept that having a small amount of residual disease is acceptable if patients live a normal life span and have few, preferably no, short or long term side effects. There's a (financial and wellbeing/utility) price to pay in achieving very deep molecular response and this may not be worth it for many CML patients especially those who are older and have significant co-morbidities. The approach of reducing dose at the point of MMR is for example being evaluated in the UK DESTINY study at present and we may have data at next year's ASH. Reducing as a prelude to stop will also be part of SPIRIT 3.

New technologies, particularly next generation sequencing and digital PCR

Next generation sequencing (NGS) is really starting to fly but it's still quite expensive (although rapidly coming down in price) and produces a ferocious amount of data requiring powerful bioinformatics. I'm a fan: I think patient sequencing reports will be as common as morphology and flow cytometry reports quite soon [399]. Technology platforms are jostling for position but Illumina seems to be in the lead and they recently announced the first '\$1,000 whole genome' (although the equipment to do it cost \$10M).

Most reports at ASH related to targeted sequencing, mainly looking at ABL kinase domain mutations (there are over 100 reported now) [815, 1810, 4525, 4531]. T315I remains the most important. Mutations associated with resistance are also being found in non-BCR-ABL genes [4514, 4516]. NGS can also identify DNA methylation patterns indicative of disease progression [4526]. Whilst these targeted approaches are useful what is potentially very exciting are whole exome (~1% of the genome) or whole genome sequencing approaches. These analyses may allow us to better understand the genomic basis of response, resistance, progression and toxicity in due course although the data analysis and interpretation will be an enormous task. We're planning some large scale sequencing analyses in SPIRIT 3.

I like the look of digital PCR [813, 1817, 1792]. There are 4 technology platforms at present – 2 chip-based and 2 droplet-based. Is this the 'iPhone of PCR technology'? dPCR potentially offers greater sensitivity [4540] and reduced cost but the runs are generally slower so throughput reduced. Because absolute numbers of molecules are measured, this approach in theory goes some way towards doing away with the need for the 'international scale' but as correlative data with conventional qPCR are somewhat lacking at present it's probably not ready for prime time just yet. But I personally think it's the future. Cepheid PCR technology also looks interesting [1809] but struggles at lower levels it seems – tech updates in progress.

At the opposite end of the tech spectrum it seems you can ship samples of blood dropped on paper across the world [4566] and still be able to do reliable PCR testing. This very practical piece of work could greatly extend the availability of PCR testing across the globe.

Some useful long term registry observations

Imatinib was first given to a CML patient in 1999 so we now have 15 years of experience with

TKIs. There was an update on the EUTOS registry [3160] as well as data on the incidence of CML across Europe [3145]. Survival with imatinib is now not much different to the normal population [1801] and increasingly we are therefore having to advise patients about planning their families. An update on the Italian Gimema registry of conception/pregnancy [1806] was therefore useful. We sometimes get asked by patients what is known about the effects of TKIs on fertility: I'm now better equipped to answer if those patients are mice... [1799].

The Swedish registration system is impressive: all patients with cancer must be registered by law (maybe we should do that in the UK?) so there are pretty reliable data available. As well as contributing to our understanding of cardiovascular risk [3134] there was an excellent presentation on the development of second malignancies in 887 patients with CML diagnosed between 2002 and 2011 – 3,293 'person years at risk' [154]. There's a 50% higher prevalence of second malignancies in CML patients compared to the 'normal' population – standard incidence ratio (SIR) is 1.5 observed/expected (95% CI 1.13–1.99). Makes you wonder if we should be doing more screening and the higher incidence seems to be associated with having CML rather than its treatment.

Data on CML in children

Although rare, there seemed to be a lot more about CML and TKIs in children this year. There were very informative surveys of outcome, mainly on imatinib [1803, 521] as well as data on predicting response [4549] and the impact of additional cytogenetic abnormalities [3137]. Data were also presented on decisions taken in children who failed imatinib [1798]. Although imatinib is producing very good outcomes [1812] it does seem to be associated with growth retardation in pre-pubescent children although not so much in older teenagers [522]. Combi-

ning imatinib with RIC transplant is also being evaluated [4568]. People generally seem to be favouring ongoing TKI therapy rather than elective transplant but what's unknown is whether these young patients could/should remain on TKIs for decades potentially. There are no paediatric TKI stopping studies yet.

And in other news...

A few new drugs were surfacing, all very early and I'm still not convinced there's room for more drugs in CML but here's a few: ABL001 is a new drug that works against T315I [398], like ponatinib. There's lots of interest in ABT199 (a Bcl-2 inhibitor) in lymphoid malignancy and now there are some data to suggest that it may be useful in combination with TKIs to eradicate CML stem cells [512]. There was a poster on combination of dasatinib with BMS-833923 (a smoothened inhibitor) [4539]. I've never heard of pyrvinium before but this anti-helminthic drug appears to be effective in blast phase CML (not in patients as yet) by inhibiting mitochondrial respiration [514]. And to round up there were data

on copanlisib (PI3K inhibitor) [3127]; synthetic anti-IL3 receptor antibodies [4521]; chaetocin (a non-specific histone lysine methyltransferase inhibitor) [4517]; ethacrynic acid derivatives [4508] and BGB324 (an AXL inhibitor) [4512].

CAR-T cells [966] continue to look very exciting in refractory acute leukaemia [380] and other indications: lymphoma [3087]; CLL [1982]; Hodgkins [806]. We're not seeing use in CML yet: there isn't such an obvious specific antigenic target and this approach is pretty hard work. Most patients develop a cytokine release syndrome [1983, 2296] that often leads to a trip to the ITU. But I suspect this will be refined given time and I think this is one of the most successful immune therapies to date.

In summary this was a pretty good ASH meeting for those interested in CML: there are some really exciting new technologies coming through and maturing clinical data that will in time help us refine the balance between risk and benefit that we need to strike to optimise treatment for our patients.