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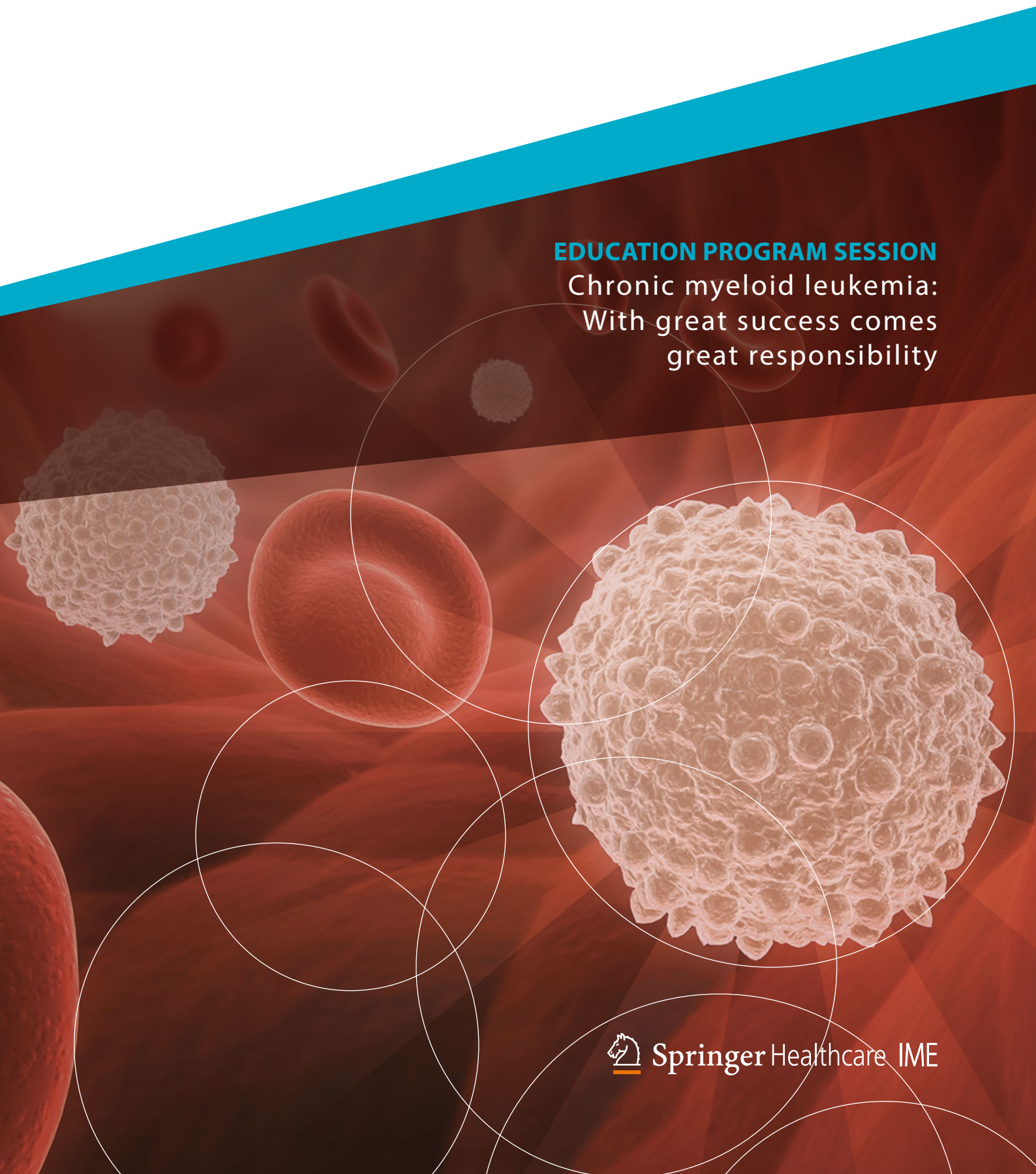

EDUCATION PROGRAM SESSION

Chronic myeloid leukemia: With great success comes great responsibility

Springer Healthcare IME

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Education program session: Chronic myeloid leukemia: With great success comes great responsibility

This education session was chaired by Professor Jane Apperley, from Imperial College London in the UK, and discussed the optimal management of patients with chronic myeloid leukaemia (CML) at diagnosis and through disease progression. Using case studies, Apperley and her co-presenters Professor Tim Hughes and Professor Charles Craddock reviewed tyrosine kinase inhibitor (TKI) treatment decisions that are made in the clinic and when allogeneic stem cell transplantation (ASCT) might be considered.

THE ARGUMENT FOR USING IMATINIB IN CML

Professor Jane Apperley
Imperial College London, UK

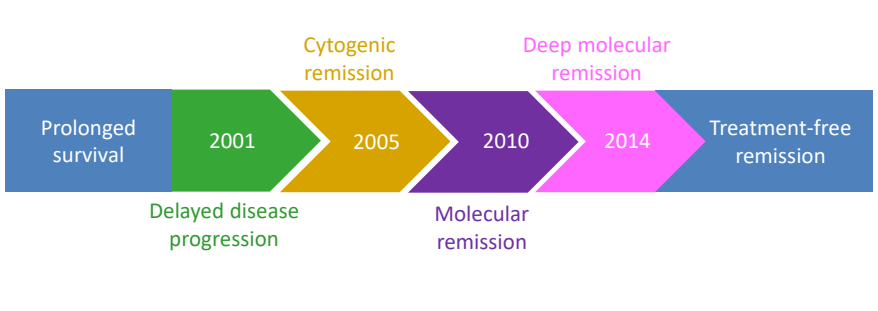
A common first-line goal for CML

Apperley opened the education session by highlighting the improvement in CML survival since the introduction of the first BCR–ABL TKI imatinib in 2000 using life expectancy curves from Scandinavia.[1]

"A patient diagnosed in 2018 can have a very reasonable hope of a life expectancy that is completely unaffected by the disease", she explained, with some patients even able to attempt discontinuation of TKI therapy completely, as shown by findings from the Stop Imatinib trial.[2]

When imatinib was first introduced, the initial treatment goal was to prolong survival and delay disease progression and this subsequently progressed to cytogenetic and then molecular remission (MR), Apperley explained, with deep MR and now treatment-free remission (TFR) where appropriate.

Recommending a deep MR – defined as a 4 log reduction or better (MR4) on the International Scale (IS) – as the common goal, the presenter explained that this outcome is significantly associated with improved overall survival (OS), as demonstrated by the German CML IV Study, and the increased likelihood of a durable and deepening response to treatment over time.[3,4] It is therefore now the threshold for trials of TFR given its association with a significantly increased likelihood of success.[5]



CML treatment goals

Adapted from a slide presented by Apperley J, ASH 2018

First- versus second-generation TKI

Treatment with a second-generation (2G) TKI, such as bosutinib, dasatinib or nilotinib, is associated with a greater likelihood of achieving MR4 compared with imatinib,[6,7,8] Apperley said, while a poster presented at ASH annual meeting 2018 for the RERISE study of the 2G TKI radotinib versus imatinib shows a similar pattern, with 76% and 56% of patients achieving major molecular response (MMR) by 48 months, respectively.[9]

However, further analysis of the German CML IV Study suggests that imatinib is just a "slower" drug than the 2G TKIs and that it is very likely that you will achieve the same deep MR if you are "patient for your patients", Apperley said.

And while progression-free survival (PFS)[8,10] and CML-related survival[8] favour use of 2G TKIs over imatinib, the rate of OS[3, 8, 10] remains comparable between the agents, suggesting that "in certain cases we might be doing some harm" to patients by the choice of a 2G TKI, she added.

Furthermore, the most common cause of death in CML is now pre-existing comorbidity, with a "very dramatic" difference in survival seen between patients with no more than two versus seven or more comorbidities[11], she said, emphasizing that the majority of patients are in their mid 60s or older and have at least some comorbidity.

To follow Hippocrates' recommendation to first do no harm, or at least do harm "as infrequently as possible", Apperley summarised that the decision on whether to use a 2G TKI versus imatinib must therefore balance the increased risk of adverse events and greater cost with the 2G agent versus the benefits of a reduced risk of progression, a deep remission and the likelihood of achieving TFR

Who should receive front-line 2G TKIs?

Apperley recommended front-line 2G TKIs for key patient groups, notably those at high risk of progression and those with additional chromosome abnormalities, for whom there are strong recommendations. For other group characteristics, the evidence base for such indications is less strong, but "may tip you over" to a 2G TKI course, she said. She summarised the groups as follows:

- Patients at high risk of progression.
  - This may include patients with intermediate Sokal risk, for whom treatment with nilotinib may offer greater protection from disease progression than imatinib.[8] And this has been shown again at the ASH 2018 annual meeting by results from the real-world CML-IT-MOS study indicating that OS at 4 years significantly differed for patients with an intermediate EUTOS long-term survival (ELTS) risk who were treated with a 2G TKI versus imatinib (99.0 vs 90.5%).[12]
- Patients with additional chromosomal abnormalities.
  - Patients with major route abnormalities, such as an additional Philadelphia chromosome (Ph), trisomy 8 or 18, or isochromosome 17q have poorer survival than those without.[13]
- Patients with Bcr-Abl1 transcript type.
  - Multiple studies have suggested that the e13a2 transcript may be a poor prognostic indicator but recent results indicate there may be a survival advantage with the e14a2 versus e13a2 script.[14]

- Patients with additional genetic abnormalities.
  - Somatic mutations in additional genes are more common in patients with a poor response to TKI therapy than those who do respond and the effect may be abrogated by use of 2G TKIs.[15,16]

  Younger patients.
  - Children and young adults up to the age of 29 years tend to have higher white blood cell counts and larger spleens than older patients, and although survival is similar, younger patients are less likely to achieve a reverse transcription–quantitative polymerase chain reaction (RT–qPCR) below 10% within 3 months than those aged over 44 years (58 vs 75%).[17]
- Women wishing to conceive.
  - Women who wish to have a family may prefer to use a 2G TKI that induces remission faster.

CASE STUDY 1 – SUE

A 22-year-old woman, 16 weeks' pregnant with three siblings, Sue does not smoke and has no comorbidities. She was positive for the Ph on all 20 metaphases but without any additional Ph and she has an E14a2 transcript. Her RT-qPCR is 58% IS.

The audience voted on their preference for first-line treatment:

Bosutinib – 10%
Dasatinib – 19%
Imatinib – 57%
Nilotinib – 8%
Trial entry – 5%

Sue required no treatment during pregnancy; she delivers a healthy baby boy, breastfeeds for 1 month and then begins imatinib. Sue achieves MR4 by 1 year and MR4.5 by 3 years, maintaining that level for 2 years.

Should she attempt TFR now or wait? The audience responded as follows:

Attempt TFR now – 64%
Wait at least another year – 28%
Make no recommendation – 1%
Not attempt TFR at any time – 1%
Reduce imatinib to half dose before TFR attempt – 6%

Indications for front-line imatinib

- Age, comorbidity and adverse events.
    - Older patients are more likely to have comorbidities and the 2G TKIs have a different adverse event profile to imatinib.
    - For example, increasing age is a predictive risk factor for pleural effusion with dasatinib, while nilotinib is associated with an increased risk of arterial thrombosis, hypertension, hypercholesterolemia and glucose elevations, and bosutinib is associated with diarrhoea, lipase elevations and liver enzyme increases.[18,19]
- Patients with a low Sokal or ELTS score.

Alternative approaches might include initiating treatment with imatinib and switching to a 2G TKI if the patient is not an optimal responder, as tried in the TIDEL-II trial, or perhaps beginning treatment with dasatinib or another potent TKI and switching to imatinib once MMR or a deeper response has been achieved.[20,21]

For patients with comorbidities who need a 2G TKI, management must include formal assessment of cardiovascular risk; regular monitoring of blood pressure, lipids, glucose, liver function and other markers; and optimisation of co-existing medical issues including use of statins, aspirin and other agents.

A dose reduction once a MR is achieved may also be appropriate, Apperley said.

Click here to view the video interview with Professor Jane Apperley

MOLECULAR MONITORING IN CML: HOW DEEP, HOW OFTEN, AND HOW SHOULD IT INFLUENCE THERAPY?

Professor Timothy Hughes
South Australian Health and Medical Research Institute, Adelaide, Australia

The ability to measure BCR-ABL % IS transcript levels in CML is a "remarkable window on the disease and the dynamics of the disease", Hughes said.

He highlighted two distinct groups of patients with a high risk of CML-related death: the 10% who have primary resistance to treatment and are likely to require ASCT, and the 10% who have secondary resistance related to kinase domain mutations.

In addition, around 30% of patients experience a plateau after an initial satisfactory response – half of whom might achieve a deep MR with a more potent TKI. And while 50% of patients achieve a deep MR, half of these patients will subsequently lose their response during a trial of TFR and require further treatment.

With just 25% of patients achieving a "truly optimal response", Hughes emphasized the need for clinicians to "be ambitious, not complacent in this disease."

Molecular monitoring – how often?

Hughes recommended monitoring patients every 3 months, increasing to monthly BCR-ABL monitoring for:

- patients with a BCR-ABL of 10% IS or higher;
- patients with a BCR-ABL rising by 0.1% or more;
- patients within the first 6 months of a trial of TFR; and
- patients who are re-establishing MMR after molecular relapse.

When to change the TKI?

There are several sets of guidelines for when to change treatment. The European Society of Medical Oncology (ESMO) guidelines say that a BCR-ABL above 0.1% is a warning sign for considering a TKI switch, while the National Comprehensive Cancer Network (NCCN) 2018 guidelines suggest that this MR level may warrant TKI dose escalation or a TKI switch.[22,23] Other factors supporting a switch of treatment may be urgency for TFR or comorbidity.

When to attempt TFR?

At 2 years, half of the EURO-SKI study patients had achieved TFR and there was a linear relationship between duration of MR4 and the likelihood of TFR success at 2 years, with a 50% probability for patients who had maintained MR4 for 3 years, rising to 53% at 4 years and 59% at 6 years.[24]

By contrast, time spent in TKI treatment before achieving MR4 was associated with a relatively small increase in the probability of retaining MMR, at around 0.86% per year.
Therefore, Hughes recommended that patients considered for TFR should have:

- achieved MR4.5;
- a MR4 duration of at least 3 years; and
- a stable MR – fluctuation in the year before trial of TFR is associated with a lower rate of success.[25]

In addition, physicians may also reflect on:

- TFR motivation and urgency;
- treatment tolerance;
- comorbidity; and
- patient compliance with monthly monitoring.

CASE STUDY 2: BOB

Bob is a 55-year-old man with one sister. He is an overweight but not obese smoker who uses statins for high cholesterol. Diagnosed with CML in 2012, he was positive for the Philadelphia chromosome (Ph) and showed an additional Ph in three of 20 metaphases. He was also positive for the E13a2 transcript and has a RT-qPCR of 86% IS.

The audience chose between the following first-line treatment options:
Bosutinib – 2%
Dasatinib – 22%
Imatinib – 64%
Nilotinib – 4%
Trial entry – 8%

Bob was entered into the phase III SPIRIT2 trial and was randomly assigned to receive imatinib, but after 3 months of treatment his BCR-ABL is 13%, rising to 17% at 4 months.

Here is what the audience suggested as next stage of care:
Continue to watch closely – 16%
Increase imatinib dose to 600/800 mg/day – 16%
Switch to 2G TKI – 65%
Switch to ponatinib – 3%
Proceed to allograft – 1%

As recommended by the audience, Bob began second-line treatment with dasatinib but at 3 months his BCR-ABL level is 20%.

The audience made the following choices:
Continue dasatinib – 2%
Switch to ponatinib – 41%
Tissue type his sibling – 47%
Switch to nilotinib – 9%
Add hydroxycarbamide – 0%

After showing resistance to both imatinib and dasatinib, Bob proceeded to RIC allograft – he had an uncomplicated course and said that he "cannot understand what all the fuss was about." He had no GVHD complications and was off immunosuppression but 1 year after transplantation his BCR-ABL ratio was 2%, without evidence of an ABL kinase mutation.

The audience chose between these treatment options:
Start imatinib – 1%
Start dasatinib – 3%
Start ponatinib – 19%
Commence DLI – 71%
Observe – 6%

One other issue is that patients may experience treatment failure before beginning 2G TKI. The STOP 2G-TKI trial indicated that the likelihood of TFR at 2 years is much poorer for patients who began a 2G TKI because of suboptimal response or resistance, compared with those who used a 2G TKI in the first line or switched because of imatinib intolerance.[26]

But the ENESTop trial showed little difference in the time to loss of response after trial of TFR in patients who switched to nilotinib because of imatinib resistance or physician preference versus those who were resistant to imatinib.[25]

"I don't think we have the full answer here but I would certainly caution against going too readily into TFR remission for a patient who had failed their imatinib therapy and achieved a good response to a second-line drug", Hughes commented.

He added that the ENESTop trial showed that patients with MR4.5 for more than a median duration of 32 months had a significantly higher rate of TFR than those with a shorter duration, at 68% versus 48%.

Latest information on depth of response and TFR

Discussing results presented at the ASH Annual Meeting 2018, Hughes pointed to "very promising data" from the ISAV study, showing that there is a higher risk of relapse during TFR for patients who are above BCR-ABL 0% using digital polymerase chain reaction digital PCR technique versus Q-RT-PCR,[27] while findings from the STIM2 study suggested there may be a threshold residual leukaemic cell load as determined by digital PCR threshold that is predictive of relapse.[28]

"It will be a challenge now for us all to get into the next generation of technology, [which will] give us better tools to decide who can stop and who needs to wait", Hughes said.

Click here to view the video interview with Professor Timothy Hughes

WE DO STILL TRANSPLANT CML, DON'T WE?

Professor Charles Craddock
Queen Elizabeth Hospital, Birmingham, UK

Introducing the topic, Charles Craddock said his role was to convince the meeting delegates that ASCT "remains an important therapeutic modality in CML – even in the imatinib era", with the ability to provide a "comparable outcome" to first-line TKI.[29]

He noted that transplant-related mortality has decreased in recent years, while the risk of acute grade III-IV graft versus host disease (GVHD) after ASCT has fallen for both sibling and other donor types.[30, 31]

"Defining patients who will benefit from [ASCT] is key to optimizing outcome in CML", he said.

What do we know about transplantation in 2018?

Craddock outlined the current knowledge on ASCT, summarising that:

- increasing the intensity of the conditioning regimen reduces relapse but not CML survival;
- a potent graft versus leukaemia (GVL) effect occurs in patients who undergo ASCT in first chronic phase (CP) but this is more modest in advanced phase (AP) patients, requiring a more intense conditioning regimen;
- donor lymphocyte infusion (DLI) is an effective salvage therapy in first CP patients, as first demonstrated by Kolb et al; [32]
- relapse is the major cause of treatment failure;
- factors associated with TKI failure and transplant-related mortality (TRM) help personalise decision-making for transplantation in CML.

Who might benefit from ASCT?

"It's easy now to predict patients who are unlikely to get a good response to a second-line TKI early", Craddock said, highlighting data showing that patients who do not achieve a BCR-ABL ratio below 10% within 3 months of a 2G TKI are less likely to respond.[33] And using the Hammersmith score system based on cytogenetic response to first-line TKI, Sokal score and recurrent neutropenia on first-line TKI, "you can again identify patients who are unlikely to do well," he added.[34]

Ponatinib is a "perfectly reasonable" suggestion as a third-line TKI, the presenter added, with around a 50% response rate for patients taking it as a second-line TKI, and a durable response for those who do well.[35] But the response rate is poorer when the drug is taken as a third-line treatment and the associated high rate of arterial occlusive events that does not reduce with dose adjustment limits it as a choice for patients with comorbidities.

Patients who should be considered for ASCT

Craddock said that individuals who should be considered candidates for ASCT include patients:

- who have required a second-line TKI in the CP;
- with a poor response or predicted to have a poor response to second-line TKI;
- with a T315I mutation;
- who have not responded to ponatinib;
- who have accelerated phase disease naïve to or with a suboptimal response to TKI; and
- those in blast phase who achieve a second CP after TKI or salvage chemotherapy.

Selecting patients for ASCT

Physicians may then determine that a patient is a suitable candidate for ASCT using the European Group for Blood and Marrow Transplantation (EBMT) scoring system, based on characteristics including donor type, patient age, disease stage and time from diagnosis,[36] but the haematopoietic cell transplantation-specific comorbidity index (HCT-CI) score is now more widely used, Craddock said.[37] This predicts TRM and OS using a weighted assessment of 17 comorbidities, where a score of 3 or above is associated with a significantly poorer outcome.

He explained that patients aged over 60 years with an HCT-CI score of 0–1 have an "excellent outcome" after allograft and comparable survival to those aged 40–49 and 50–59 years,[38] but the risk of TRM increases sharply with a HCT-CI score above 1 in patients aged over 60 years,[39] and age has since been introduced into the HCT-CI score.[40]

"Patients over 60 who have no or only one comorbidity can tolerate allogeneic transplant very well and their toxicity is not much different from younger patients", he summarised.

Managing disease relapse after ASCT

Craddock said BCR-ABL monitoring every 3 months is mandated for the first 3 years after ASCT as 30–70% of CML patients in CP will relapse but he emphasized that donor lymphocyte infusion (DLI) can achieve a durable molecular remission for up to 90% of patients who receive an allograft in their first CP.[41]

The major complication of DLI is GVHD, with a significantly increased risk found particularly among patients with a history of GVHD or those who require DLI within a year of transplantation. But in the absence of these risk factors, the molecular remission rate is 56%, Craddock commented.[42]

TKI salvage is an "emerging alternative" to DLI, the presenter continued, delivering CMR in up to 60% of patients who have relapsed after allograft and this strategy appears to offer durable responses. Again, this is most effective in patients who receive an allograft in their first CP and it is yet unknown whether outcome is affected by choice of TKI or TKI resistance prior to transplantation, he said.

For patients with advanced phase CML, there is very little GVL effect and TKI monotherapy fails to deliver a durable response, but for patients with disease duration of less than 12 months, a haemoglobin level above 100 g/L and peripheral blood blasts above 5%, imatinib may offer a comparable outcome to allograft, Craddock reported.[43]

While blast crisis is now a rare complication of CML,there is still an unmet need and there is not a consistent strategy to return patients to a second CP for allograft as a curative therapy, the presenter said.[44]

Myeloid blast crisis patients may respond to a TKI guided by mutational status given alone and/or with FLAG-IDA induction chemotherapy (fludarabine, idarubicin, granulocyte-colony stimulating factor, high-dose cytarabine), while lymphoid blast crisis patients have shown good results with standard acute lymphocytic leukaemia induction therapies, he observed.[45]

Craddock said that while ASCT significantly improves OS compared with TKI alone in blast crisis,[46] early research suggests that ponatinib may have significant activity in this stage of disease,[47] and results expected from the MATCHPOINT study by Mhairi Copeland and team (University of Glasgow, UK) in 2019 may shed light on the optimal use of ponatinib in combination with FLAG-IDA for blast transformation.

Improving CML outcomes after ASCT

Craddock summarised that avoiding relapse is the most important way of improving CML outcomes after allograft.[48] And outlined the key factors for avoiding relapse.

- Minimising disease burden before transplantation.
- Optimising the conditioning regimen, with research showing that a reduced intensity strategy is as effective as a standard myeloablative conditioning (MAC) approach,[49] while for patients undergoing MAC, TRM is significantly reduced by combining busulfan with fludarabine instead of cyclophosphamide.[50]
    - Patients who may benefit from MAC may include healthy adults aged less than 50 years and those in a second CP or in advanced phase disease, while a reduced intensity conditioning (RIC) regimen should be considered for patients older than 55 years or with a HCT-CI score above 3, possibly alongside TKI maintenance.
- Exploring the possibility of using post-transplant adjunctive therapy to manipulate disease kinetics to prevent relapse before GVL can take place, or using a treatment to boost GVL, as well as delaying use of DLI until GVHD toxicity is lower.

Click here to view the video interview with Professor Charles Craddock

Oral Abstract Report on CML Therapy:
First Line Trials and Prognostic Factors of Treatment-Free Remission > click here

Abstract 457 – Spirit 2: Final 5-year analysis of the UK National Cancer Research Institute randomized study comparing imatinib with dasatinib in patients with newly diagnosed chronic phase CML

Stephen O'Brien, from Newcastle University in the UK, presented the final 5-year results of the phase III SPIRIT 2 trial comparing dasatinib with imatinib in patients with newly diagnosed chronic phase chronic myeloid leukaemia (CML).

SPIRIT 2, involving 812 patients, "is the largest trial comparing imatinib and dasatinib", O'Brien told delegates.

The investigators demonstrated that the 406 patients who were randomly assigned to receive dasatinib 100 mg/day had a significantly better PCR response rate at 5 years than the 406 participants given imatinib 400 mg/day, with MR3 and MR4 rates of 83.0% versus 63.0% and 77.5% versus 57.2%, respectively. However, there was no significant difference in the primary endpoint of 5-year event-free survival between the dasatinib and imatinib arms, with corresponding rates of 91.0% and 89.0%.

O'Brien noted that "a fairly unprecedented" proportion of patients remained on treatment for the 5-year study duration, with just 6.9% of participants in the dasatinib arm and 4.7% of those given imatinib discontinuing treatment. Pleural effusion occurred in 36% of dasatinib-treated patients, and the incidence was significantly higher in this group.

Abstract 462 – The evaluation of residual disease by digital PCR, and TKI duration are critical predictive factors for molecular recurrence after for stopping imatinib first-line in chronic phase CML patients: Results of the STIM2 study

Abstract 461 – Imatinib suspension and validation (ISAV) study: Final results at 79 months

Two studies presented at the meeting focused on stopping imatinib treatment among CML patients in molecular remission. Franck Emmanuel Nicolini, from INSERM U590 in Lyon, France, and co-investigators from the STIM2 study found that duration of imatinib treatment was a "critical predictive factor" of TFR, with patients who had a treatment duration of less than 75 months having a significant 42.6% lower likelihood of maintaining remission after stopping imatinib than those with a longer treatment duration. The researchers also demonstrated that residual leukaemic load as measured by digital droplet digital droplet PCR (ddPCR) was linked to the probability of achieving treatment-free remission; patients with a ddPCR measurement of less than 0.023% IS were a significant 45.4% less likely to meet this endpoint than those with a residual load of 0.023% IS or higher.

Carlo Gambacorti-Passerini , from University of Milano Bicocca in Monza, Italy, presented the final results from the ISAV study, showing that of 112 patients who discontinued imatinib therapy after being in complete MR for at least 18 months, 52.3% experienced a disease relapse over a median 59.2 months of follow-up. The majority (69.6%) of relapses occurred within 9 months of imatinib discontinuation, but Gambacorti-Passerini stressed that three late relapses occurred, at 31-month, 36-month, and 56-month timepoints.

"Therefore, patients who discontinue imatinib should be monitored for a long period of time", he concluded.

Abstract 458 – Outcome of 472 chronic myeloid leukemia patients treated with frontline nilotinib: A Gimema CML WP analysis

A study by Gabriele Gugliotta, from the University of Bologna in Italy, and fellow researchers demonstrated that first-line nilotinib treatment may require optimisation according to age in patients with CP CML. Although molecular response rates were comparable among nilotinib-treated patients in different age groups, older people had an increased likelihood of experiencing arterial thrombotic events (ATEs). A total of 15.2% of 157 patients aged 60 years or older experienced ATEs over 4 years of follow-up, compared with 4.1% of 217 patients aged 40–59 years, and none of the 98 patients aged 18–39 years. Gugliotta concluded that treatment optimisation should aim to reduce the risk of adverse events in older patients and increase efficacy in younger people.

Abstract 460 – Nilotinib vs nilotinib plus pegylated interferon-alpha2b induction and nilotinib or pegylated interferon-alpha2b maintenance therapy for newly diagnosed BCR–ABL+ chronic myeloid leukemia patients in chronic phase: Interim analysis of the Tiger (CML V)-study

Abstract 459 – Combination of nilotinib and pegylated interferon alfa-2b results in high molecular response rates in chronic phase CML: Interim results of the ALLG CML 11 Pinnacle Study

Two studies investigated the efficacy of nilotinib in combination with pegylated interferon alpha2b (Peg-IFN) among patients with newly diagnosed CP CML. Andreas Hochhaus, from Universitätsklinikum Jena in Germany, outlined the first interim analysis of the phase III TIGER trial, in which 692 patients were randomly assigned to receive nilotinib 300 mg twice daily with or without Peg-IFN, given at a dose of 30–50 µg/week and started after more than 6 weeks of nilotinib monotherapy. The cumulative incidence of MMR at the 18-month follow-up was 0.91 and 0.86 in the two groups, in which the treatment allocation was concealed. Hochhaus noted that the majority of participants experienced adverse events, most frequently fatigue, headache, pruritis, flu-like symptoms and thrombocytopenia, and approximately 40% experienced grade 3 or more severe adverse events. He concluded that the combination of nilotinib and Peg-IFN is "feasible", and told delegates that the final primary outcome data of MMR at 18 months will be available in 2019.

The second study on this combination – an interim analysis of the single-arm phase II Pinnacle study presented by David Yeung from the South Australian Health and Medical Research Institute in Adelaide – also demonstrated high MR rates. The MMR at 12 months was 78.3% among 60 patients treated with the regimen, given as nilotinib 300 mg twice daily with the addition of Peg-IFN at 30–50 µg/week from month 3 until the 2-year follow-up.

Oral Abstract Report on CML Therapy:
TFR Failure, Resistance, and New Drug Development > click here

Novel TKIs in clinical trial

Phase I clinical trial results were reported for the fourth-generation TKI, PF-114 mesylate, the third-generation TKI, HQP1351, and asciminib, the first allosteric TKI targeting the T315I mutation.

Abstract 790 – Phase-1 study of PF-114 mesylate in CML failing prior tyrosine kinase-inhibitor therapy

For CML patients who are resistant or intolerant to at least two prior TKIs, the maximum tolerated dose of PF-114 mesylate was 600 mg, with cohorts expanded for doses at 200, 300 and 400 mg/day. Grade 2–3 haematological toxicity was "not common" and found only in patients with a history of such side effects, while skin disorders were the most frequent non-haematological event, and there were "no vascular occlusions or deterioration of cardiovascular parameters", said presenting author Anna Turkina, from the National Research Center for Hematology in Moscow, Russia.

Preliminary analysis showed 3-, 6- and 12-month MMR rates of 10%, 21% and 36%, respectively, for doses of 200-300 mg/day, prompting the launch of a phase II trial in 2019, she told delegates.

Abstract 791 – Safety and efficacy of HQP1351, a third-generation oral BCR-ABL inhibitor in patients with tyrosine kinase inhibitor-resistant chronic myelogenous leukemia: Preliminary results of phase I study

Qian Jiang, from Peking University People's Hospital in Beijing, China, reported that HQP1351, a potent TKI against a broad spectrum of BCR-ABL mutations including T3151, was trialed in patients with TKI-resistant CP or AP CML. Among 79 participants who received the TKI for at least 3 months, a MMR was reported for 31% of CP and 8% of AP patients, with the highest rates found for those carrying the T315I mutation, at 47% and 11%, respectively. Jiang said that treatment was "well tolerated" and the most frequent adverse events were grade 3-4 thrombocytopenia and grade 1 hypertriglyceridaemia and skin pigmentation, and the recommended phase II trial dose was set at 40 mg every other day.

Abstract 792 – Asciminib, a specific allosteric BCR-ABL1 inhibitor, in patients with chronic myeloid leukemia carrying the T315I mutation in a phase I trial

The T315I mutation is also the target of asciminib, inducing an inactive conformation via the BCR-ABL1 myristoyl-binding site, explained presenting author Delphine Rea, from Hôpital Saint-Louis in Paris, France. Patients in CP or AP with a T315I mutation who had received at least one TKI were given asciminib 200 mg twice daily; 36.7% of 32 patients achieved MMR after a median of 12.2 weeks, while 19.4% achieved MR4 and 16.1% MR4.5. Ponatinib-naïve patients had higher rates than those who had previously used the agent for MMR (61.5 vs 17.6%), MR4 (30.8 vs 11.1%) and MR4.5 (30.8 vs 5.6%). Describing asciminib as "safe and tolerable", with just one discontinuation in this first-in-human trial because of adverse events, Rea said that the agent was "a promising treatment option in these patients with a high unmet medical need" and emphasized that recruitment is ongoing for this population.

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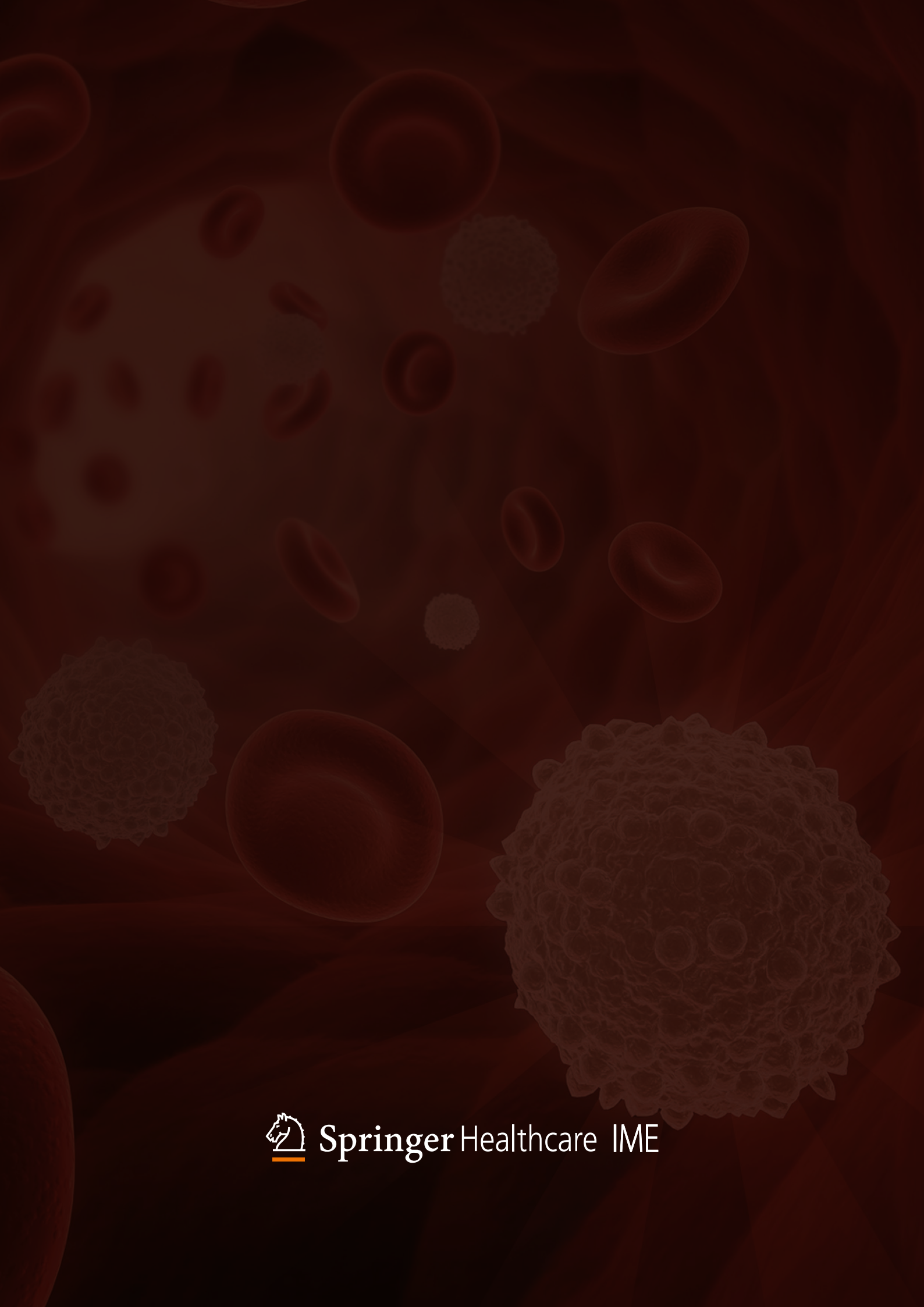

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