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Making Cancer History®

New Directions in the Management of Chronic Myeloid Leukemia

In This Issue

INTRODUCTION

The treatment of patients with CML ranks as one of the great medical success stories of the past 30 years[1]. The life expectancy of all patients with newly diagnosed CML-CP (chronic phase) in the tyrosine kinase inhibitor (TKI) era is nearly identical to that of the general population, particularly for patients who achieve complete cytogenetic remission (CCyR) within one year[2]. However, some problems remain. Approximately 25% of patients either have primary or develop secondary resistance to imatinib, often due to mutations in the BCR-ABL kinase domain[3]. Of the latter, the "gatekeeper" T315I mutation confers resistance to all first- and second-generation TKIs, viz. imatinib, dasatinib, nilotinib and bosutinib[4]. Although the 3rd generation TKI ponatinib exhibits impressive efficacy against Bcr-Abl^{T315I} and other mutants, it has toxicity that limits its use in some patients[5, 6]. Omacetaxine mepesuccinate, a semi-synthetic derivative of homoharringtonine that acts through inhibition of translation, retains efficacy against Bcr-Abl^{T315I} and is approved for the treatment of patients with CP or AP (accelerated phase) disease after failure of or intolerance to ≥2 TKIs, but its activity is modest and responses are frequently short-lived[7, 8].

Furthermore, in contrast to the dramatic improvement in survival of patients with CML-CP in the TKI era, median survival of those in blast phase (BP) is still only around 3-11 months[9]. Progression to BP is characterized by BCR-ABL overexpression, differentiation arrest, genomic instability, clonal evolution and activation of alternate cellular survival pathways, leading to loss of addiction to BCR-ABL signaling[10]. This, therefore, remains an area of high unmet need. To some extent, the same can be said of patients in accelerated phase (AP) whose prognosis, although not as dismal as that of patients in BP, still remains poor and a large percentage of such patients will eventually succumb to their disease.

Given the inconvenience, side effects and high cost[11] of lifelong TKI therapy for CML, there is considerable interest in TKI discontinuation strategies. Studies such as the French STIM[12], the Australian TWISTER[13] and our own experience[14] with imatinib discontinuation in CML-CP patients with a sustained complete molecular remission (CMR) showed that only approximately 40% of such patients could safely discontinue therapy, and that nearly all patients with molecular evidence of disease relapse after discontinuation could be successfully salvaged with reintroduction of imatinib. In addition to the high rate of relapse after discontinuation, only a minority of patients are eligible for such an approach as most patients do not reach sustained undetectable transcript levels when measured with a PCR test of sufficient sensitivity (i.e., detection up to 5-log reduction) as is required for consideration of this approach. Because of this, many avenues of targeting CML stem cells using combinations of Bcr-Abl TKIs with other targeted agents are being explored, with the goal of curing the disease[15]. The trials currently enrolling patients with all phases of CML at the MD Anderson Cancer Center that address these and other unanswered questions are summarized below.

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NEW CLINICAL TRIALS FOR CML

Phase I trial of oral ABL001

ABL001 is a novel, allosteric inhibitor of BCR-ABL[16]. Because it binds at a site different from the ATP-binding pocket where all other currently available TKIs bind, it is not affected by the T315I mutation. This study enrolls patients with CML-CP or –AP who are resistant to/intolerant of ≥2 TKIs, as well as those with the T315I mutation who exhibit relapsed/refractory disease after ≥1 TKI, provided that no other effective therapy exists. Patients in BP are excluded. ABL001 is being evaluated both alone and in combination with nilotinib.

Phase II study of ponatinib

Ponatinib is highly effective for patients with CML in all stages of the disease. At the current standard dose of 45 mg daily, it is associated with an increased risk of arterio-thrombotic adverse events. The PACE trial6 showed significant relationships between dose intensity of ponatinib and the occurrence of grade ≥3 adverse effects, while meaningful responses have been observed with doses as low as 15 mg/d in the phase I trial[17]. In the search for a safer but equally effective dose of ponatinib, this trial randomizes patients with CML-CP who are resistant to ≥2 prior TKIs to three different starting doses of ponatinib: 15, 30 and 45 mg daily.

Phase I trial of dasatinib and nivolumab

Nivolumab is a fully human, IgG4 (kappa) monoclonal antibody against PD-1 (immune checkpoint inhibitor) that is already FDA-approved for use in patients with previously treated metastatic melanoma[18] and NSCLC[19]. In addition, results have been highly promising in patients with relapsed or refractory Hodgkin's lymphoma (HL)[20]. There is significant evidence of CML being prone to immune recognition and eradication. In this study, dasatinib and nivolumab are combined to manage patients with resistant disease. Patients must have CML-CP or –AP and have had ≥2 prior TKIs for their CML. They must have had intolerance (except to dasatinib) or progression, resistance or suboptimal response to the most recent TKI. Dasatinib is dosed at 100 mg/d in CP patients and 140 mg/d in AP patients. Nivolumab is administered IV every 2 weeks beginning on day 15. The dose of nivolumab is escalated from 1 to 3 mg/kg in successive cohorts.

Phase I/II study of omacetaxine mepesuccinate

Currently, omacetaxine is approved for the treatment of patients with resistance to at least 2 prior TKIs. The standard induction dose is 1.25 mg/m^2 twice daily for 14 days on a 28-day cycle. Because of the need to adjust the dose to body weight, the treatment may need to be given in the clinic, which is inconvenient for patients. This trial is for patients with CML-CP or –AP who have failed and/or demonstrated intolerance to ≥2 prior TKIs and explores a fixed dose of omacetaxine (2.5 mg), administered subcutaneously twice daily for 7 (maintenance) or 14 (induction) days. Fixed dosing is more conducive to self-administration, which would facilitate use for patients. Patients with a known T315I mutation must have previously received and failed ponatinib, unless medically contraindicated. Cycles are 28 days long. Induction cycles are given until hematologic response is achieved, followed by maintenance treatment.

Phase I/II trial of dasatinib plus decitabine

The outcome of patients with BP and AP remains poor. Single agent TKI therapy induces responses in approximately 30% of patients and these tend to be short-lived, particularly among patients in BP. There is in vitro synergy between hypomethylating agents and tyrosine kinase inhibitors, setting the foundation for this study. This trial enrolls patients with CML-AP or –BP, both newly diagnosed and previously treated. CML-BP is defined, per the standard definition used in all TKI trials, by the presence of ≥30% blasts in the peripheral blood or bone marrow or the presence of extramedullary disease[21]. The starting dasatinib dose is 100 mg/d, with the target dose being 140 mg/d; in the first cycle, it is only administered for 2 weeks. Cycles are 4 weeks long. Two doses of decitabine, both given for 10 days per cycle during induction[22], are being explored: 10 mg/m^2/d and 20 mg/m^2/d. Decitabine is given for 5 days per cycle during maintenance.

Phase I/II trial of nilotinib and MEK-162 (ARRY-162)

Bcr-Abl signals downstream to the RAS/RAF/MEK/ERK survival pathway[23]. In cells with wild type BRAF, pharmacologic BRAF inhibition paradoxically leads to MEK/ERK activation via CRAF[24, 25], which can be blocked by MEK inhibitors, forming the basis of synergism between nilotinib and MEK inhibitors in drug-resistant CML[26]. MEK-162 is an orally available, potent, selective, small-molecule MEK1/2 inhibitor. Patients in AP/BP must have failed ≥1 prior TKI, while patients in CP have to have been resistant or intolerant to ≥2 prior TKIs (with the exception of nilotinib for TKI-intolerant patients). The nilotinib dose is 400 mg bid.

Phase II trial of cladribine, idarubicin, high-dose cytarabine and investigator's choice of TKI

Patients with CML-BP are usually treated with acute leukemia-type regimens with the addition of Bcr-Abl TKIs, but outcomes remain poor, particularly for those in myeloid BP9. Cladribine has been shown to prolong survival when added to an anthracycline-cytarabine backbone in a multi-center, randomized, phase III trial in AML[27]. The present trial has a frontline cohort and a salvage cohort, so that both newly diagnosed and previously treated, relapsed/refractory patients with CML-BP (myeloid) are eligible.

Phase I/II trial of bosutinib and inotuzumab ozogamycin

Inotuzumab ozogamycin is a novel, CD22-targeted monoclonal antibody conjugated to calicheamicin (antibody-drug conjugate) that is in phase III clinical trials in ALL[28]. This trial enrolls adults with relapsed/refractory Ph+ ALL or CML in lymphoid BP. CD22 must be expressed by ≥20% of the blasts. Patients with T315I mutations are excluded due to the lack of activity of bosutinib against this "gatekeeper" mutation. The bosutinib dose is escalated from 300 to 500 mg daily in the phase I portion. Inotuzumab ozogamycin is administered by IV infusion over 1 hour on days 1, 8 and 15. Cycles are 28 days long.

Phase I trial of oral DS-3032B

DS-3032B is an MDM2 inhibitor. MDM2 is a physiologic negative regulator of p53 function that leads to degradation of p53 through ubiquitination[29]. MDM2 inhibitors disrupt the p53-MDM2 interaction, activating the tumor suppressor functions (i.e., cell cycle arrest, apoptosis induction) of wild-type p53[30]. Patients with relapsed/refractory CML-BP may enroll on this study. Patients with TP53 abnormalities are not eligible, since intact TP53 function is required for the mechanism of action of this drug. DS-3032B is administered orally once daily on days 1-21 of a 28-day cycle. The study has dose escalation and expansion parts.

Phase I/II trial of ruxolitinib added to Bcr-Abl TKI

Considerable preclinical evidence implicates JAK2 as a regulator of Bcr-Abl signaling in CML[31]. Cytokine signaling through JAK-STAT mediates TKI resistance in CML progenitors[32, 33], and JAK2 inhibition can reverse resistance to Bcr-Abl TKIs in patient-derived CML cells[34]. Importantly, TKIs alone do not eradicate, in vitro or in vivo, the earliest leukemic progenitors[35-37], something that can be achieved in vitro with JAK2 inhibitors. Adults with CML- CP or –AP who have been on their current TKI for ≥18 months are eligible for this study, which has dose escalation and expansion phases. Patients receiving imatinib in either the frontline or salvage settings are eligible. Achievement of CCyR is not required for study entry in phase I as long as patients are in CHR; however, subjects must be in CCyR for entry into phase II of the study. Additionally, patients must have detectable Bcr-Abl transcript levels (never achieved MMR, lost MMR after achieving it, no sustained MMR after ≥2 years of TKI therapy, or no sustained CMR after ≥5 years of TKI therapy).

Phase II trial of eltrombopag

Thrombocytpopenia remains a challenging adverse event for some patients treated with TKIs. It is the adverse event most commonly leading to treatment discontinuation with all TKIs, and the one with the highest incidence of cross-intolerance. Eltrombopag has shown efficacy in managing immune thrombocytopenia (ITP)[38] and aplastic anemia[39]. In this trial, patients receiving any FDA-approved TKI who experience significant thrombocytopenia receive eltrombopag while continuing their TKI therapy. Patients with CML with platelets <50 x 10^9/L after 3 months of TKI therapy are eligible; however, patients in AP/BP must not be meeting any criteria for AP/BP other than thrombocytopenia and/or clonal evolution. The starting dose of eltrombopag is 50 mg/d and the dose can be escalated up to 300 mg/d based on the platelet response. Responding patients may have the dose of TKI escalated if judged clinically appropriate once they respond to eltrombopag.

Phase I/II trial of axitinib and bosutinib

Axitinib, a small-molecule multi-kinase inhibitor FDA-approved for second-line therapy of advanced clear cell renal cell carcinoma, was recently found to potently inhibit the T315I mutant form of Bcr-Abl[40]. This trial explores rotating (in CP patients) as well as combined (in AP/BP patients) TKI therapy with axitinib and bosutinib. CP patients receive standard doses of both agents (5 mg bid of axitinib alternating with 500 mg/d of bosutinib) and must have failed or been intolerant to ≥2 prior TKIs. Those with the T315I mutation begin with axitinib, and those without with bosutinib. AP patients must have had ≥1 prior TKI. BP patients can be treatment-naïve or previously treated. There will be a dose-escalation phase in AP/BP patients, followed by a dose expansion cohort at the recommended phase II dose level. Cycle length is 12 weeks. This trial will be opening for accrual shortly.

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CLL Treatment Priorities

1. Untreated

- Fludarabine + Cytoxan + Rituximab (FCR) (2008-0431)
- Ofatumumab (2011-0520)
- TRU-016 + Rituximab (2012-0626)
- Nivolumab + Ibrutinib (2014-0931)
- Lirilumab + Rituximab (2014-0933)

2. Prior Therapy

- Sapacitabine + Cytoxan + Rituximab (2010-0516)
- CD19 CAR (2011-1169)
- ROR1R CAR-T (2012-0932)
- GDC-0199 + Obinutuzumab (2013-0486)
- Ublituximab + TGR-1202 (2013-0566)
- Ibrutinib +/- Rituximab (2013-0703)
- PRT062070 (2013-0880)
- ACP-196 (2013-0907)
- ABT-199 (2014-0405)
- IPI-145 + Obinutuzumab (2014-0794)
- Urelumab + Rituximab (2014-0932)

3. Other Studies

- Ruxolitinib for CLL Fatigue (2013-0044)
- Lenalidomide (2013-0371)
- Richter's: Selinexor (2014-0601)

4. Hairy Cell

- 2CDA + Rituximab (2004-0223)
- PCI-32765 (2013-0299)

AML/MDS Treatment Priorities

1. Newly Diagnosed

A. Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17):
- ATRA + Arsenic +/– Gemtuzumab (2010-0981)

B. Cytogenetic feature: Inv16 or t(8:21): Fludarabine + Ara-C + Idarubicin (2007-0147)

C. Younger Patients:
- CIA vs FAI (2010-0788)
- 3 + 7 vs IA+Vorinostat (S1203)
- Cladribine + IA + Sorafenib (2012-0648)
- Nivolumab + IA (2014-0907)

D. Older Patients:
- Omacetaxine + Decitabine (2013-0812)
- SGI-110 (2013-0843)
- Cladribine + LD Ara-C/DAC (2011-0987)
- DAC 5 vs. 10day (2012-1017)
- Vosaroxin + DAC (2013-0099)
- Sorafenib + Aza (2014-0076)
- Ruxolitinib + Decitabine (2014-0344)
- CPX-351 (2014-0548)
- Ibrutinib +/- Ara-C (2014-0950)
- SGI-110 vs. Treatment Choice (2014-1051)

E. Mixed Phenotype:
- Clofarabine + Idarubicin + Ara-C + Vincristine (2013-0073)

2. Salvage Programs

- BL-8040 (2012-1097)
- AC220 + Aza or Ara-C (2012-1047)
- DAC + CIA (2012-1064)
- Trametinib + GSK2141795 (2013-0001)
- Rigosertib + Aza (2013-0030)
- Eltrombopag (2013-0225)
- WT2725 (2013-0404)
- ASP2215 (2013-0672)
- MEK162 + BYL719 (2013-0813)
- Omacetaxine (2013-0870)
- SGI-110 (2013-0901)
- SL-401 (2013-0979/2014-0860)
- AC220 vs Salvage Therapy (2014-0058)
- KPT-330 (2014-0187)
- Ruxolitinib + Dac (2014-0344)
- Dac+ CIA+/- AlloSCT (2014-0358)
- BVD-523 (2014-0391)
- AG-221 (2014-0408)
- ABT-199 + Aza or Dac (2014-0490)
- SGN-CD33A + DAC or Aza (2014-0615)
- SGN-CD33A (2014-0744)
- BGB324 (2014-0756)
- E6201 (2014-0777)
- Nivolumab + Aza (2014-0861)
- Lirilumab + Aza (2014-0862)
- ADI-PEG (2014-0865)
- AG-120 (2014-0800)
- Lorvotuzumab (2014-0926)
- FLX925 (2014-1000)
- IDH305 (2014-1006)
- CC-486 (2015-0056)
- IA or Aza + Crenolanib (2015-0207)
- AMG330 (2015-0296)
- Rigosertib (2015-0360)

3. Low Risk MDS and CMML with <10% Blasts

- DAC vs. Aza (2012-0507/2014-0112)
- Horse ATG (2012-0334)
- Bortezomib (2012-0
- Oral Aza vs. Best Supportive Care (2012-0733)
- Ruxolitinib (2013-0012)
- Pacritinib (2013-0224)
- MEDI 4736 (2013-1041)
- FF-10501-01 (2014-0014)
- ASTX 727 (2014-0089)
- AZA +/– Birinapant (2014-0399)
- OPN-305 (2014-0432)
- Nivolumab + Ipilimumab +Aza (2014-0930)
- IDH305 (2014-1006)

4. MDS/MPN

- Ruxolitinib + Aza (2012-0737)
- Ruxolitinib (2014-0764)

5. Maintenance/MRD

- Lenalidomide (2014-0116)
- Ixazomib (2014-0379)
- SGN-CD33A (2014-0744)
- SL-401 (2014-0860)
- Nivolumab (2015-0213)

CML Treatment Priorities

1. TKI Failures, T315I Mutations or Advanced Phases

- Dasatinib + DAC (2011-0333)
- Cladribine + IA+ Sorafenib +TKI (2012-0648)
- Ponatinib (2015-0212)
- Omacetaxine (2014-0229)
- Nilotinib + MEK-162 (2014-0128)
- Dasatinib + Nivolumab (2015-0068)

2. Minimal Residual Disease

- Ruxolitinib (2012-0697)

Myeloproliferative Disorders

1. Myelofibrosis

- NS-018 (2011-0090)
- Sotatercept (2012-0534)
- Ruxolitinib + Aza (2012-0737)
- PRM-151 (2013-0051)
- LCL-161 (2013-0612)
- Oral Pacritinib vs Best Available Therapy (2013-1001)
- Momelotinib (2014-0145)
- Momelotinib vs. Best Available Therapy (2014-0258)
- PF-04449913 vs. Placebo (2014-0415)
- Ruxolitinib + Pracinostat (2014-0445)
- Lorvotuzumab (2014-0926)
- Nivolumab (2014-0962)
- SL-401 (2014-0976)

2. Systemic Mastocytosis

- Brentuximab (2012-0734)

Phase I/II Agents for Hematologic Malignancies

- L-Grb2 Antisense (2003-0578)
- Nelarabine (2009-0717)
- KB004 (2010-0509)
- CWP232291 (2011-0253)
- DFP-10917 (2012-0262)
- MEK 162 (2013-0116)
- GSK525762 (2013-0527)
- CB-839 (2014-0152)
- Bosutinib + Inotuzumab (2014-0435)
- APTO-253 (2014-0528)
- DS-3032B (2014-0565)
- ONC201 (2014-0731)
- ABL001 (2014-1019)
- AG-881 (2015-0343)
- FT-1101 (2015-0516)

ALL Treatment Priorities

1. Newly Diagnosed or Primary Refractory

(one non-hyper-CVAD induction)

- Age >60: Low dose Hyper CVD + CMC-544 (2010-0991)
- Hyper CVAD + Ofatumumab (2010-0708)
- Hyper CVAD + Liposomal Vincristine (2008-0598)
- T cell: Hyper CVAD + Nelarabine (2006-0328)
- Ph+: Hyper CVAD + Ponatinib (2011-0030)
- Burkitts: EPOCH + Ofatumumab (2014-0123)

2. Salvage Programs

- Low Dose Hyper CVAD + CMC-544 (2010-0991)
- Rituximab (2011-0844)
- BMS-906024 (2011-0382)
- DAC + CIA (2012-1064)
- Ibrutinib (2013-0459)
- EPOCH + Ofatumumab (2014-0123)
- Ruxolitinib or Dasatinib + Hyper CVAD (2014-0521)
- LY3039478 + Dex (2015-0020)

3. CNS Disease

- Intrathecal Rituximab (2011-0844)

4. Minimal Residual Disease

- Blinatumomab (2014-0844)

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CONCLUSION

Improvements in CML prognosis have been dramatic. But there remain many questions and areas of research. In addition to the clinical trials described above, the CML program continues to build on the ever expanding knowledge of the disease to offer better treatment options.

For information about these studies, the Chronic Myeloid Leukemia program, or the Leukemia program in general, contact Prithviraj Bose, Jorge Cortes, or any Leukemia physician.

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