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Speaker Presentations

SP-01
IS TARGETED THERAPY ON-TARGET?

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Precision medicine promises to bridge the gap between our increased understanding of heterogeneity of the biology of haematologic neoplasms and current therapy for most people with these cancers. Paradoxically the term precision medicine is imprecise and describes at least 5 distinct concepts including: (1) using molecular or omics data (e.g. genomics, epigenomics, transcriptomics, proteomics) to delineate or define subtypes of these cancer; (2) using these data to select the best therapy for someone with a haematologic neoplasm; (3) using these data to monitor therapy-response such as measurable residual disease [MRD]-testing; (4) using results of MRD-testing to select from amongst therapy-options; and (5) using these data to identify persons with hereditary forms of these cancers with potential therapy and surveillance implications.These concepts are, of course, not mutually exclusive and many are confounded.

Regardless of which application(s) of precision medicine one favours there are relatively few data the prognosis of newly-diagnosed persons with cancer has changed substantially in the past 5–10 years. As such, precision medicine remains a hypothesis needing confirmation of efficacy in appropriate clinical trials. There are, of course important exceptions such as persons with chronic lymphocytic leukaemia (CLL) receiving ibrutinib and in acute lymphoblastic leukaemia (ALL) and lymphomas where results of MRD-testing are useful for monitoring therapy efficacy. However, claims of usefulness of other uses of MRD-testing in non-lymphoid neoplasmsare untested in randomized trials.

In considering precision medicine there is often confusion regarding differences between biological, prognostic and predictive categories and endpoints. For example, hierarchal analyses of mutations may tell us how and why some cancers develop but this information need not correlate with prognosis or predictive value. However, there are seldom proper epidemiological analyses to permit statistical or causal inference.

Even if new cancer subtypes defined by NGS data correlate with response duration and/or cancer-free survival it is important to consider whether these data independently estimate prognosis, a question usually analyzed in multivariate analyses. And, the ultimate utility in estimating prognosis and/or predicting therapy-response for any novel trait is to show it offers additional value beyond known prognostic variables. The appropriate way to test this is to quantify the additional area under the curve (AUC) calculated in a receiver operator characteristic (ROC) curve. This is rarely done and when done has proved disappointing. Somewhat paradoxically the strongest data supporting use of mutation analyses after induction therapy to predict relapse is mutation agnostic. Also, recent data indicate complex inter-relationships between mutations and even between types of mutations. Finally, there is the question whether data from NGS analyses predict therapy-response rather than only prognosis.

Another area of the complexity of precision medicine relates to MRD-testing. Among persons in 1st remission there are prognostic associations between test results and clinical outcomes. However, there are substantial error rates, 10–30% false positives and negatives. There are also no data from randomized trials these data predict response to subsequent therapies or that outcomes would have been different had one waited for histological or radiological relapse rather than acting on results of MRD-testing.

Chronic myeloid leukaemia (CML) is a relatively simple cancer caused by one necessary and sufficient canonical mutation, BCR/ABL1 compared with 10s to 100s of non-canonical mutations typical of most cancers. Also, CML is best regarded as a pre-cancer rather than a cancer. As such the extraordinary effectiveness of tyrosine kinase-inhibitors to BCR/ABL1 such as imatinib is probably not a reasonable expectation in AML. Another model is MPN-associated myelofibrosis where JAK2-inhibitors such as ruxolitinib are effective in reducing splenomegaly and symptoms but not in reducing the size of the neoplastic clone or achieving remissions. Ruxolitinib is not targeted therapy as its equally effective in most persons with MPN-associated myelofibrosis whether they have wild-type JAK2, JAK2V617F, CALR or MPL mutations, probably because these mutations activate the STAT5 signaling pathway.

We must develop safer, more effective cancer therapies. The promise of precision medicine has already resulted in important insights into cancer biology. Whether these insights will result in therapy-advances for most persons with cancer is unclear but we are hopeful despite the substantial challenges. We must do better but we must also be careful not to claim success absent robust proof. We need to focous on the hope and not the hype of precision medicine.

SP-02
CHRONIC MYELOID LEUKEMIA BEYOND 2016—SOME IMPORTANT QUESTIONS

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Imatinib mesylate and other BCR-ABL selective tyrosine kinase inhibitors (TKIs) have changed the therapeutic approach to, and prognosis of patients Philadelphia chromosome-positive chronic myeloid leukemia (CML) (1-8). With TKIs therapies, the annual mortality in CML has been reduced from a historical rate of 10% in the first 2 years and 15 to 20% subsequently to an annual mortality rate of 1–2%. Treated appropriately and compliantly, and monitored for early signs of resistance, patients with CML have an expected 15-year survival rate of 80–85%. Survivals are not different with imatinib and second generation TKIs because of the availability of effective salvage therapies among patients identified early to have cytogenetic relapse

and treated appropriately. Imatinib, nilotinib and dasatinib are approved for frontline therapy (4, 5). For patients with CML resistance or treatment intolerance, nilotinib, dasatinib and bosutinib are highly active salvage therapies. TKI selection depends on prior exposure, co-morbid conditions, and identification of CML resistant mutations. Ponatinib, a third generation TKI, is selectively effective against T315 I mutations, and highly effective generally across other mutations. It is valuable as subsequent salvage therapy (9, 10). Long-term side- effects with TKIs are emerging and require proper management. These include renal dysfunction; rare neuro-toxicities; vaso-spastic conditions including myocardial insufficiency and infarct, transient cerebral ischemic attacks or cerebro-vascular accidents, peripheral arterial disease; systemic and pulmonary hypertension; worsening of diabetes; rare pancreatitis, etc.

Several questions pertain as to optimal therapy and monitoring of CML. These include:

1. The role of frontline therapy with generic imatinib versus second TKIs. Second TKIs could be reserved as first-year therapy to reduce the incidence of transformation, followed by imatinib therapy once patients achieve cytogenetic CR. Alternatively second TKIs may be used in high-risk CML and in younger patients (e.g. age younger than 50 to 60 years) to induce higher rates of durable complete molecular responses (CMR) which may increase the rates of TKI treatment discontinuation.
2. Strategies to improve the rates of durable CMRs and potential molecular cures (e.g. pegylated interferon, checkpoint inhibitors, BCL-2 inhibitors, JAK-2 inhibitors, etc.)?
3. Optimal management of CML in transformation.
4. Optimal treatment monitoring and timing of interventions. Is the aim of therapy achievement of complete cytogenetic response or deeper molecular responses? Should we consider a change of TKI therapy based on BCR-ABL transcript levels (International Standard) of >10% at 3 or 6 months into frontline therapy?
5. Should BCR-ABL mutations detection be performed with more sensitive next generation sequencing (versus the current Sanger sequencing)?
6. Optimal role and timing of allogeneic stem cell transplant (SCT) in advanced nations versus emerging nations (where SCT could be a one-time curative therapy at a cost of less than $20,000).
7. Treatment interruption of TKIs among patients with durable CMR. Management of women with CML on TKIs in relation to pregnancy.
8. Dose-schedule ranges of each of the TKIs that allow continued benefit with equal efficacy and reduced toxicities? For example, is the approved dose of ponatinib 45 mg daily the best dose, or are daily doses of 30 mg or 15 mg appropriate depending on response and side-effects?

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SP-03
IS 400 MG OD THE CORRECT DOSAGE OF IMATINIB?

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Rationale for treatment optimization of imatinib

- Initial imatinib therapy never optimized
- Maximum tolerated dose never determined
- Dose escalation effective (low OCT-1 activity, mild resistance mutations)
- Higher doses effective in AP and BC
- IFN and imatinib synergistic with alternative modes of action
- Early and more rapid reduction of BCR-ABL would reduce genetic instability and progress to advanced phase

Conclusions:

- 45% higher probability of MMR after 12 months with IM 800 mg compared to IM 400 mg ($p = 0.0088$)
- Efficacy estimates of IM 400 vs. 800 and IM 400 vs. 2G-TKI cannot be compared directly.
- But given the fairly similar prognostic profiles of patients, MMR rates achieved with IM 800 mg and 2G-TKI are comparable
- When choosing MMR at 12 months as primary endpoint, new therapies need to be compared with IM 800 and not with the inferior IM 400
- With the availability of generic imatinib, high dose imatinib should be more often considered for routine clinical use.
- Imatinib 400 mg is a well tolerated, effective dose
- Higher imatinib doses achieve response faster similar to 2G-TKI
- Higher imatinib doses should be carefully monitored for adverse events and dosage adopted accordingly
- The median well tolerated imatinib dosage ranges around 600 mg OD

SP-04
ACUTE MYELOID LEUKEMIA (AML)—PROGRESS AND PROMISES

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Over the past 4 decades, major progress has occurred in understanding the pathophysiology of AML and in treating the disease [1]. Frontline AML therapy results in a cure rate of 30 to 40% among younger patients with AML. The "3+7 regimen", 3 days of daunorubicin + 7 days of standard cytarabine, considered still by many AML experts as the gold standard, is a poor standard of care. A meta-analysis of 3 randomized trials and a recent European randomized trial showed that high-dose cytarabine during induction improves survival among younger patients with AML [2,3]. Idarubicin 12 mg/m^2 daily x 3 is equally effective or superior to daunorubicin; daunorubicin 60 mg/m^2 daily × 3 is equally effective to 90 mg/m^2 daily × 3 and less toxic; daunorubicin 45mg/m^2 daily × 3 is inferior. Adding an adenosine nucleoside analogue (fludarabine, cladribine, clofarabine) to anthracycline + cytarabine (e.g. FLAG-IDA regimen) improves survival if given and tolerated [4,5]. A meta-analysis of 5 studies showed that the addition of gemtuzumab ozogamycin 3 to 6 mg/m^2 × 1–2 to chemotherapy improves survival in AML, particularly in favorable-intermediate AML disease. Older patients may benefit better from lower intensity strategies that provide similar efficacy to 3+7 and less toxicities [6].

Several AML subtypes need individualized therapies. Acute promyelocytic leukemia (APL; 5 to 10% of AML) benefits better from non-chemotherapy regimens including ATRA and arsenic trioxide, a regimen associated with a cure rate of 90% [7,8]. Patients with core-binding factor AML have a cure rate of 80% with FLAG-IDA ± gemtuzumab ozogamycin (Myelotarg; CD-33 monoclonal antibody bound to calicheamicin) [4,9].

Cytogenetic and molecular profiling have improved our prognostic and predictive capacities, and led to targeted therapies. Patients with FLT-3 ITD or FLT-3 positive AML (30% of AML) benefit from the addition of FLT-3 inhibitors