Advances in haematological malignancies – focus on lymphoid disease

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Overview

• Background
• Kinase inhibitors
• Monoclonal antibodies
• Promoters of apoptosis
• Others
• Conclusions
Traditional Chemotherapeutics

- Used for > 50 years
- Optimization of regimens have lead to improved outcomes in selected diseases
  - Many diseases remain incurable especially after relapse
- Toxic often due to non selective off target effects on normal organs
Common side effects of traditional chemotherapy

- Cystitis
- secondary malignancies
- Infertility
- Cytopenias
- Nausea
- GI toxicity
- Pulmonary fibrosis
- Renal impairment
- Peripheral neuropathy,
- Hair loss,
- Hyponatremia,
- Constipation
- Diarrhea
- Cardiomyopathy

➢ Need for more effective and safer ways to treat leukaemia and lymphoma
New Treatments

• Scientific discoveries are driving the development of new therapies for the treatment of hematological malignancies

• Bewildering array of novel therapies now available on clinical trials, compassionate access, private prescriptions and on the PBS

• Central to understanding these new agents efficacy and toxicity profile is understanding their design
Cancer is multifactorial

Specifically targeting the dysfunctional pathways in a given tumour may lead to more effective and safer treatments

Hanahan and Weinberg, Cell, 2011
Kinase Inhibitors

BTK inhibitors – Ibrutinib
PI3 Kinase inhibitors - Idelalisib
FLT3 inhibitors – Sorafenib
Jak2 – Ruxolitinib
Tyrosine kinase inhibitors - Ponatinib
Kinase Inhibitors

A protein kinase is an enzyme that modifies proteins by chemically adding phosphate groups (phosphorylation)

- Proteins are turned on or off by phosphorylation
- Kinases have a critical role in cellular signaling and replication

By targeting specific protein kinases, these drugs can inhibit specific deregulated cellular pathways in cancer and other disorders.
Ibrutinib is a targeted Bruton's tyrosine kinase inhibitor (BTK).

BTK is an essential component of the B cell receptor signaling pathway mediating interactions with tumor microenvironment and promoting proliferation and survival of cancer cells.
Ibrutinib

Chronic Lymphocytic Leukaemia:
• phase 1-2 studies show ORR 71% with PFS of 75% at 26 months independent of traditional RFs e.g. del17p
  (Byrd et. al.; 2013; NEJM)

Mantle Cell Lymphoma:
• phase 2 studies show ORR 68% with 21% CR, median PFS 13.9 months (OS not reached)
  (Wang et. al.; 2013; NEJM)
Idelalisib

- first in class kinase inhibitor
- targets the catalytic subunit of the class I phosphoinositide 3 kinase (PI3 kinase)
  - another enzyme down stream of the B cell receptor antigen,
- primarily in haematopoietic lineages
- resulting in immunomodulatory and anti neoplastic effects
Idelalisib - Chronic Lymphocytic Leukaemia

- total 220 pts
- blinded randomised control trial
- Median duration of PFS
  - idelalisib and rituximab - not yet reached
  - placebo and rituximab, 5.5 months (P<0.001)

- The median duration of OS in the two study groups had also not been reached;
- at 12 months:
- OS rate was 92% in the idelalisib group versus 80% in the placebo group at 12 months (P=0.02).

Sorafenib - A FLT3 inhibitor

FLT3 Internal Tandem Duplication
• ~25% of AML resulting in constitutive activation of the kinase leading to activation of down stream signalling pathways, higher blast counts, more relapses and lower CR rate
• Sorafenib is an oral small molecule that inhibits a number of kinases including FLT3
Sorafenib

Phase I/II studies in young pts. with AML in combination with Ida and cytarabine 75% CR (93% in subjects with FLT3 pos AML) (Ravandi, et. al.; JCO; 2010)
Ruxolitinib

- Many myeloproliferative disorders e.g. Essential thrombocythaemia, Polycythaemia vera or myelofibrosis have activating JAK2 or MPL mutations (remainder have mutations in CALR)

- These lead to constitutive activation of JAK / STAT pathway and the manifestations of the disease

- Ruxolitinib selectively inhibits JAK1 and 2 and can be helpful in controlling the symptoms of myelofibrosis

- Trials in ET and PV pending
Ruxolitinib

Phase III studies in MF show reduced splenomegaly, B symptoms and improved quality of life.
Ponatinib - the next TKI in CML?

Multi targeted tyrosine kinase inhibitor for CML and ph+ve ALL

Designed to target CML with the resistant T3151 mutations

However......

Cost $138,000 / year
Associated with life threatening risk of
(i) Thromboembolism
(ii) Cardiovascular disease
Ponatinib is an effective treatment in multi drug resistant CML

Cumulative incidence of cardiovascular events in CP CML pts treated with ponatinib vs. nilotinib

Nicolini, et. al.; Blood; 2013
New Monoclonal Antibodies

- Anti CD20 – Ofatumumab
- Anti CD30 – Brentuximab
- Anti CD19 and Anti CD3 Bite - Blinatumumab
- Anti CD123 – CSL 362
- Immuno-radiotherapy - ibritumomab
- CAR T Cells
Monoclonal Antibodies

• All tumour cells express specific antigens on their surface

• By raising antibodies to tumor antigens exogenously, tumour cells can be marked specifically for cell death

• Enables selective targeting of the malignant cells with sparing of normal cells

• Rituximab is the prototype antibody with efficacy in multiple B cell malignancies
Monoclonal Antibodies - Nomenclature

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# Monoclonal Antibodies - Nomenclature

## Target Substem Prefix

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Ofatumumab

Monoclonal anti CD20 antibody whose epitope is distinct from rituximab resulting in tighter binding to CD20 and slower off rate
Ofatumumab

In rituximab refractory FL
ORR 13\% at 500 mg weekly
x 8 with PFS 5.8 months

In fludarabine refractory
CLL ORR 43 \textendash\ 55\%
depending on rituximab pre
treatment status with PFS
5.3 \textendash\ 5.6 mo
Brentuximab

CD 30 expressed on Hodgkin Lymphoma, anaplastic large cell lymphoma and some T cell lymphomas

Brentuximab is an antibody drug conjugate against CD30

The antibody binds to the malignant cell and releases directly into the cell

- minimizing toxicity
- maximizing efficacy
In relapsed / refractory Hodgkin Lymphoma with Brentuximab as monotherapy,

- ORR of 75%
- CR rate of 34%
- PFS 5.6 mo overall and 20.5 mo if CR
- Now considered a bridge to transplant
Blinatumumab

Monoclonal antibody with bi specific T cell engages (Bites)

Binds B and T cells together to increase toxicity
Blinatumomab

Phase II studies in MRD positive B ALL demonstrated induction of 80% MRD response rate.
CSL 362

- Developed in Melbourne
- IL-3 receptor alpha subunit is known as CD123
- CD123 expressed on AML blasts
- CSL-362 is a monoclonal antibody against CD123
- On going trials in AML especially in the setting of prevention of relapse post induction
Ibritumomab

- Monoclonal anti CD20 antibody
- conjugated to a radioactive isotope
- delivers targeted radiation to B cells in addition to potentially inducing antibody mediated and complement dependent cytotoxicity
Ibritumomab

Relapsed / refractory Follicular Lymphoma
Randomised Controlled Trial: Ibritumomab vs. Rituximab

- ORR ibritumomab group 80% cf 56% for rituximab group (p=0.002) CR rate 30% vs. 16% (p=0.04) in favor of ibritumomab
- Time to progression not significantly different

_Witzig, et. al.; JCO; 2002_
CAR T Cells

1) T Cell Collection
2) T Cell Transfection
3) T Cell Adoptive Transfer
4) Patient Monitoring

Chimeric antigen receptor T cells
• engineered T cells
• bind to a specific antigen e.g. CD20 in CLL.
• The monoclonal antibody is grafted on to the T cell via retroviral vectors *ex vivo* then transfused back into the patient to attack cancer cells
CAR T Cells

Case report NEJM 2011

P53 deleted multiply relapsed / refractory CLL pt. given autologous T cells expressing anti CD19 chimeric antigen receptor
Promoters of Apoptosis

Bcl-2 Inhibitors - ABT-199
SMAC mimetics
• Bcl-2 is central to programmed cell death or apoptosis in response to stress signals

• Bcl-2 underlies the development of several B cell malignancies and also mediates resistance to chemotherapy
ABT-199

- Selectively inhibiting Bcl-2 can result in ORR of ~ 70% in CLL and some NHL such as MCL (PFS not reached)

Images at 4 weeks of treatment before cohort dose reached

**BH3 mimetics**
- Small molecule mimics of BH3-only proteins
SMAC Mimetics

- Caspases mediate apoptosis inducing mitochondrial disruption

- SMAC mimetics (second mitochondrial derived activator of caspases) are antagonists of the inhibitors of apoptosis (IAP) proteins and reinstate a malignant cells' apoptotic potential

- Trial results awaited
Others

- BRAF Inhibitors – vemurafenib
- Histone deacetylase inhibitors – panobinostat
- DNA methyl transferase inhibitors - azacitidine
- Immunomodulatory – lenalidomide
- mTOR inhibitors - temsirolimus
Vemurafenib

Raf enzyme inhibitor name derived from the mutant form of RAF V600E mutated B-RAF inhibition

Interrupts the B-raf/MEK/ERK pathway inducing apoptosis
Vemurafenib

- Universal BRAFV600E mutations in Hairy Cell Leukaemia (HCL)

- Phase II studies in HCL indicate 5/5 complete hematological recovery, 2/5 CR (1 MRD neg) and 3/5 marrow PR
Panobinostat

Pan histone deacetylase (HDAC) inhibitor

HDACs regulate DNA transcription and are up-regulated in cancer cells conferring increased cell survival.

HDAC inhibition results in cell cycle arrest resulting in cell death.
Panobinostat

- Local data demonstrates some impressive responses of refractory cutaneous T cell lymphoma (n=9)
- 2 CRs, 4 PRs, 1 SD and 2 PD

(Ellis, et al.; 2008; Clin Ca Res)
Azacitidine results in demethylation of DNA

In MDS this restores HSCs ability to mature normally
Azacitidine

In high risk MDS compared with supportive care alone

- 60% responded vs 5% (p<0.001)
- Median time to leukemic transformation for Aza 21 months vs 13 months P=0.007
- Median survival 18 months vs 11 months p =0.003

Silverman, et. al.; JCO; 2002
Lenalidomide

Multi system effects including inhibition of angiogenesis, enhancement of immune recognition of the malignant cells, induction of apoptosis as well as effects on the microenvironment
Lenalidomide

- Established role in the management of myeloma
- 2006 List, et al, in NJEM showed better outcomes in 5q- MDS pts treated with lenalidomide

Now in clinical trials in CLL and NHL; early reports suggest efficacy in these diseases also. Possible role in maintenance therapy.
Temsirilimus

Inhibits mammalian target of rapamycin (mTOR)
Temsirirolimus

- 35 relapsed / refractory Mantle Cell Lymphoma patients
- Phase II study
- ORR 38%, with 1x CR (3%)

Median time to progression 6.5 months

Witzig, et. al.; JCO; 2005
Summary

• Novel insights into cancer biology that arise from basic science are leading to:
  – Identification of new ways of specifically targeting processes in malignant cells
  – New drugs to treat cancer that may either and / or result in
    • Improved responses in patients
    • More favourable toxicity profiles compared with standard therapy
• However these drugs come at an enormous cost to the companies developing them and subsequently to governments, and patients
Summary

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• However these drugs come at an enormous cost to the companies developing them and subsequently to governments, and patients

• Ongoing challenges include
  – Improving access to new agents in an equitable but sustainable fashion
  – Clinician knowledge of the basic science and the ways in which this can be manipulated to improve pt. care
  – Ensuring that unexpected toxicities are detected early
  – Understanding the relative efficacies with no head to head or comparable clinical trials