Targeted Treatments for Cancer: Success & Challenges

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February 20th, 2017
DISCLOSURES

• Previous consultant for Seattle Genetics
• No other or current financial interest
Cancer Mortality has decreased between 2003 and 2012

*AAPC is significantly different from zero (p<.05).*

Source: Annual Report to the Nation on the Status of Cancer 1975-2012
The Mortality from Cancer has decreased on a Global Scale (1990-2015)

How much is due to Targeted Therapy?
Definitions & Basics

• What is Targeted Therapy?
• Not Chemotherapy
• Not Immunotherapy
• Not Radiation
• Ideally target only expressed on tumor cells, not on normal cells
• Target should be amenable to killing; if hit, it induces cell death
• Personalized medicine: yes, but in a stricter sense
What Targets are useful for Oncology?

- Hormone Receptors
- Surface Molecules
- Kinases
- Enzymes
- DNA binding sites
- RNA binding sites
- Proteasome
- Artificial binding sites (CAR-T cells)
- Gene therapy (replace missing genes)
How can we hit Targets?

Monoclonal antibodies binding to growth receptors
Antibodies conjugated with toxins
Antibodies conjugated with radioactive isotopes
Small molecules interacting in signal transduction
Diseases where prognosis has improved with targeted therapy

- Progress is incremental
- Breast cancer: 1970s tamoxifen
- Prostate cancer: 1940s testosterone ablation
- Acute Promyelocytic Leukemia
- Chronic Myeloid Leukemia
- Too early to tell (long-term outcomes)
- ALK-positive lung cancer
- Ros-1 positive lung cancer
- CD30 in Hodgkin Lymphoma
- CD38 in multiple myeloma
Examples for Targeted Treatments

- Diseases, type of targeting, outcomes, 6 types of cancer
- Impact on Life Expectancy
- Challenges
- Problems
- New targets
- MATCH trial
- Outlook into the future
- Summary
1) Acute Promyelocytic Leukemia

The bone marrow aspirate shows numerous abnormal promyelocytes with prominent cytoplasmic granules, characteristic of hypergranular acute promyelocytic leukemia.
Acute Promyelocytic Leukemia

Reciprocal translocation of chromosomes 15 and 17
Acute Promyelocytic Leukemia

The diagnosis can be established by FISH and PCR

Akhtar K et al, Clin Pract 2011
Treatments for APL

1) Chemotherapy
2) All-trans retinoic acid
   (differentiation, binding to receptor)
3) Autologous transplantation
4) Arsenic trioxide (m.o.a. unclear)
5) Supportive treatment
Outcome of APL in different time periods

SEER data base, cumulative relative survival

Chen Y, et al., Cancer, 2012
2) Chronic Myelogenous Leukemia

- Rare, annual incidence in U.S. 1.75 cases/100,000
- $t(9;22) \rightarrow bcr/abl$ fusion gene
- Over-expression of a tyrosine kinase
- Imatinib (2 phenylaminopyridine class)
Mortality due to CML in U.S. & Japan

1993-2008
(standardized, age-adjusted)

Chihara D, et al., The Oncologist, 2012
3) Lung Cancer is Heterogeneous

Frequency of driver mutations in A) adenocarcinomas and B) squamous carcinomas
Frequency may differ depending on age, ethnicity, smoking status and gender

3a) ALK + Lung Cancer

ALK is a highly conserved receptor tyrosine kinase and belongs to insulin receptor superfamily. First ALK rearrangement described in 1994 in anaplastic large cell lymphoma (t2;5)(p23;q35) resulting in constitutive activation of ALK. ALK rearrangements in NSCLC discovered in 2007 (fusion gene of ALK and EML4).
First Line Treatment for ALK+ Lung Cancer

- **ALK rearrangement positive**
  - **ALK rearrangement discovered prior to first-line chemotherapy**
    - **Crizotinib** (category 1)
      - 250 mg p.o. BID
  - **ALK rearrangement discovered during first-line chemotherapy**
    - Complete planned chemotherapy, including maintenance therapy, or interrupt, followed by crizotinib
  - Progression

From Wikipedia, aminopyridine structure

NCCN guidelines
Second Line Treatment for ALK+ Lung Cancer

**SUBSEQUENT THERAPY**

- Consider local therapy
- Continue crizotinib
  - or
  - Ceritinib or alectinib

- Consider local therapy and
- Continue crizotinib
  - or
  - Ceritinib or alectinib
  - See NCCN Guidelines for CNS Cancers

- Progression
  - See First-line therapy options
    - Adenocarcinoma (NSCL-24)
    - Squamous cell carcinoma (NSCL-25)
    - or
    - PD-L1 expression positive (≥50%)
    - See First-Line Therapy (NSCL-23)

**NCCN guidelines**
3b) ROS1 + Lung Cancer

- Ros1 gene located on chromosome 6q22
- Receptor tyrosine kinase, activated by chromosomal rearrangements, 1 of 12 partner genes
- Shares 77% AA identity within kinase domain with ALK
- Patients with Ros1 mutations are most often non-smokers, virtually all have adenocarcinoma
50 patients with advanced NSCLC were enrolled in the extension cohort of a phase 1 study, most had received at least 1 line of treatment, 72 % responded, med. duration of response 17.6 months
Case of a patient with lung cancer

55 year old woman, PET scan 6/2013
Patient with Lung Cancer

55 year old woman of Vietnamese origin, never smoker
Chronic cough for about 2 years
Diagnosis: lung adenocarcinoma
Paraffin block sent for FISH, **ALK pos**; EGF-R non-mutated (by PCR)
T4N2M1 (multiple bone metastases, brain metastasis, adrenal gland)
Radiation to chest, brain
Treated with **crizotinib** 8/2013- 12/2014
Progression, started on **ceritinib**, 12/2014- 8/2015
Progressed with liver metastasis
9/2015 started on chemotherapy with carboplatin/ pemetrexed (tolerated well,6 cycles)
Resolution of liver metastasis
2/2016 maintenance pemetrexed started
Both the incidence and the death rate from lung cancer have declined, however this is not due to the introduction of targeted treatments.
4) CD 30 in Hodgkin Lymphoma

- Hodgkin Lymphoma paradigm for a curable cancer, but some patients relapse
- CD30 is a surface receptor and belongs to the TNF receptor superfamily
- Expressed on few normal cells (activated T cells, some thymocytes)
- Expressed on HRS cells of most cases of Hodgkin lymphomas (and other NHLs)

Immunohistochemistry for CD30: lymph node with Hodgkin lymphoma (Dartmouth Dept. of Pathology)
CD30 Targeting in Hodgkin Lymphoma

Mechanism of action of brentuximab vedotin: binds to CD30, enters cell via endocytosis, MMAE released, disrupts mitosis at microtubulin level, causes apoptosis

MMAE: Monomethylaurostatin E

Outcome of CD30 Targeting in Hodgkin Lymphoma (HL)

Original indication for Brentuximab Vedotin (BV):
Relapse after autologous stem cell transplantation or patient too sick for auto-SCT
In relapsed or refractory HL, 75% responded, 25% in remission after 4 years
Side effects generally mild, except neuropathy (42%, 8% severe), 35% nausea, 34% fatigue
Now BV incorporated into some first-line protocols
The Prognosis of Hodgkin Lymphoma has improved

The relative survival of patients in different age groups increased comparing 1980-84 with 2000-04 (SEER)  

Brenner et al, Blood 2008
The Prognosis of Hodgkin Lymphoma has improved

The relative survival of patients in different age groups increased comparing 1980-84 with 2000-04 (SEER)  

Brenner et al, Blood 2008
5) CD 38 in Multiple Myeloma

- CD38 is nucleotide regulating ectoenzyme (involved in Ca ++ metabolism) and has receptor properties (ligand CD31)
- Widely expressed in physiology at a low level, more on activated cells, plasma cells and certain malignancies

CD38 in different cell lineages. Strong lateral association with professional signaling complexes, preferentially located in rafts.

From Malavasi et al, Physiol Rev 2008
5) CD38 Targeting in Multiple Myeloma

Multiple myeloma is a genetically heterogeneous disease, but major progress was made in last 15 or 20 years

The Shreveport Myeloma Project, Overall Survival of 188 newly diagnosed patients with multiple myeloma treated at LSU Shreveport in 2 different time periods,

CD38 Targeting

CD38 is expressed in malignant plasma cells

Immunohistochemistry, RMcAB, Sigma/ Aldrich

Flow cytometry, Mishra et al, Ind J Pathol, 2012
CD38 Targeting as Single Agent

11/2015 FDA Approval (after 3 lines of therapy)

OS = overall survival

Usmani et al, Blood, 2016
CD38 Targeting in Combination

11/2016 FDA Approval (after 1 line of therapy)
Combination with lenalidomide- dexamethasone or bortezomib-dexamethasone

PFS - progression-free survival

Dimopoulos et al, NEJM, 2016
Palumbo et al, NEJM, 2016
Problems of Targeted Therapies

Huge cost, value?
Daratumumab was assigned moderate to high value at ASCO plenary session

Some studies were never repeated
Patients with comorbidities were excluded
Drug approved may not work in certain subgroups of patients
Optimal sequence of targeted therapies often unclear
Problems

Special Communication

Unintended Consequences of Expensive Cancer Therapeutics—The Pursuit of Marginal Indications and a Me-Too Mentality That Stifles Innovation and Creativity
The John Conley Lecture

Tito Fojo, MD, PhD; Sham Mailankody, MD; Andrew Lo, PhD

...of cancer drugs an undeniably important variable. The use of expensive therapies with marginal benefits for their approved indications and for unproven indications is contributing to the rising cost of cancer care. We believe that expensive therapies are stifling progress by (1) encouraging enormous expenditures of time, money, and resources on marginal therapeutic indications and (2) promoting a me-too mentality that is stifling innovation and creativity. The modest gains of Food and Drug Administration-approved therapies and the limited progress against major cancers is evidence of a lowering of the efficacy bar that, together with high drug prices, has inadvertently incentivized the pursuit of marginal outcomes and a me-too mentality evidenced by the duplication of effort and redundant pharmaceutical pipelines. We discuss the economic realities that are driving this process and...

Fojo T, et al, JAMA Oncol HNS, 2014
The authors investigated 71 FDA approvals from 2002 to 2014 (excluding leukemia, lymphoma, myeloma) for cancer and found that PFS increased on average by 2.5 and OS by 2.1 months.

Fojo T, et al, JAMA Oncol HNS, 2014
Further Problems & Challenges

- Common cancers like pancreatic cancer have no targeted treatments
- Common mutations like k-ras have no targeting drug
- Different targets cannot always be hit at the same time
- Combinations with chemotherapy may or may not increase response (cetuximab for metastatic colorectal cancer, works preferentially in kras wt+ left-sided tumors)
- Treatments that work in metastatic disease may not work as adjuvant treatment (sunitinib or sorafenib for RCC)
Challenges
Unexpected Off-Target Effects

• **Cardiovascular**
• HER-2 monoclonal antibody -> congestive heart failure
• Ponatinib -> coronary, cerebral, peripheral vascular events
• Crizotinib -> bradycardia, prolongation of QT
• Ibrutinib -> atrial fibrillation
• Immune checkpoint inhibitors -> myocarditis

From Moslehi, 2016
Solutions

Clinical experience will mitigate unexpected side effects
Cost will decrease by market forces
Government sponsored studies will facilitate targeted treatments
MATCH
MEF2D for ALL
Molecular Analysis for Treatment Choice

MATCH trial, sponsored by NCI, open since 8/2015
Refractory cancers, lymphomas, myelomas, rare cancers
Up to 6000 patients will be enrolled
WES performed, 4000 variants across 143 genes will be screened
For 24 actionable mutations, drugs will be provided for free
MATCH TRIAL

Similar projects are also performed in the private world ....
New Targets Discovered by Whole Genome Sequencing

560 cases of Acute Lymphoblastic Leukemia were analyzed by RNA sequencing, in 22 cases rearrangements between MEF2D and 5 other genes were found.

Gu et al, Nature Communications
New Targets Discovered by Whole Genome Sequencing

These cases have a distinct gene expression profile, older age and poor outcome.

The rearrangements result in enhanced MEF2D transcriptional activity, lymphoid transformation, enhanced HDAC9 expression and sensitivity to histone deacetylase inhibitor treatment.
What will be next?

- CAR T-CELLS
- BLOCKERS OF AUTOPHAGY
- MICRORNAS
- CAR T-CELLS
- PD1/PDL1 TREATMENTS
- CANCER STEM CELLS
- TELOMERASES
- GENOME-DIRECTED TREATMENTS
- GENOME EDITING
- HAPLO
Conclusions

• Spectacular progress has been made in the last 20 years, many malignancies like leukemias, lymphomas have become curable or the survival has been extended by many years

• Progress is made in other areas like lung cancer, but the extension of life often is only in months, metastatic cancer is still fatal in almost all cases

• Challenges to progress are the cost of targeted treatments and new toxicities

• Biomedical research will result in further improvements
Epilogue

- 1970s-90 Cytotoxic chemotherapy
- 1990s-2000 Dawn of molecular & immune treatments, proteins and cytokines cloned
- 2000- today Whole Genome Sequencing & multiple targets & multiple targeted treatments implemented
References

Acknowledgements

- Slide Bank of the American Society of Hematology
- Moslehi JJ Cardiovascular toxic effects of targeted cancer therapies, NEJM, 10/2016
- Ye M, et al ALK and ROS1 as targeted therapy paradigms and clinical implications to overcome crizotinib resistance, Oncotarget 2016

- I would like to thank Dr. Nicholas Verne (Tulane) and Dr. Bill Ray (ACLI) for inviting me and organizing this symposium