A Complicated Case of Gastric Cancer

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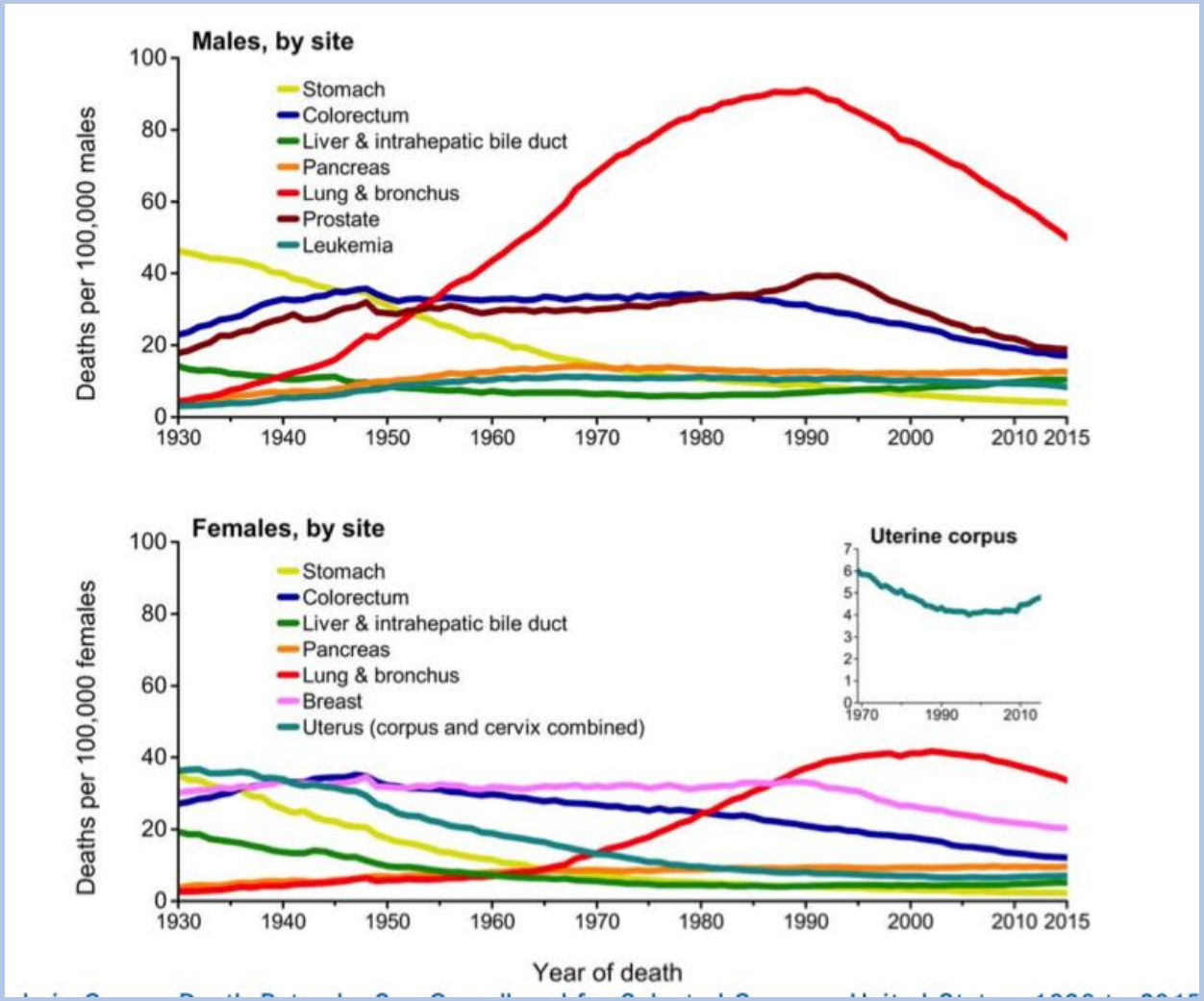
Disclosure

- No relevant financial relationships in the past twelve months by presenter or spouse/partner.

- The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

Incidence and Mortality Trends



Epidemiology

- 5th most common cancer worldwide
- Estimated new cases in US in 2018: 26,240
- Estimated Deaths: 10, 800
- More than 50% of patients are diagnosed with metastatic disease and another 25% develop recurrent metastatic disease

Population Distribution

Incidence	All races	Whites	Blacks	Asians	Indians	Hispanics
Male	9.2	7.9	14.3	14.1	11.6	12.9
Female	4.7	3.5	7.8	8.1	6.5	7.8
Mortality						
Male	4.3	3.4	8.5	6.8	7.3	6.7
Female	2.3	1.7	4.0	4.2	3.5	4.0

Treatment of Metastatic Disease (1st line)

Gastric cancer collaborative group showed: Adding a given chemotherapeutic agent to any chemotherapy improved overall survival by 11% (P<0.01) and PFS by 26% (P<0.0001).

Eur J Cancer. 2013 May;49(7):1565-77

	Cisplatin + 5 FU [1]	Cisplatin+ Capecitabine[1]	EOX[2]	DCF[3]	mDCF[4]	FLOT[5]
OS (mos)	9.3	10.5	11.2	9.2	10.2	11.1
PFS (mos)	5	5.6	7	5.6	7.2	5.2
RR (%)	32%	46%	48%	37%	49%	58%

1. Kang, Y. *Annals of Oncology*, Apr 2009.
2. Cunningham, D. *NEJM,* Jan 2008.
3. Van Cutsem, E. J*ournal of Clinical Oncology*, Nov 2006.
4. Wang, J. *Gastric Cancer,* Jan 2016.
5. Al-Batran, S. *Ann Oncology,* Nov 2008.

Treatment of Metastatic Disease (2nd line)

	Docetaxel[1]	Paclitaxel[2(4)]	Irinotecan[4]	Ramucirumab[3]	Ram + Paclitaxel[2]
OS (mos)	5.2	7.4 (9.5)	8.4	5.2	9.6
PFS (mos)	3	2.9 (3.6)	2.3	2.1	4.4
RR (%)	7	16 (21)	14	3	28

1. Ford, H. *Lancet Oncol,* Jan 2014.
2. Wilke, H. *Lancet Oncol,* Oct 2014.
3. Fuchs, C. *Lancet Oncol,* Jan 2014.
4. Hironaka, S. *J Clin Oncol,* Dec 2013.

PDL1 Expression

- PD-L1 is a co-inhibitory molecule expressed on the surface of tumor-infiltrating macrophages, antigen-presenting cells, and the tumor cells.

	PDL1 +
AGC[1]	22.8 in TC and 61.4 TIC
AGC[2]	35% by mRNA
ATTRACTION	12-16% (IHC, TC)
KEYNOTE-061	57.1 (IHC TC and TIC)

1. Yuan, J. Oncotarget, 2016
2. Kawazoe, A. Gastric Cancer, 2017

Molecular Classification: TCGA

- TCGA analysis is the most comprehensive: whole-genome sequencing, microarray profiling of genomic amplifications and deletions, messenger RNA and micro-RNA expression, DNA methylation

295 primary GC	EBV	Microsatellite instability (MSI)	Chromosomal instability (CIN)	Genomically stable subtype
Percent	9%	22%	20%	50%
Additional features	PDL 1&2 amplification	Hypermutated	Diffuse type	Alteration in RTK (EGFR, HER2, HER3, ...)

Nature 2014

Molecular Classification: ACRG

- Gene expression profiling, genome-wide copy number microarrays, and targeted gene sequencing

300 primary GC	MSI	MSS-EMT	MSS-TP53+	MSS-TP53-
Percent	22%	15%	26%	36%
Additional features	Antrum loc. Lower stage Intestinal type Best survival	Younger age Diffuse type Higher stage Worst survival	EBV+	

Cristescu, R. Nature Medicine, 2015

Molecular Classification: Oesophageal cancer clinical and molecular stratification (OCCAMS)

- Whole genome sequencing

129 esophageal cancer	T>G mutational pattern	DDR Impaired	C>A/T pattern
Percent	53%	18%	29%
Additional features	High mutational burden, high neoantigen load	Prevalent defects in the homologous recombination pathway	Evidence of an ageing imprint

Secrier, M. Nature Genet, 2016

Single Agent Immunotherapy

	Nivolumab[1]	KEYNOTE-059 (PDL1+)[2]	KEYNOTE-061 PDL1+[3]	Avelumab
OS (mos)	5.3 (6.2)	5.6	9.1	4.6
PFS (mos)	1.6	2	1.5	1.4
RR (%)	11 (12)	11.6 (15.5)	16	2.2

1. Kang, Y. *Lancet Oncol,* Dec 2017.
2. Fuchs, C. *Lancet Oncol,* May 2018.
3. Shitara, K. *Lancet Oncol,* July 2018.

Combination Immunotherapy

	Nivo 1 + Ipi 3 (PDL1+)	Nivo 3 + Ipi 1 (PDL1+)
OS (mos)	6.9	4.8
PFS (mos)	1.4	1.6
RR (%)	24	8

Janjigian Y. Presented at: ASCO Annual Meeting; 2017

Past the Dark Ages of Chemotherapy!

- https://www.youtube.com/watch?v=UtllgbUiTt0

Toxicity

PD1/PDL1	All grades (%)	Garde 3 & 4	PD1 + CTLA4	Garde 3 & 4
Hypothyroidism	8			
Hyperthyroidism	4			
Hepatitis	1	1	AST/ALT increase	14%
Colitis	1	<1		
Pneumonitis	3	<1		
Fatigue	12%-18%	2		
Decreased appetite	8%	<1		
Diarrhea	5%	<1	Diarrhea	14%
Arthralgia	5.8	<1		

Janjigian Y. Presented at: ASCO Annual Meeting; 2017

Case Presentation

- A 38 yo female presented with epigastric pain and nausea. She received PPI for two months with no improvement. She then was referred to a gastroenterologist for EGD.
- EGD revealed an ulcer on the greater curvature. Biopsy was negative for malignancy.
- Two months later due to persistence of symptoms she had a second EGD with biopsy: poorly differentiated adenocarcinoma

Workup

- CT CAP: gastric wall thickening, no liver or lung lesion, retroperitoneal nodes enlarged with largest node 1.3-1.4 cm
- EUS: T2 N0
- PET scan: FDG avid gastric mass and retroperitoneal nodes. With the largest node 1.6 cm.
- Molecular analysis of gastric mass:
  - HER2: not amplified
  - MSS
  - PDL1: + CPS 5
  - TP53: Mutated

Treatment

- She was enrolled on a clinical trial and started on treatment with nivolumab + ipilumumab
- 3 days after first dose, she called and reported severe hip pain. She was advised to use over the counter prescriptions for pain control.
- She presented on Day #8 for follow up, walking with a cane!
- **Arthralgia, grade 3!!**
- Received NSAID prescription and by day of her next visit, arthralgia was grade 1. Other toxicities included: rash and itching both grade 1.

Treatment (continued)

- She received cycle #2 and 3. Again noted worsening arthralgia on day 3-4.
- After cycle #3, her family took her to see her PCP who prescribed prednisone 20 mg daily. She took 3 days of prednisone with improvement in symptoms. She was seen in follow up and instructed to stop her prednisone.
- A CT scan revealed stable disease (15% reduction in the size of retroperitoneal nodes). Her symptom of abdominal pain is completely resolved.
- Treatment # 4 was administered and on day 15 she had elevated AST and ALT.

Hepatitis

- Treatment #4 was held. She was instructed to return in one week for lab check
- Her bili was 5.5, AST and ALT both above 1000.
- She was admitted to hospital for hydration, methylprednisolone, and close follow up
- Her bilirubin normalized and her liver enzymes trended down. She was discharged home with steroid 1mg/kg and follow up in clinic
- Her enzymes returned to normal and steroid was tappered off over 6 weeks

Follow-up Care

- Follow-up CT scan revealed normalized thickening of gastric wall and small retroperitoneal node all less than 0.5 cm.
- She underwent total gastrectomy:
  - T1N3 gastric adenocarcinoma, mixed type.
  - poor treatment effect
- 8 weeks after her surgery, CT scan revealed increased size of retroperitoneal nodes to now 1.2 cm
  - She started FOLFOX

Conclusion

- Durable response to immunotherapy is the appeal of this treatment modality.
- The population who benefit from this treatment is perhaps small.
- Predictive biomarkers for benefit from immunotherapy can advance the care of this population.
- Toxicities are underreported and underestimated.
- There is no justification for use of these agents outside of the approved indications and clinical trials.