Pemetrexed: A potential new therapeutic option for the treatment of Thymidylate Synthase (TS) negative recurrent primary and systemic malignancies with CNS metastasis

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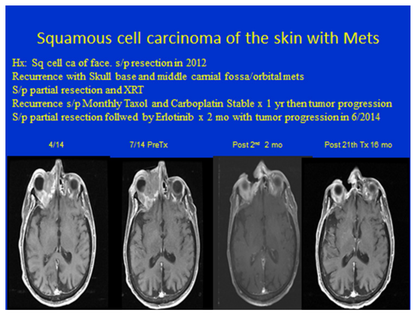
Background

- Fluoropyrimidine analogues, 5FU, Capecitabine and Pemetrexate, inhibit thymidylate synthase and they have been widely used for the treatment of systemic malignancies.
- Capecitabine can penetrate CNS and has shown some efficacy in the treatment of breast cancers with CNS metastasis. However, the role of Pemetrexed in the treatment of recurrent primary and systemic malignancies with CNS metastasis is not known.
- Pemetrexed is a multitargeted antifolate drug similar to methotrexate, but, unlike methotrexate, has the advantage of targeting more than 1 site in folate metabolism. It inhibits three enzymes used in purine and pyrimidine synthesis – Thymidine Synthetase (TS), Dihydrofolate reductase, and glycinamide ribonucleotide.
- We have treated 34 patients (pts) with previously heavily-treated recurrent primary and systemic malignancies with CNS metastasis based on the results of the molecular profiling.
- 17/34 pts were found to have TS Deficiency and 10/17 TS Deficient pts were treated with Pemetrexed.

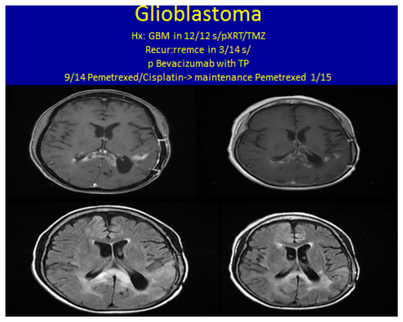
Methods

- Treatments (Tx) were provided between July 2014 and June 2016.
- Recurrence was defined based on the updated RANO criteria and the pathology report if surgery was performed.
- Molecular profiling was performed by Caris Life Sciences, Inc. Multitechnology platform (IHC, FISH, CISH, MGMT promoter methylation, NG SEQ and fragment analysis/pyro SEQ) was performed on formalin-fixed, paraffin-embedded tumor samples in a CLIA certified lab.
- Age, performance status, previous treatment regimen, extent of CNS involvement, route of administration, distance, tolerability, toxicity profile were carefully factored in choosing the Pemetrexed Tx for each pt.
- Out of 17 pts, 10 pts, (1 Glioblastoma, 3 Anaplastic Astrocytoma, 1 Gr. II Astrocytoma, 2 Meningioma, 2 Squamous cell Ca, 1 Chordoma) who were found to have TS Deficiency on the molecular profiling, received pemetrexed intravenously every 3 weeks.
- MRI imaging was performed before the Tx and every 1-2 months as indicated.

Results, continued



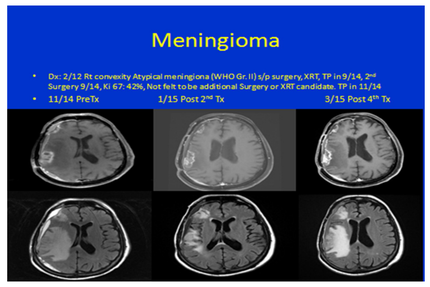
Biomarkers:TS, TLE3, TUBB3, TOP2A, RRM1, TOPO1, MGMT Methylation
Tx: Pemetrexed/Cisplatin->Pemetrexed Maint



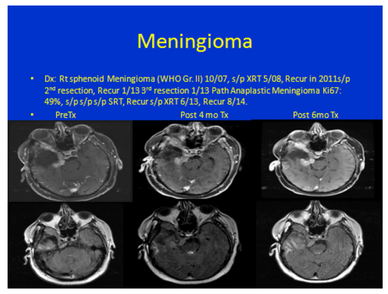
Biomarkers:TS, PGP, ERCC1, TLE3, RRM1, TUBB3, MGMT Unmethylated
Tx: Pemetrexed/Cisplatin->Pemetrexed Maint

Biomarkers: TS, TOPO1, TLE3, TUBB3, RRM1, PD-1. PDL-1, C-KIT, TP53
Tx: Pemetrexed

Biomarkers: TS, Topo1, RRM1
Tx: Pemetrexed



Biomarkers:TS, TLE3, TUBB3, TOP2A, RRM1, BRCA, PD-1, TP53
Tx: Pemetrexed/Cisplatin -> Maint Pemetrexed



Biomarkers:TS, PGP, TUBB3, TOP2A,
Tx: Capecitabine

	Pt. #	Age	Gender/Diagnosis	Patient Biomarkers	Previous Tx	Tx	Response
Systemic malignancy with CNS involvement			**Male (2 pts)**				
	1	82	Squamous cell Ca	TS, TBB3, TOPO2A, TOPO1, MGMT	Dx: 10/11, 9/12: Taxol/Carboplatin x 7 SD ,10/13,Resection, 2/14:: TMZ/Tarceva TP,: 7/14 multiple surgeries and RT/SRT	Pemetrexed/Cisplatin	PR x > 24 mo still on Tx
	2	87	Squamous cell Ca	TS, TBB3, TLE3, TOPO2A, TOPO1, SPARC	Dx: 2007 s/p resection Recur 2012 s/p Gamma Knife s/p caroplatin, Erbitux Rec:: 10/14	Pemetrexed	SD x > 20 mo Tx d/c due to Pt died from other condition
			Other notable pts with TS Deficiency treated with other chemoTx				
			Female (Total 2 pts)				
		68	Endometrial	TS, TUBB3, TOPO2A, MGMT, ERCC1		Docetaxel/Cisplatin	TP
		68	Leiomyosarcoma	TS, TUBB3, TLE3, TOPO2A,, RRM1,		Gemcitabine/Carboplatin	SD x 6 mo
Meningioma			**Females** (Total 2 pts)				
	3	53	Meningioma Gr 2	TS, TLE3, TUBB3, MGMT, ERCC1, TOPO2A, RRM1, TP53	Dx: 1998 s/p Resec Rec: 1994 RT, s/p resect 1999, multiple Rec:. TMZ	Pemetrexed/Cisplatin	SD x 4 mo
	4	44	Meningioma Gr 3	TS, ERCC1, MGMT, TUBB3, TOPO2A	Dx: 2010 s/p resection, XRT Recur: 10//13 s/p SRT Rec: 8/15 s/p Resect,	Pemetrexed/Cisplatin	SD x 5 mo Tx stopped due to Tx unrelated infection
			Other notable pts with TS Deficiency treated with other chemoTx				
			Male (Total 2 pts)				
		67	Meningiomas Gr 2	TS, TUBB3, RRM1, MGMT, cMET, ER/PR, TP53		Temozolomide	SD x 4 mo
		66	Meningiomas Gr 3	TS, TLE3, TUBB3, TOPO2A,,		Capecitabine	SD x 3mo+
Glioblastoma			**Female** (Total 1pts)				
	5	64	Glioblastoma	TS, TLE3, TUBB3, ERCC1, RRM1	Dx: 12/12 s/p RT/TMZ, Rec: 4/14 s/p Bevacizumab Rec: 7/14	Pemetrexed	SD x 4 mo
Anaplastic Astrocytoma			**Male** (Total 1 pt)				
	6	48	Anaplastic astrocytoma	TS, RRM1, MGMT	Dx: 7/11, s/p RT/TMZ, Lost F/U Rec: 4/14 s/p TMZ Rec: 4/15 s/p Carboplatin, Bevacizumab Rec: 1/16	Pemetrexed	SD x 4 mo
	7	51	Anaplastic astrocytoma	TS, RRM1	Dx: 6/14 Recur 7/14 s/p RT/TMZRec: 2/16	Pemetrexed	TP
			Female (1pt)				
	8	54	Anaplastic Astrocytoma	PGP, TLE3, TUBB3, TOPO1, TS, RRM1	Dx: 9/12, Rec in 5/14 s/p Carboplatin x 2 TP, Bx 8/15 s/p BCNU x 2,1 TP 11/14	Pemetrexed	SD x 2 mo
Low Grade glioma			Female (1pt)				
	9	58	Low grade glioma	TS, RRM1, TOPO1	Dx: 3/10 s/p XRT Rec 5/15 Rec ur Hx: NSCLCa 9/14 s/p Carboplatin, Pemetrexed, Carboplatin/Paclitaxel 5/15	Pemetrexed	SD x 5 mo
Rare CNS Malignancies			**Male** (Total1 pt)				
	10	67	Chordoma	TS, RRM1, TOPO1	Multiple srugeries and RT/SRT	Pemetrexed/cisplatin	SD x 3 mo+
			Other notable pt with TS Deficiency treated with other chemoTx				
			Female (Total 1 pt)				
		72	Esthesioneuroblastoma	TS, MGMT, RRM1, TOPO1		Temozolomide	SD x 8 mo

Results

- Total pts: 10. M:F 6:4, Age: 48-88 years old. Median age 64.1 years old.
- Treatment period: July 2014 – June 2016.
- 1/1 Glioblastoma pt: SD for 4 mo.
- 2/3 anaplastic astrocytoma pts: SD for 2 mo and 4 mo.
- 1/1 Gr. II astrocytoma pt: SD for 5 mo.
- 2/2 meningioma pts: SD for 4 mo and 5 mo respectively. Both pts also received concurrent cisplatin based on ERCC1 and BRCA1 markers.
- 2/2 pts with squamous cell Ca of skin with skull base/brain metastasis: 1 PR for 24 mo, 1 SD for 28 mo respectively. 1 pt died from non-chemotherapy related medical condition and 1 pt is still receiving treatment 24+ mo.
- 1/1 chordoma pt involving cervical/skull base: SD for 11 mo.
- Toxicities were very mild except 2 meningioma pt and 1 glioblastoma (Gr. 3-4) who also received cisplatin.

Discussion

- Although the total number of pts were small, TS targeted therapy seems to provide a durable response in various malignancies with TS Deficiency.
- Pemetrexed treatment for TS Deficient recurrent primary and systemic malignancies with CNS metastasis demonstrated an excellent response rate of 90% (PR:1, SD:8, TP:1).
- Toxicities were minimal and tumor responses were durable.
- For systemic disease with CNS metastasis, especially in squamous cell carcinoma of skin/skull base, if present, TS could be a reasonable potential target for Tx. Similar finding was also seen in pts with meningioma and chordoma.
- Previously not well known marker, TS Deficiency, in meningiomas, were found in the most of the meningioma pts and fluoropyrimidine analogues could be considered as potential treatment.
- Unlike in most glioblastomas, TS Deficiency was present in 3/3 pts with anaplastic astrocytomas, thus, making a potential target for TS directed therapy.

Conclusions

- TS deficiency has been found in many malignancies and if present, it could be a potential target for fluoropyrimidine analogues.
- Treatment of various recurrent malignancies with pemetrexed and its derivative capecitabine was successful although the response and duration of the treatment tends to be more favorable for systemic malignancies with CNS metastasis than primary malignant gliomas.
- The previously heavily treated meningiomas and rare CNS malignancies such as recurrent chordoma that had TS deficiency also responded favorably to Pemetrexed.
- Particularly in the elderly population, in light of excellent toxicity profile, Pemetrexed should be considered as a part of the first treatment options for TS deficient CNS malignancies.
- A TS directed trial for pts with TS deficient recurrent CNS malignancies is warranted.

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