29P

Sarcoma patients need precision oncology: Molecular Tumor Board is the right way?

A.Cosimati[1], C.E. Onesti[2], F. Salvatori[1], F. Riva[1], S. Vari[2], D. Renna[2], D. Buccilli[1], R. Covello[3], B. Casini[3], F. Rollo[3], G. Ciliberto[4], V. Ferraresi[2]

1 Medical Oncology, Sapienza - Università di Roma, Rome, Italy, 2 UOSD Sarcomas and Rare Tumors, IRCCS Regina Elena National Cancer Institute Rome, Italy, 3 UOC Pathology Department, IRCCS Regina Elena National Cancer Institute, Rome, Italy, 4 Scientific Direction, IRCCS Regina Elena National Cancer Institute, Rome, Italy

MAP AMSTERDAM NETHERLANDS 14-16 OCTOBER 2022 — MOLECULAR ANALYSIS FOR PRECISION ONCOLOGY CONGRESS

BACKGROUND

The aim of molecular tumor board (MTB) is to identify potential therapeutic strategies, based on genetic analysis, for patients (pts) not responding to standard therapies. All tumor types are eligible for MTB discussion and sarcomas are one of the common target due to the low number of standard and innovative treatments. Here we analyze the role of MTB in a sarcoma referral center in Italy.

METHODS

We presented data from MTB including pts affected by soft tissue (STS) and bone sarcoma (BS) followed at Regina Elena National Cancer Institute in Rome and discussed from December 2019 to May 2022. The molecular analysis required were: FoundationOne Heme (FO), ArcherFusionPlex Sarcoma Panel (ARCHER SARCOMA), Exome Sequencing, Oncomine Focus Assay (FOCUS), Oncomine Comprehensive Assay Plus (OCA PLUS), Oncomine Precision Assay (OPA), Cosmic mutations from oncogenes and tumor suppressor genes (CHPv2), Promega MSI PCR Testing Kit and immunohistochemistry for PD-L1. All tests were performed by pathology department of our Institute, except for FO.

RESULTS

We discussed 19 pts affected by STS (14 pts) and BS (5 pts), male/female 15/4, median age 51.26 years (SD 16.19). FoundationOne Heme (FO) was performed in 74%, ArcherFusionPlex Sarcoma Panel (ARCHER SARCOMA) in 42%, Oncomine Focus Assay (FOCUS) in 58%, Exome Sequencing in 21%, Oncomine Comprehensive Assay Plus (OCA PLUS) in 21%, Oncomine Precision Assay (OPA) in 5%, Cosmic mutations from oncogenes and tumor suppressor genes (CHPv2) in 10%, Promega MSI PCR Testing Kit in 16%, and immunohistochemistry for PD-L1 in 16% of pts. Techniques were chosen depending on the type of kit available, the cost, the alterations searched and the time to obtain results. Druggable targets were found in 11 pts: mTOR mutation (m), HGF amplification (amp), ATM splice site m, MET amp, KRAS m, CDK4 amp, MYC amp, PTCH1 m, PIK3CA m, MDM4 amp and PD-L1 overexpression. Three patients (16%) received precision therapy: Imatinib and Everolimus for mTOR m in cordoma, Cabozantinib for HGF amp in fibroblstic osteosarcoma and Pembrolizumab in angiosarcoma with PD-L 1 >10%. Eight pts continued standard therapy due to maintenance of response (5 pts) or to absence of literature supporting target treatment (3 pts). Molecular analysis allowed reformulation of diagnosis for one patient due to the presence of EWSR1-CREB3L2 fusion, typical of low-grade fibromyxoid sarcoma, that led to a histology-based treatment choice. Two pts were addressed to best supportive care (10%) and 3 pts (16%) died. (Tab. 1)

CONCLUSION

MTB could be an effective tool for decision-making in sarcoma, but the lack of literature data and drug access hinder treatment choice. Enrollment in clinical trials could lead to overcome the problem. Moreover, the timing for requesting molecular analyses, at diagnosis or at the end of standard therapies, as well as the type of material (FFPE tissue at diagnosis vs. rebiopsy), needs to be defined, considering both the tumor heterogeneity and the delay in obtaining results and starting treatment.

Corresponding author:
Antonella Cosimati, M.D.,
Sarcomas and Rare Tumors Unit,
IRCCS Regina Elena National Cancer institute,
Rome, Italy Via Elio Chianesi 53, 00144, Rome.
e-mail: antonella.cosimati@ifo.it

Conflict of interest
Nothing to declare.

AGE/SEX	HYSTOTYPE	MOLECULAR ANALYSIS REQUIRED	FO	NGS FOCUS-OCA PLUS/OPA PANEL	IHC; FISH; MSI (PCR/REAL Time PCR)	NGS ARCHER	EXOME SEQUENCING	THERAPY
61/M	Cordoma	NGS FOCUS MSI PDL1	-	mTOR E1799K, IDH2 R1272K	MSS PDL1 1%	-	-	**IMATINIB-EVEROLIMUS**
27/F	Fibroblastic Osteosarcoma	FO NGS FOCUS NGS ARCHER SARCOMA	HGF amp; BRAF amp, CDKN2A/B loss, JUN amp - equivocal, MAP2K4 complex rearrangement, TP53 Y236H	WT	-	NEGATIVE	-	**CABOZANTINIB**
70/F	Angiosarcoma	FO PDL 1	ATM splice site c.4611_4611+9delGGTAATTTTC, C11orf30 (EMSY) amp, CDKN2A/B CDKN2A loss, CDKN2B loss, FOXP1 amp, FOXP1 amp, MITF amp, MYST3 amp - equivocal	-	PDL1 10%	-	-	**PEMBROLIZUMAB**
34/M	Soft Tissue Clear Cell Sarcoma	FO NGS CHPV2	MET amp	BRAF WT	-	-	-	CT STANDARD
47/M	Fibrosarcoma	FO MSI PDL1	KRAS G13C, CDKN2A/B CDKN2A loss, CDKN2B loss, RUNX1 amp, TP53 splice site c.1101-75_1121>28	-	MSS PDL1 NEGATIVE	-	-	CT STANDARD
41/M	Myxofibrosarcoma	FO NGS FOCUS MSI	CDK4 amp, MAP2K1 (MEK1) E333A, MDM2 amp, FRS2 amp, JUN amp	CDK4 GAIN	MSS	-	-	CT STANDARD
67/M	Myoepithelial Carcinoma	FO NGS FOCUS	MYC amp; ASXL1 L896fs*7	WT- (SNV, INDEL, CNV) DNA, NO FUSION RNA	-	-	-	CT STANDARD
46/M	Liposarcoma	FO NGS FOCUS	FUSION: FUS-DDIT3	WT- (SNV, INDEL, CNV) DNA, RNA LOW QUALITY	-	-	-	CT STANDARD
57/F	Low-grade Fibromyxoid Sarcoma	FO	EWSR1-CREB3L2, CDK6 amp - equivocal, HGF amp - equivocal	-	-	-	-	**CT BASED ON NEW HISTOLOGY**
71/M	Leiomyosarcoma	FO	PTCH1M1V, IGF1R amp - equivocal, MALT1 amp - equivocal, RB1 loss, TP53 splice site 376-2A>G	-	-	-	-	CT STANDARD
27/M	CIC rearranged sarcoma	FO NGS ARCHER SARCOMA	CIC CIC-DUX4 fusion	-	-	FUSION: CIC(exon20)-DUX4(exon1)	-	DEATH
18/M	High Grade Chondroblastic Osteo-sarcoma	FO NGS FOCUS NGS ARCHER SARCOMA EXOME SEQUENCING NGS OCA PLUS	RNA LOW QUALITY DNA: CCNE1 amp - equivocal, TP53 rearrangement in-tron 9, TMB -Microsatellite status - Cannot Be Determined	FOCUS WT (SNV, INDEL, CNV), RNA LOW QUALITY	MSS PDL1 NEGATIVE	NEGATIVE	CNV AMP (TUBB4A, CCNE1), TMB:24,4 (High), MSS	DEATH
70/M	Cordoma	FO	PBRM1 splice site c.1541+1G>A	-	-	-	-	CT STANDARD
55/M	High Grade Fibroblastic Osteosarco-ma	FO NGS FOCUS DNA NGS ARCHER SARCOMA NGS OCAPLUS	SAMPLE NOT ADEQUATE	FOCUS CDK4 AMP	-	NEGATIVE	-	BSC
61/M	GIST	FO NGS CHPV2	KIT N564_Y578del, D816E, D820A; CDKN2A/B CDKN2B loss, CDKN2A loss; RB1 splice site 2107-1G>A, loss exons 3-17	KIT D816E EXON 17	-	-	-	CT STANDARD
51/M	Pleomorphic Sarcoma	NGS FOCUS DNA NGS ARCHER SARCOMA EXOME SEQUENCING	-	FOCUS WT (SNV, INDEL, CNV)	-	NEGATIVE	TMB: 6,06, MSS, CNV CD79B	BSC
58/F	Undifferentiated Sarcoma	NGS FOCUS DNA NGS ARCHER SARCOMA EXOME SEQUENCING NGS OCA PLUS	-	FOCUS WT (SNV, INDEL, CNV)	MSS PDL1 NEGATIVE	NEGATIVE	TMB: 25.9, MSS, POLE Y2008Sfs*3 no cosmic, POLE P1159Lfs*19 no co-smic, PMS1 C102* no cosmic	CT STANDARD
44/M	Intimal cardiac sarcoma	NGS FOCUS DNA NGS ARCHER SARCOMA EXOME SEQUENCING NGS OCA PLUS	-	FOCUS PIK3CA E542K	MSS PDL1 NEGATIVE	NEGATIVE	TMB: 19.44 (High), MSI-HIGH, CNV MDM4	CT STANDARD
69/M	Pleomorphic Spindle Cell Sarcoma	NGS FOCUS DNA NGS ARCHER SARCOMA NGS OPA	-	FOCUS WT (SNV, INDEL, CNV)	-	NEGATIVE	-	DEATH

Tab. 1 Patients' characteristics, molecular analysis required, results and therapy (update September 2022)

FO: FoundationOne Heme

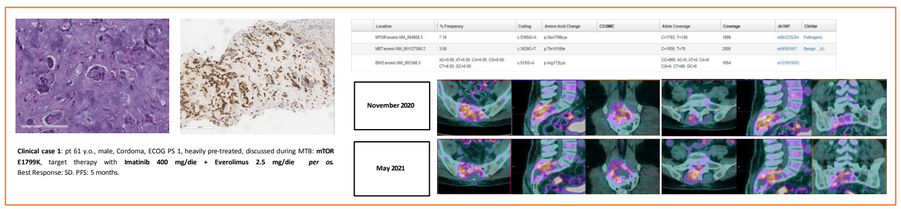
FOCUS : Oncomine Thermofisher Scientific (NGS DNA+RNA 52 gene panel for SNV, INDEL ,CNV, FUSION),

ARCHER SARCOMA: Archer Fusion Plex Sarcoma (NGS RNA 63 gene fusion panel),

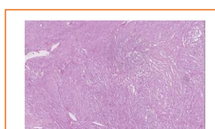
CHPV2: COSMIC mutations from oncogenes and tumor suppressor genes (NGS DNA 50 genes)

OCA PLUS: Oncomine Thermofisher Scientific (NGS DNA+RNA 500 gene panel for SNV, INDEL ,CNV, FUSION, TMB, LOH, MSI),

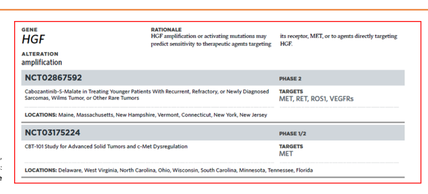
OPA: Oncomine Precision Assay Thermofisher Scientiific for detection of biomarkers in 50 genes (NGS DNA+RNA),

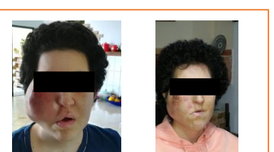


Clinical case 1: pt 61 y.o., male, Cordoma, ECOG PS 1, heavily pre-treated, discussed during MTB: **mTOR E1799K**, target therapy with **Imatinib 400 mg/die + Everolimus 2.5 mg/die** ***per os***. Best Response: SD. PFS: 5 months.



Clinical case 2: pt 27 y.o. female, Fibroblastic Osteosarcoma, ECOG PS 1, heavily pre-treated disease, discussed during MTB: **HGF amplification**, target therapy with **Cabozantinib 60 mg/die** ***per os.*** Best Response: NC.





After only one month of therapy