PERCORSO DIAGNOSTICO PER IL PAZIENTE CON MIELOMA MULTIPLO

GRUPPO DI STUDIO MIELOMA MULTIPLO

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OBIETTIVI:

- Rendere omogeneo il percorso diagnostico terapeutico del Mieloma Multiplo (MM) nei diversi centri regionali.

Nel sospetto di Mieloma Multiplo il paziente deve essere inviato in VISITA CAS presso centro ematologico di riferimento.

ACCERTAMENTI DA ESEGUIRE ALLA DIAGNOSI DI MIELOMA MULTIPLO

- Emocromo
- Creatinina
- Transaminasi
- Bilirubina totale
- Fosfatasi alcalina
- Proteine totali
- Albumina
- Siero β2-microglobulina
- LDH
- PCR
- Calcio
- Fosfato
- Sodio
- Potassio
- Acido urico
- e-GFR
- Elettroforesi proteica
- Immunofissazione sierica e urinaria
- esame urine completo
- Nefelometria per IgG-IgA-IgM

- Catene leggere libere sieriche e ratio FLC
- Proteinuria di 24h
- M-proteina urine qualitativa (Bence Jones)
- M-proteina urine quantitativa (Bence Jones) nelle urine di 24h quantificata su urine 24 ore
- PT,PTT,fibrinogeno
- NT-proBNP o BNP e troponina
- Sierologia per HBV,HCV,HIV
- Biopsia osteomidollare
- Aspirato midollare per:
    - Morfologia,
    - Immunofenotipo, opzionale nei pazienti frail
    - Analisi FISH, opzionale nei pazienti frail
- ECG/RX torace
- Ecocardiografia secondo giudizio medico
- Indagini radiologiche :
    - Whole body TC/RMN whole body/RMN Colonna+bacino e/oRX scheletro
    - TCPET se clinicamente indicata
    - Rx panoramica dentaria + visita odontostomatologica

Se sospetto di Amiloidosi AL:

biopsia grasso periombelocale e/o biopsia su ghiandola salivare minore con tipizzazione della sostanza amiloide.

DEFINIZIONE DI MIELOMA secondo International Myeloma Working Group (1)

Plasma cell disorder	Definition
Smouldering multiple myeloma	Both criteria must be met: • Serum M protein (IgG or IgA) ≥ 30 g/L or urinary M protein ≥ 500 mg per 24 h and/or clonal BM plasma cells 10%–60% • Absence of myeloma-defining events or amyloidosis
Multiple myeloma	Clonal BM plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events: • Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: - Hypercalcaemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL) - Renal insufficiency: CrCl < 40 mL/min or serum creatinine > 177 μmol/L (> 2 mg/dL) - Anaemia: haemoglobin value of > 20 g/L below the lower limit of normal or a haemoglobin value < 100 g/L - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT • Any one or more of the following biomarkers of malignancy: - ≥ 60% clonal BM plasma cells - Involved/uninvolved serum-free light chain ratio ≥ 100 - > 1 focal lesion on MRI studies (each focal lesion must be ≥ 5 mm in size)

STADIAZIONE

Secondo International Staging System (3)
Stadio I Beta2-M < 3.5 mg/dl e albumina ≥ 3.5 g/dl (sopravvivenza mediana: 60 mesi)
Stadio II Beta2-M < 3.5 mg/dl e albumina < 3.5 g/dl *oppure* Beta2-M >3.5 mg/dl e < 5.5 mg/dl (sopravvivenza mediana: 44 mesi)
Stadio III Beta2-M ≥ 5.5 mg/dl (sopravvivenza mediana: 29 mesi)

Secondo Durie & Salmon (2)
Stadio I Hb > 10 g/dl Calcio sierico < 10.5 mg/dl Scheletro normale IgG < 5 g/dl o IgA < 3 g/dl Bence Jones proteinuria < 4 g/24 ore
Stadio II Nessun adattamento allo stadio I e III
Stadio III Una o più delle seguenti condizioni: Hb < 8,5 g/dl Calcemia > 12 mg/dl Più di 3 lesioni ossee IgG > 7 g/dl, IgA > 5 g/dl Bence Jones proteinuria > 12 g/24 ore
Sottostadio A. Creatininemia < 2 mg/dl B. Creatininemia > 2 mg/dl

Stadio III
ISS III **High risk citogenetico e/o LDH elevato**

INDICAZIONI AL TRATTAMENTO (1, 8)

Viene presa in considerazione per i pazienti affetti da MM che presentino uno o più dei seguenti eventi:

1. criteri CRAB così definiti:

- ipercalcemia calcemia >11 mg/dl
- compromissione renale:creatininemia >2 o clearance creatinina <40 ml/min
- anemia Hb<10 gr/dL o riduzione di almeno 2 gr/dL rispetto al limite inferiore di normalità

- lesioni ossee uno o più lesioni litiche su ,TC low-dose ,Rx sistematica ossea o TC-PET

2. biomarkers di malignità identificati dall'IMWG così definiti:

- plasmacellule monoclonali midollari >60%
- >1 lesione ossea focale di dimensioni maggiori di 5 mm con MRI
- Involved:uninvolved FLC ratio ≥ 100.

CRITERI DI RISPOSTA secondo IMWG 2011

Response subcategory	Response criteria
Molecular CR	CR plus negative ASO-PCR, sensitivity 10^{-5}
Immunophenotypic CR	Stringent CR plus Absence of phenotypically aberrant PCs (clonal) in BM with a minimum of 1 million total BM cells analysed by multiparametric flow cytometry (with >4 colours)
Stringent CR	CR as defined below plus Normal FLC ratio and Absence of clonal PCs by immunohistochemistry or 2- to 4-colour flow cytometry
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤ 5% PCs in BM
VGPR	Serum and urine M protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M protein plus urine M protein level <100 mg per 24 h
PR	≥ 50% reduction of serum M protein and reduction in 24h urinary M protein by ≥ 90% or to < 200 mg per 24 h If the serum and urine M protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria If serum and urine M protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in PCs is required in place of M protein, provided baseline BM PC percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Progressive disease	Increase of 25% from lowest confirmed response value in one of the following criteria: Serum M protein (absolute increase must be ≥ 0.5 g/dL) Serum M protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL Urine M protein (absolute increase must be ≥ 200 mg/24 h)

CRITERI DI RISPOSTA secondo IMWG 2016

Response subcategory		Response criteria
IMWG MRD negativity criteria	Sustained MRD-negative	MRD-negative in the marrow (next-generation flow and/or NGS) and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g. MRD-negative at 5 years)
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry on BM aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD-negative	Absence of clonal plasma cells by NGS on BM aspirates in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of BM aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Imaging + MRD-negative	MRD-negative as defined by next-generation flow cytometry or NGS plus Disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to < mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue