Ipercalcemia nei tumori solidi

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definizione

- Sd. Clinica, differente eziologia (da cause benigne a Paraneoplastica), quadro clinico variabile
- 90%: iperparatiroidismo e tumori (10-30%)
- Significato prognostico negativo → MS < 6 mesi, spesso evento terminale (coma metabolico, IRA)
- > MM, SCC (Polmone, H&N, Esofago, Cervice uterina), Rene, Mammella, Linfomi

Stewart AF, NEJM 2005
Ralston SH, Ann Intern Med 1990

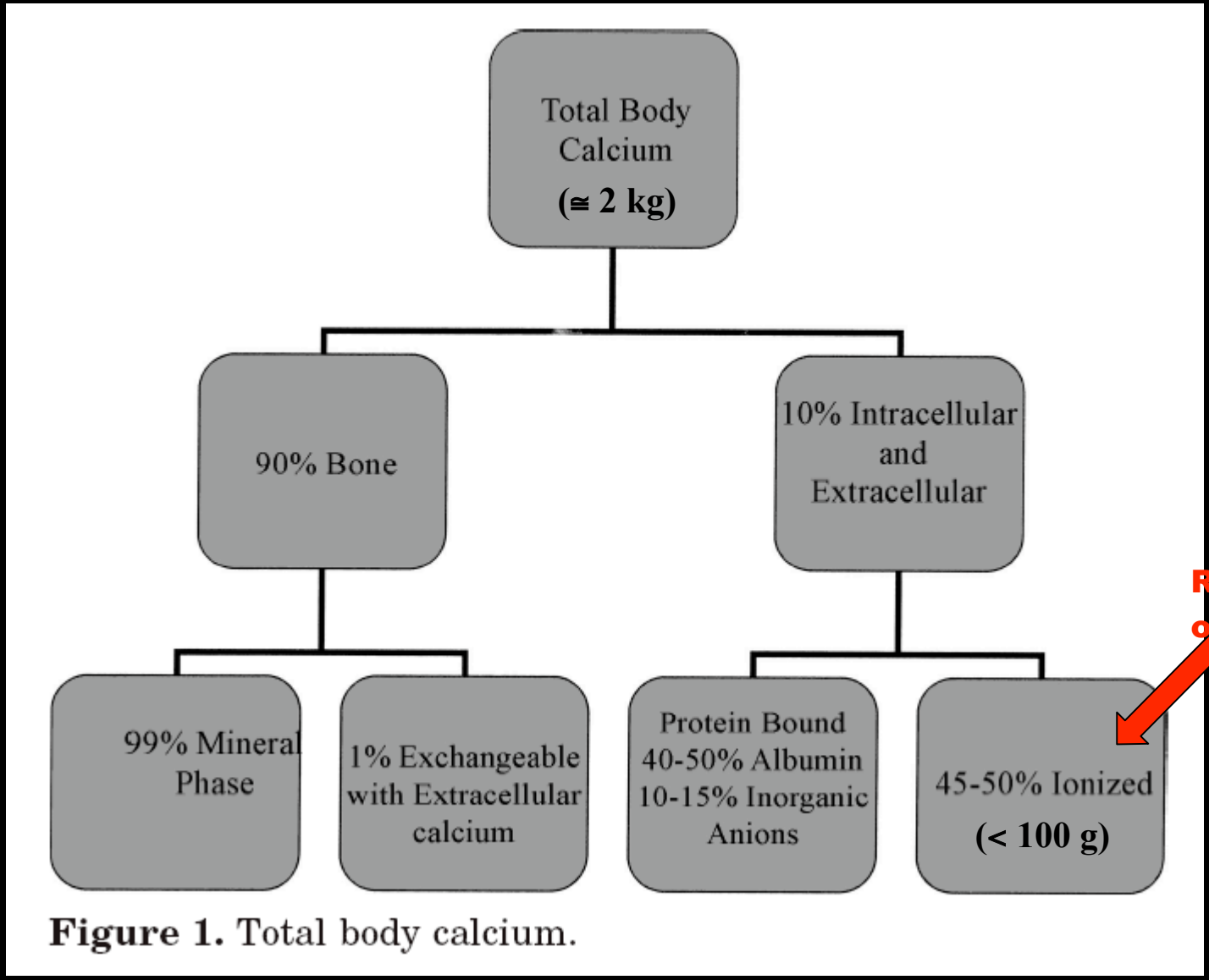


Figure 1. Total body calcium.

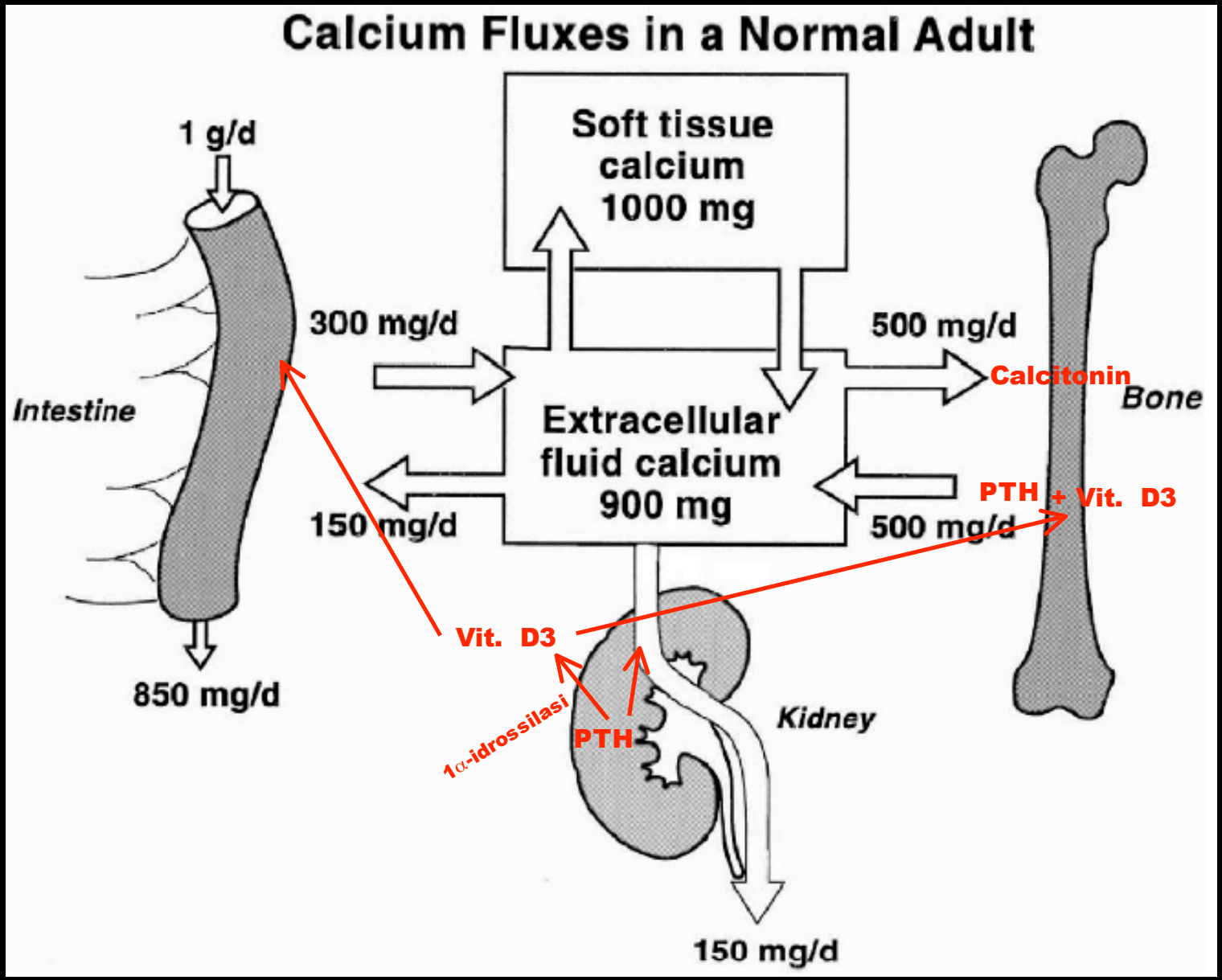
Regolazione ormonale

Shepard MM, Am J Med Sci, 2007

calcio totale / calcio ionizzato

- **Ipoalbuminemia → ↓ Ca totale, = Ca ionizzato**
- **Iperglobulinemia → ↑ Ca totale, = Ca ionizzato**
- **Acidosi → ↓ affinità Ca – Albumina → ↑ Ca ionizzato**
- **Alcalosi → ↑ affinità Ca – Albumina → ↓ Ca ionizzato**

omeostasi calcica



cause di ipercalcemia

- **1. Correlata alle Paratiroidi**
  - IperPTH primario (adenoma, MEN)
  - Litio carbonato
  - Ipercalcemia ipocalciurica familiare
- **2. Paraneoplastica**
  - Mts ossee
  - Tumori solidi e neoplasie ematologiche (HHM)
- **3. da Vit. D**
  - Intossicazione esogena
  - Sarcoidosi ed altre granulomatosi sistemiche

- **4. da elevato turnover osseo**
  - **Ipertiroidismo**
  - **Immobilizzazione**
  - **Diuretici tiazidici**
  - **Intossicazione da Vit. A**

- **5. da insufficienza renale cronica**
  - **Iper PTH secondario grave**
  - **Intossicazione da alluminio**
  - **Milk-alkali Syndrome**

Mod. da Harrison's, Princ Int Med, 16° Ed, 2005

sintomi

- Variabili in relazione a
  - PS del paziente
  - Rapidità di insorgenza
  - Entità dell'ipercalcemia
    - LIEVE 10.5 → 11.9 mg/dL (2.6 → 2.9 mM/L)
    - MODERATA 12 → 13 mg/dL (3 → 3.4 mM/L)
    - SEVERA > 14 mg/dL (> 3.5 mM/L)

- **Gastrointestinali**
  - anoressia, nausea, vomito, stipsi, addominalgie
- **Renali**
  - poliuria fino al diabete insipido nefrogenico
  - disfunzione tubulare renale
  - IRA da disidratazione
  - nefrolitiasi
- **Muscoloscheletrici**
  - astenia muscolare con ipertono
- **Neurologici**
  - depressione, cefalea, confusione mentale, coma
- **Cardiaci / ECG**
  - QT ↓, T ↑, BAV I°, aritmie (bradicardia), ↑ tossicità

ipercalcemia e tumori

Table 1. Types of Hypercalcemia Associated with Cancer.*

Type	Frequency (%)	Bone Metastases	Causal Agent	Typical Tumors
Local osteolytic hypercalcemia	20	Common, extensive	Cytokines, chemokines, PTHrP	Breast cancer, multiple myeloma, lymphoma
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous-cell cancer, (e.g., of head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer
$1,25(OH)_2D$-secreting lymphomas	<1	Variable	$1,25(OH)_2D$	Lymphoma (all types)
Ectopic hyperparathyroidism	<1	Variable	PTH	Variable

Stewart AF, NEJM 2005

terapia

Table 2. Pharmacologic Therapy for Hypercalcemia Associated with Cancer.*

Intervention	Dose	Adverse Effect
Hydration or calciuresis		
Intravenous saline	200–500 ml/hr, depending on the cardiovascular and renal status of the patient	Congestive heart failure
Furosemide	20–40 mg intravenously, after rehydration has been achieved	Dehydration, hypokalemia
Phosphate repletion		
Oral phosphorus (if serum phosphorus ≤3.0 mg/dl)†	For example, 250 mg Neutraphos orally, four times daily until serum phosphorus level >3.0 mg/dl or until serum creatinine level increases	Renal failure, hypocalcemia, seizures, abnormalities of cardiac conduction, diarrhea
First-line medications		
Intravenous bisphosphonates‡		
Pamidronate	60–90 mg intravenously over a 2-hr period in a solution of 50–200 ml of saline or 5% dextrose in water§	Renal failure, transient flu-like syndrome with aches, chills, and fever
Zoledronate	4 mg intravenously over a 15-min period in a solution of 50 ml of saline or 5% dextrose in water	Renal failure, transient flu-like syndrome with aches, chills, and fever
Second-line medications		
Glucocorticoids¶	For example, prednisone, 60 mg orally daily for 10 days	Potential interference with chemotherapy; hypokalemia, hyperglycemia, hypertension, Cushing's syndrome, immunosuppression
Mithramycin	A single dose of 25 μg/kg of body weight over a 4-to-6-hour period in saline	Thrombocytopenia, platelet-aggregation defect, anemia, leukopenia, hepatitis, renal failure‖
Calcitonin	4–8 IU per kilogram subcutaneously or intramuscularly every 12 hr	Flushing, nausea
Gallium nitrate	100–200 mg/m² of body-surface area intravenously given continuously over a 24-hr period for five days	Renal failure

Stewart AF, NEJM 2005

Bisfosfonati ed ipercalcemia

- **Superiori alla sola idratazione in RCT**

(Ralston SH, Calcif Tissue Int 2004)

- **Pamidronato: + efficace di Clodronato e Mitramicina,**
  = a Gallio Nitrato

(Vinholes J, JCO 1997,
Thurlimann B, Ann Oncol 1992,
Cvitkovic F, Cancer J 2006)

- **Zoledronato** 4 e 8 mg vs Pamidronato 90 mg:
  - 2 RCT "pooled", 275 pz
    - normocalcemia 10° giorno: 88 vs 86 vs 69%
    - durata della risposta: 32 vs 43 vs 18 dd
    - nefrotox (↑ creatinina G3-4): 7.5% vs 4%

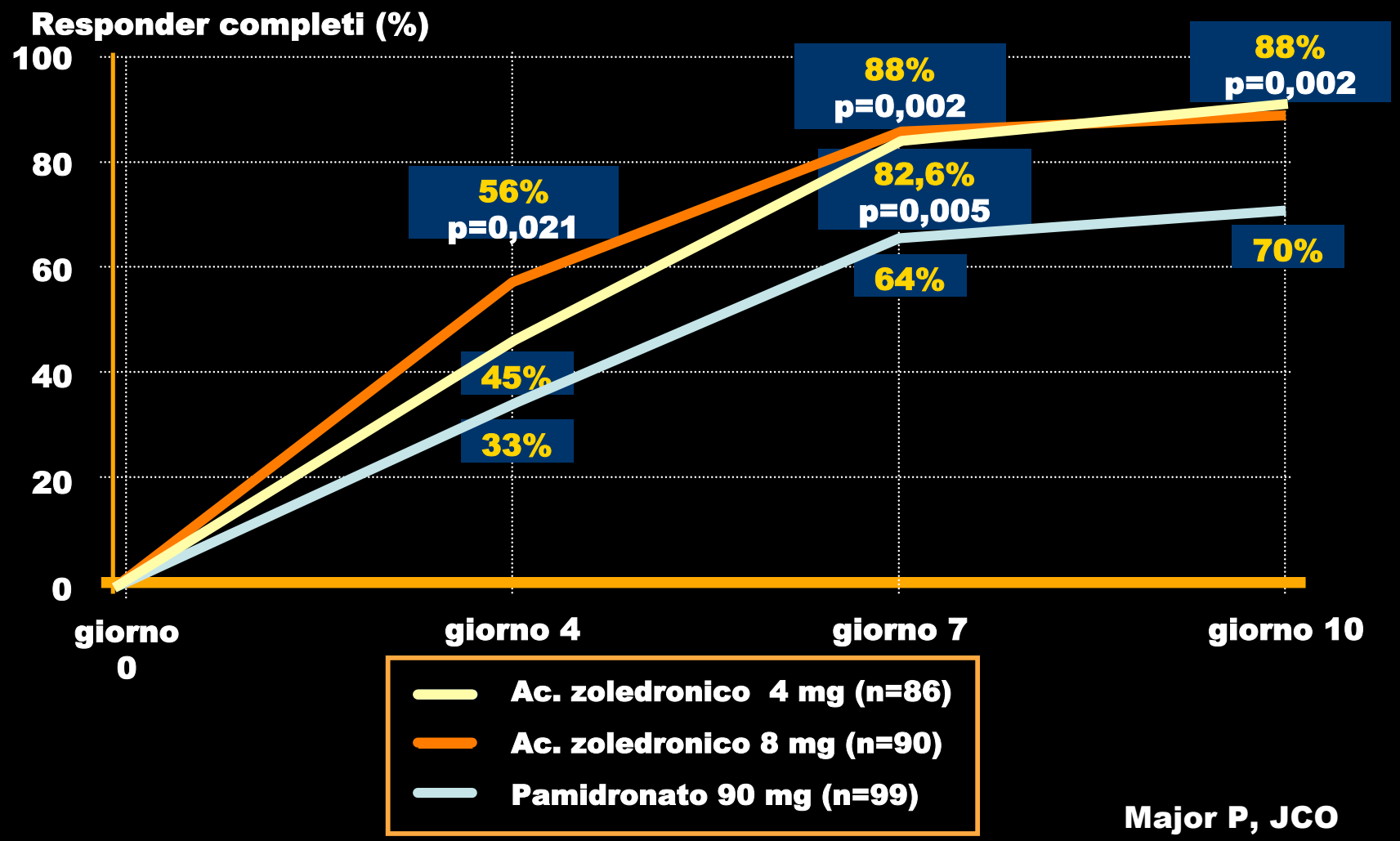
Superiorità di Zoledronato, > nefrotox se infusione rapida, ↓ dose se FG 30-50 mL/min, evitare se < 30 mL/min

(Major P, JCO 2001)

- **Ibandronato** 6 mg iv vs Pamidronato 90 mg:
  - comparabile RR 76 vs 75%
  - > durata della risposta
  - nefrotossicità rara

Percherstorfer M, Supp Care Cancer 2003

Zoledronato vs Pamidronato



Major P, JCO 2001

terapie sperimentali

- **Osteoprotegerina (OPG) ricombinante (AMGN-0007)**

  inibitore del sist. RANK/RANKL → ↓ differenziazione / attività OC
  ↑ apoptosi OC

  → potente inibizione del riassorbimento osseo e controllo dell'ipercalcemia in modelli murini

  Morony S, Endocrinology 2005

  Bekker PJ, J Bone Miner Res 2004

- **Denosumab (AMG162), MoAb umano anti RANKL**

  Effetto OPG-like, < riassorbimento osseo, studi nel mieloma e ca mammario

  McClung MR, NEJM 2006

Ipercalcemia da prevalente inibizione dell'escrezione renale → scarsa efficacia di farmaci anti osteoclastici

P .L. Piovano

SOC Oncologia
A.S.O. SS Antonio e Biagio
e Cesare Arrigo

Alessandria