MONITORIZAÇÃO DE TERAPIAS DIRIGIDAS EM HEMATOLOGIA

Onde estamos em 2025?

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XXIV JORNADAS CIENTÍFICAS DE ANÁLISES CLÍNICAS E DE GENÉTICA HUMANA

MONITORIZAÇÃO DE TERAPIAS DIRIGIDAS EM HEMATOLOGIA

Introdução às Terapias Dirigidas em Hematologia

Principais Terapias Dirigidas em Hematologia

Métodos de Monitorização

Desafios e Considerações Clínicas

Avanços Recentes e Futuro da Monitorização

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Introdução às Terapias Dirigidas em Hematologia

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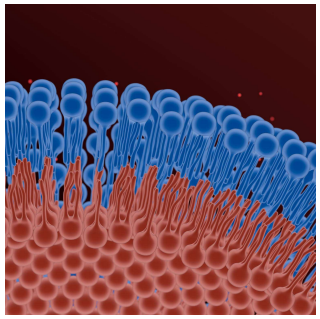
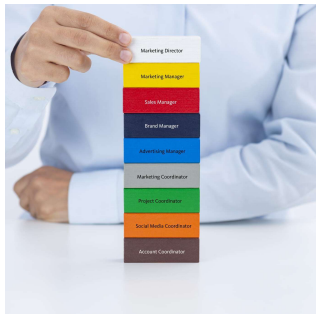
Introdução às Terapias Dirigidas em Hematologia



O que são terapêuticas dirigidas?

Terapias dirigidas são tratamentos que visam alvos moleculares específicos relacionados ao cancro, proporcionando uma abordagem mais precisa.



Benefícios em comparação às terapias tradicionais

Essas terapias oferecem opções mais eficazes e com menos efeitos secundários do que as terapias convencionais, que afetam células normais e neoplásicas.

Eficácia das terapias dirigidas

As terapias dirigidas têm demonstrado resultados promissores em doentes, melhorando a taxa de resposta e a qualidade de vida.

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E na Hematologia?

Quimioterapia Tradicional

A quimioterapia tradicional foi a primeira linha de tratamento para diversas doenças hematológicas, embora não fosse específica e tivesse efeitos secundários significativos.

Inibidores de Tirosina-Quinase

Os inibidores de tirosina-quinase representaram um avanço significativo, oferecendo tratamentos mais direcionados e eficazes para pacientes com certas condições hematológicas.

Desenvolvimento de Terapias celulares dirigidas

O desenvolvimento de terapias dirigidas trouxe novas possibilidades de tratamento, melhorando os resultados clínicos e a qualidade de vida dos pacientes.

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Benefícios das Terapias Dirigidas

As terapias dirigidas proporcionam uma abordagem mais precisa no tratamento, resultando em menos efeitos colaterais e maior eficácia.

Limitações das Terapias Dirigidas

Apesar de suas vantagens, as terapias dirigidas podem enfrentar resistência ao tratamento e requerem monitoramento rigoroso para eficácia contínua.

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Inibidores de tirosina quinase (ex.: Imatinib para LMC)

Anticorpos monoclonais (ex.: Rituximab para linfomas)

Inibidores de BCL-2 (ex.: Venetoclax para LLC)

Inibidores do proteassoma (ex.: Bortezomib para mieloma múltiplo)

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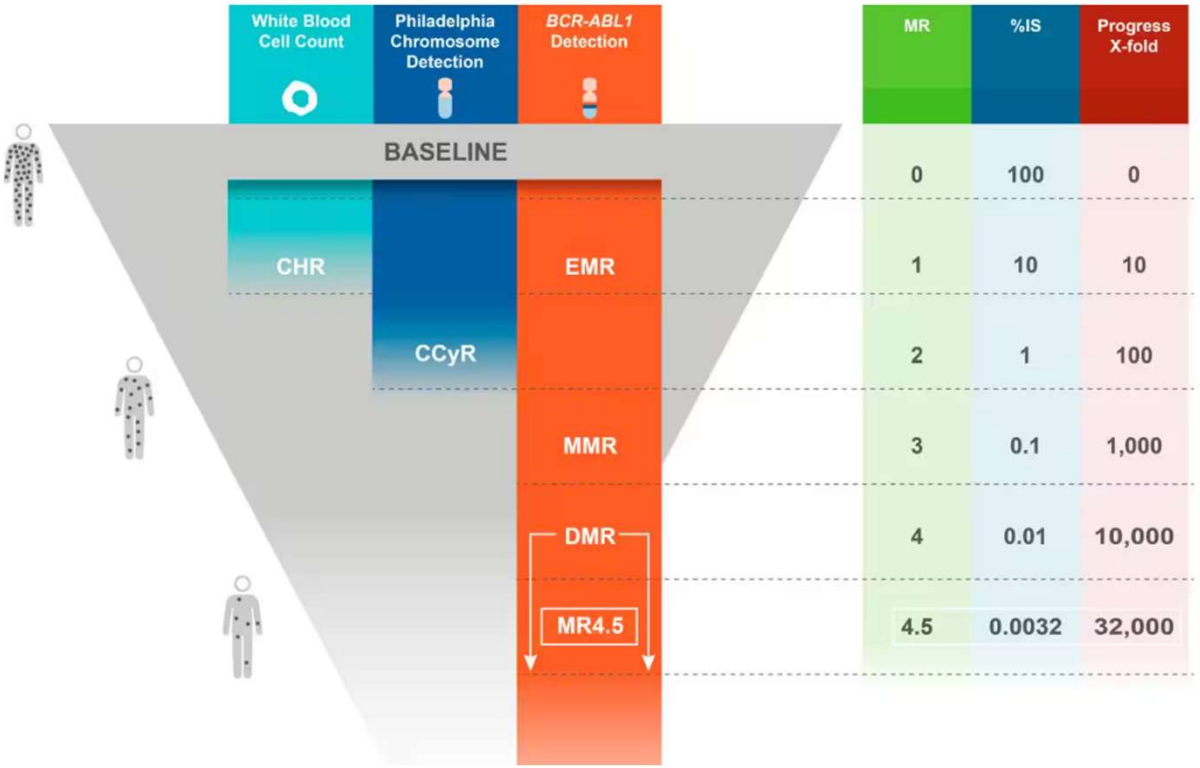
Principais Terapias Dirigidas em Hematologia – Inibidores Tirosina Quinase



BCR::ABL1 (IS)	3 months	6 months	12 months[a]
> 10%	YELLOW	RED	
> 1% – 10%	GREEN		YELLOW
> 0.1% – 1%	GREEN		LIGHT GREEN
≤ 0.1%	GREEN		

Color	Concern	Treatment Team Considerations	Recommendations
RED	TKI-resistant disease	• Evaluate patient adherence and drug interactions • Consider mutational analysis	• Switch to alternate TKI • Evaluate for allogeneic stem cell transplantation
YELLOW	Possible TKI resistance	• Evaluate patient adherence and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic testing to assess for MCyR at 3 months or CCyR at 12 months	• Switch to alternate TKI ***OR*** • Continue same TKI (other than imatinib) ***OR*** • Dose escalation of imatinib (to a max of 800 mg) ***AND*** • Consider evaluation for allogeneic stem cell transplantation
LIGHT GREEN	TKI-sensitive disease	• If treatment goal is long-term survival: ≤1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient[b]
GREEN	TKI-sensitive disease	• Monitor response and manage side effects	• Continue same TKI[c]

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Principais Terapias Dirigidas em Hematologia – Inibidores Tirosina Quinase

BCR::ABL1 (IS)	3 months	6 months	12 months[n]
>10%[o]	YELLOW	RED	
>1%–10%[p]	GREEN		ORANGE
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	CLINICAL CONSIDERATIONS[r]	RECOMMENDATIONS[r,i]
RED	TKI-resistant disease[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s] • Consider bone marrow cytogenetic analysis to assess additional chromosomal abnormalities (ACAs)	Switch to alternate TKI (CML-5) (other than imatinib) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s]	Switch to alternate TKI (CML-5) or Continue same TKI[o]
ORANGE **NEW**	Possible TKI resistance[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s] • Consider bone marrow cytogenetic analysis to assess for CCyR at 12 mo	Consider switch to alternate TKI[p] (CML-5) or Continue the same TKI if CCyR is achieved
LIGHT GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • If treatment goal is long-term survival: ≤1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient[q,t]
GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • Monitor response (CML-G)	Continue same TKI[u]

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THERAPY	CONTRAINDICATED MUTATIONS[aa]
Asciminib	A337T, P465S, M244V, or F359V/I/C
Bosutinib	T315I, V299L, G250E, or F317L[bb]
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib or allogeneic HCT (CML-6)	None[cc]

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Principais Terapias Dirigidas em Hematologia – Inibidores Tirosina Quinase

MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

Test	Recommendation
Hematologic	• CBC every 1–2 weeks for the first 1–2 months (or until stable normalization of blood counts) and thereafter as indicated based on the persistence of cytopenias
Bone marrow cytogenetics[1]	• At diagnosis • Response milestones not reached • Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1%
qPCR using IS	• At diagnosis • Every 3 months after initiating treatment. After *BCR::ABL1* (IS) ≤1% (MR2.0)[2] has been achieved, every 3 months for 2 years and every 3–6 months thereafter • If there is a 1-log increase in *BCR::ABL1* transcript levels with MMR, qPCR should be repeated in 1–3 months
BCR::ABL1 kinase domain mutation analysis[3]	• CP-CML ▸ Response milestones not reached ◊ Any sign of loss of hematologic response ◊ Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1% ◊ 1-log increase in *BCR::ABL1* transcript levels and loss of MMR • Disease progression to AP-CML or BP-CML[3]

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Os critérios de resposta são diferentes de patologia para patologia

Habitualmente avaliado por resposta PET ou TAC

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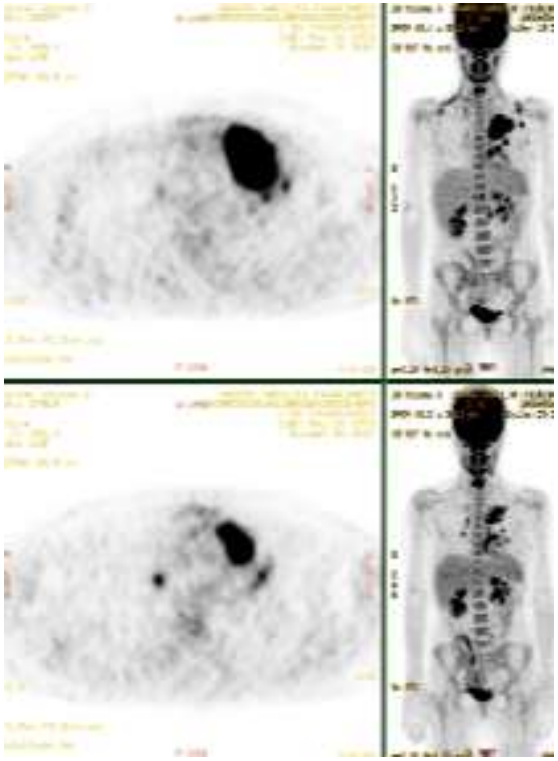

Rituximab para Linfoma Folicular, Manto, B difuso, marginal, LLC…

Obinutuzumab para LLC (1ª linha)

Venetoclax para LLC (1ª linha e RR)

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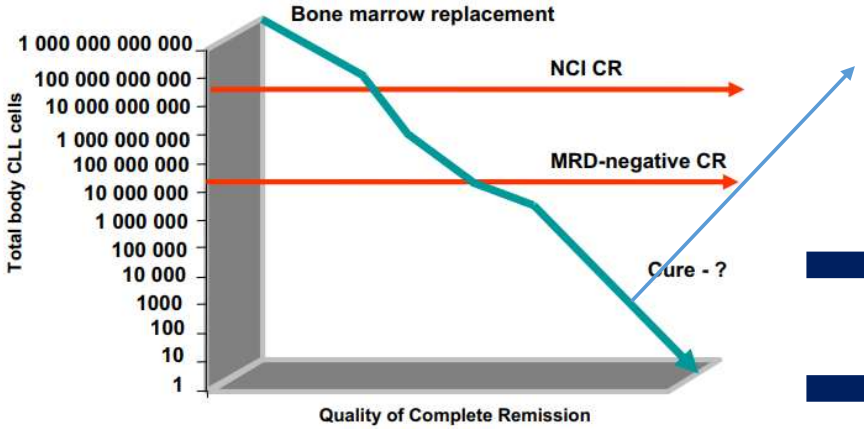
Principais Terapias Dirigidas em Hematologia – MoAb AntiCD20 ou IBCL2

Conceito de DRM (doença residual mensurável)



- Doença residual mensurável INDETETÁVEL
- Doença residual mensurável NEGATIVA

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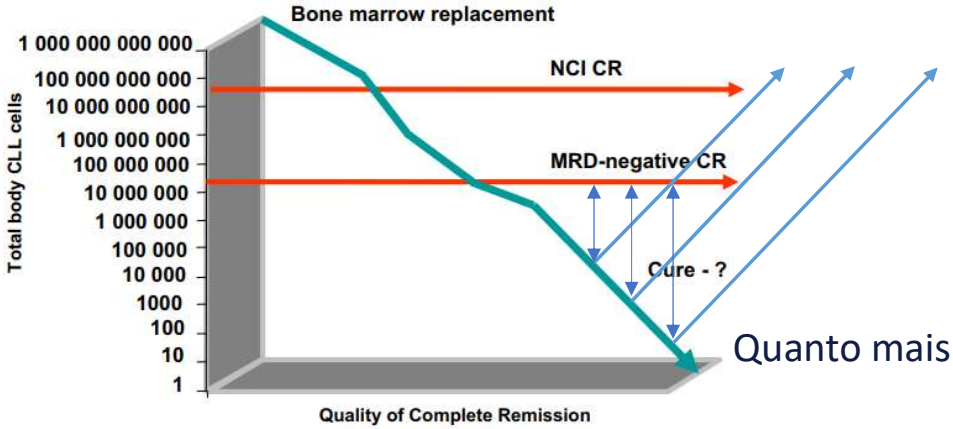

Quanto mais profunda for a resposta… Maior a durabilidade da remissão

Profundidade de resposta relacionada com duração da remissão?

Cinética da DRM… em LLC e MM (ainda experimental)

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Principais Terapias Dirigidas em Hematologia – DRM

Conceito de DRM (doença residual mensurável) – Onde se aplica?

	Multi-color flow cytometry	qPCR for fusion genes	ASO-qPCR for IG/TR genes	High-throughput NGS
Sensitivity	10^{-4}	10^{-4} to 10^{-5}	10^{-4} to 10^{-5}	10^{-6}
Applicability	>90%	40-50%	90-95%	>90%
Advantages	- Rapid - Relatively inexpensive - DfN method does not require access to diagnostic specimen	- Sensitive - Standard primers used for specific fusions	- Sensitive - Applicable to most patients - Standardized guidelines in Europe	- Very sensitive - Applicable to almost all patients - Clone-unbiased (can track multiple clones and evolution) - Only US FDA-approved assay (ClonoSEQ) - Data for MRD use in peripheral blood
Limitations	- Variable sensitivity - Requires technical expertise - Fresh cells required - Less standardized - Immunophenotypic shifts can lead to false negative results	- Not applicable to all patients	- Time-consuming - Expensive - Relies on pre-treatment sample - Requires extensive experience and labor	- Expensive - Longer turn-around time than MFC - Requires diagnostic pre-treatment sample

ALL: acute lymphoblastic leukemia; ASO: allele-specific oligonucleotide; DfN: different-from-normal; FDA: Food and Drug Administration; IG: immunoglobulin; MFC. multicolor flow cytometry; NGS, next-generation sequencing; qPCR, quantitative polymerase chain reaction; TCR, T-cell receptor.

Haematologica 2022, Measurable residual disease in acute lymphoblastic leukemia: methods and clinical context in adult patients

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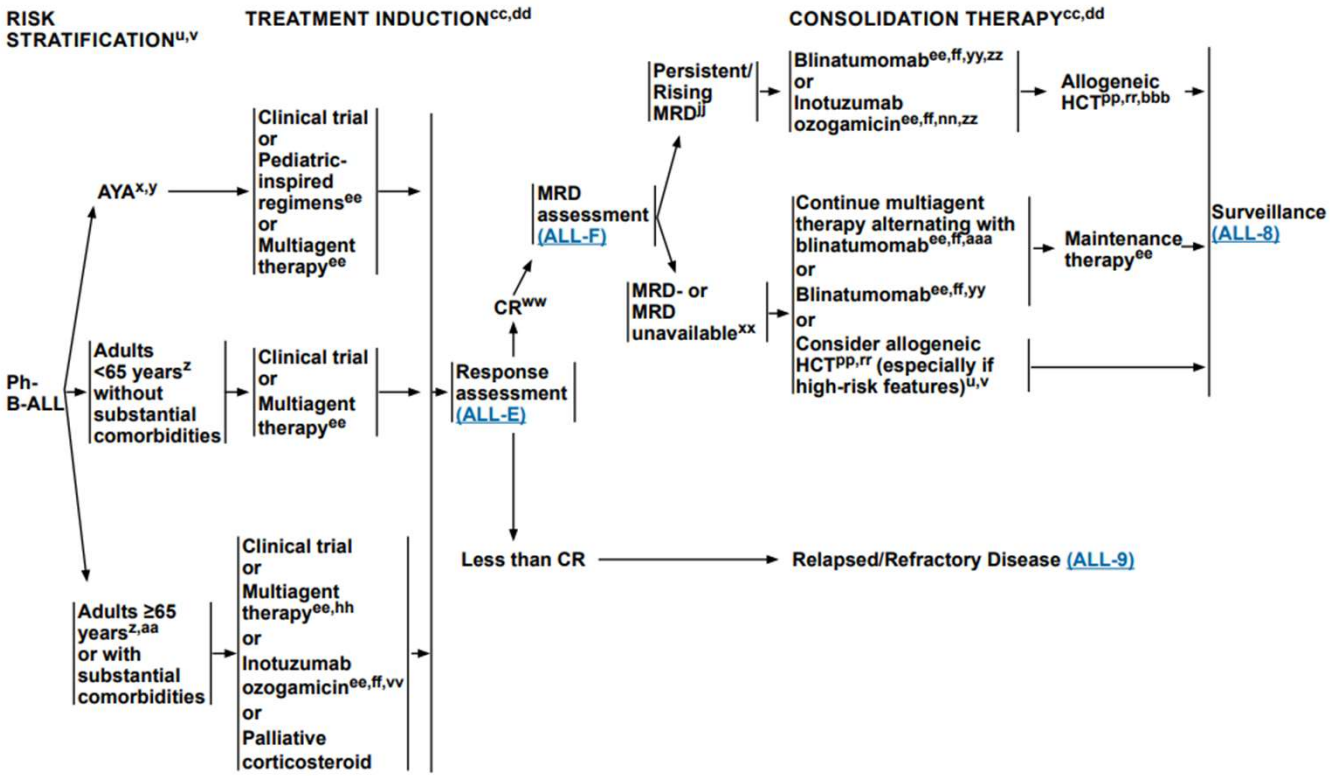
Principais Terapias Dirigidas em Hematologia – DRM



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Principais Terapias Dirigidas em Hematologia – DRM

MINIMAL/MEASURABLE RESIDUAL DISEASE ASSESSMENT

- MRD refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods or standard immunophenotyping.
- MRD quantification is an essential component of patient evaluation over the course of sequential ALL therapy.
- Studies in children and adults with ALL have demonstrated a strong correlation between the presence of MRD during remission and risk for relapse, as well as the prognostic significance of MRD measurements after induction and consolidation therapy.[1]
- The preferred sample for MRD assessment is the first small volume (of up to 3 mL) pull of the bone marrow aspirate, if feasible.
- If validated MRD assessment technology with appropriate sensitivity (at least 10^{-4}) is not available locally, there are commercially available tests.
- The most frequently used methods for MRD quantification include an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and T-cell receptor (TCR) loci (does not require patient-specific primers) (preferred), flow cytometry assays[2,3] specifically designed to detect abnormal MRD immunophenotypes at low frequency, real-time quantitative PCR (RQ-PCR) assays (eg, clonally rearranged Ig, TCR genes), and RT-qPCR assays (eg, *BCR::ABL1*).
- High-sensitivity flow cytometry with validated analysis algorithms or PCR methods can quantify leukemic cells at a sensitivity threshold of 1×10^{-4} (0.01%) bone marrow mononuclear cells (MNCs).[2,3] NGS and some PCR methods can detect leukemic cells at a sensitivity threshold of 1×10^{-6} (0.0001%) MNCs.[4,5]
  - If MRD is negative by flow cytometry, an FDA-approved NGS assay should be considered to confirm negativity.
- For flow cytometric quantification of MRD, notify laboratory performing the assay if the patient has received immunotherapy (such as monoclonal antibodies, bispecific antibodies, or CAR T cells) or HCT as these treatments can affect interpretation. Such testing should be performed in a laboratory with experience performing MRD testing in this clinical setting.
- Timing of MRD assessment:
  - Upon completion of initial induction.
  - End of consolidation
  - Additional time points should be guided by the regimen used and risk features.
  - Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.
  - For some techniques, a baseline sample (ie, prior to treatment) is needed to characterize the leukemic clone for subsequent MRD assessment.

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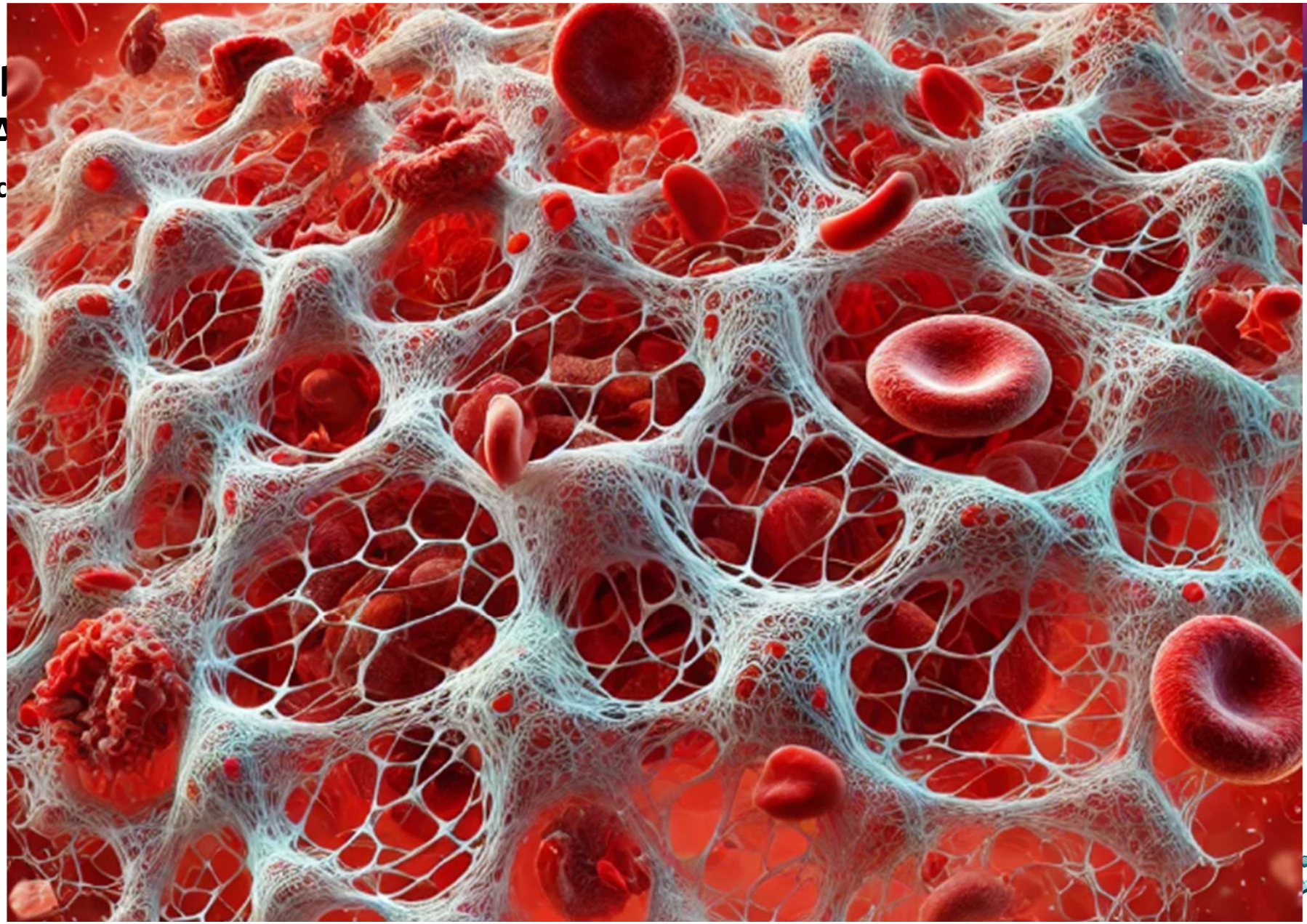

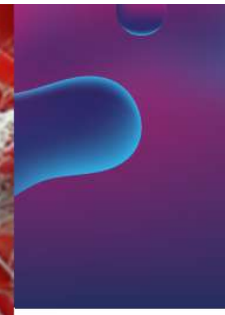

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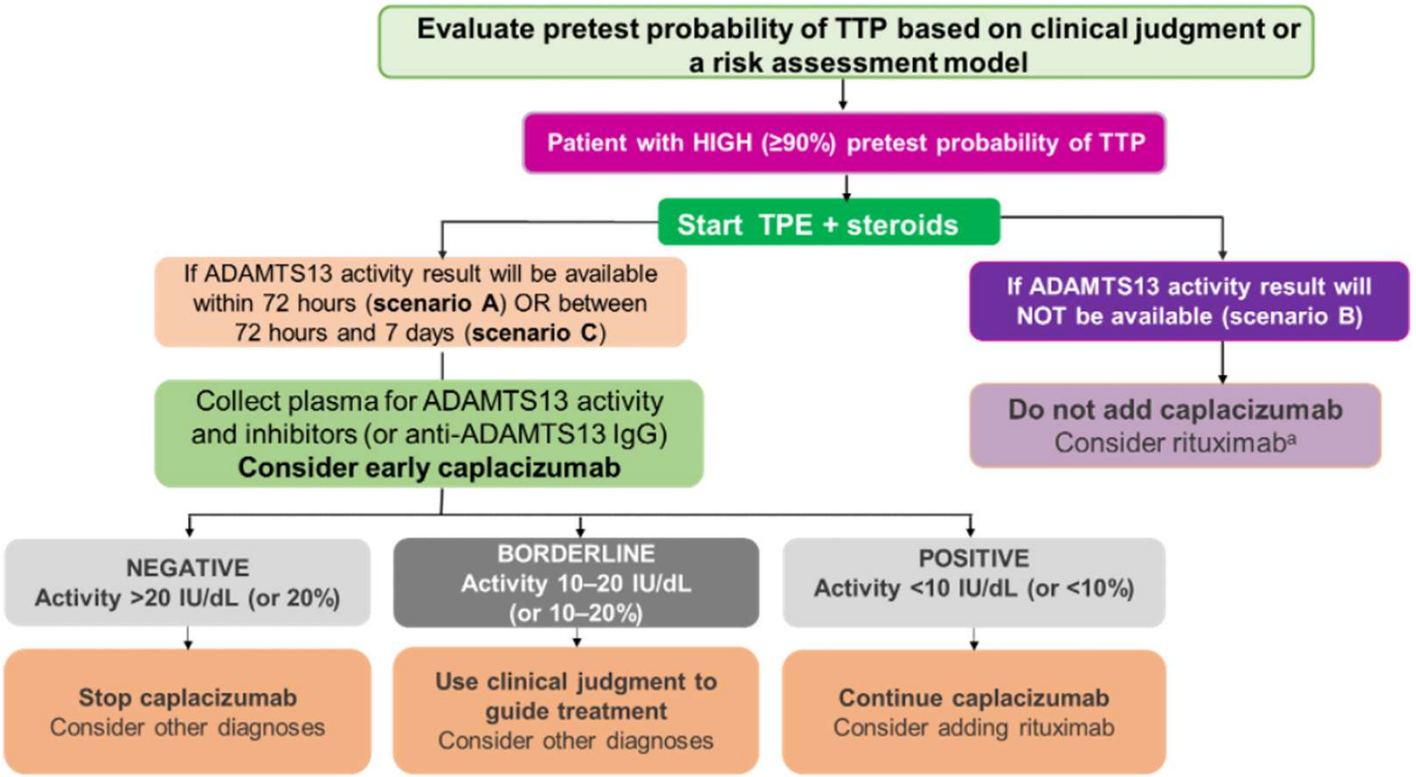
Principais Terapias Dirigidas em Hematologia – E actividade de doença?



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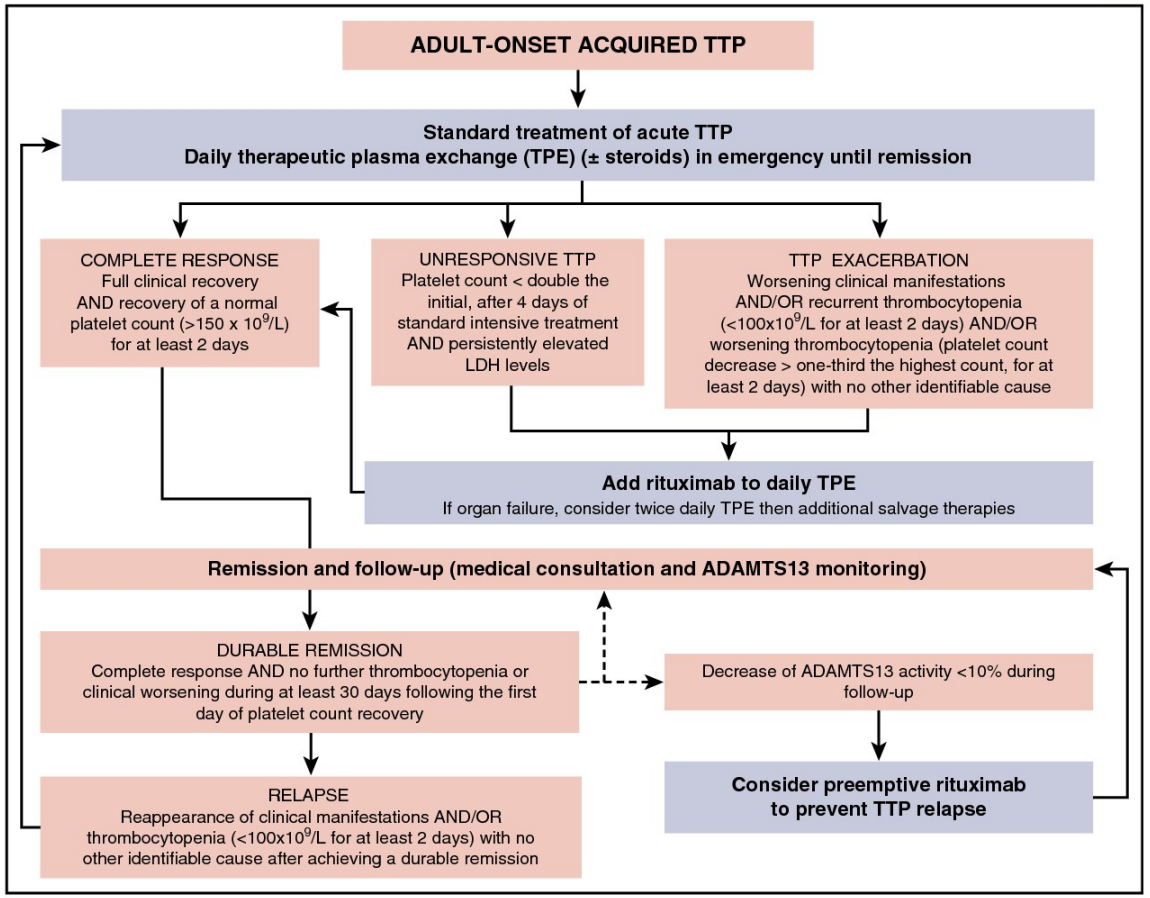
Principais Terapias Dirigidas em Hematologia – E actividade de doença?



gure 5. Flowchart for the therapeutic management of adult-onset acquired TTP. The standard treatment of adult-onset acute acquired TTP is daily therapeutic plasm

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Discussão

Acessibilidade?

Protocolos?

Adequação aos ensaios clínicos e representatividade clínica?

Realidade da monitorização ajustada à prática clínica?

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