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2020 NIH Chronic GvHD Consensus Project

WG2b: Preemptive Therapy of Chronic GVHD

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Introduction

- Preemptive therapy
  - Therapeutic intervention
    - Local or systemic
  - Distinct from pre-transplant prophylaxis
    - Delivered post-transplant (HCT)
    - Targeted to those at high risk for cGVHD development
  - Risk assessment
    - Clinical factors
      - Early non-diagnostic features
      - Connection to WG2a (early diagnosis)
    - Risk assignment biomarkers
      - Identify risk for subsequent cGVHD development among those without clinically diagnosed cGVHD

Opportunities and Challenges

- Potential advantage
  - Deliver intervention to those with high risk of cGVHD development

- Core knowledge gaps
  - Defining a population at risk
    - Risk assignment biomarkers
    - High positive predictive value
  - Prioritizing interventions
    - Mechanistic rationale
    - Safe, targeted, appropriately timed, logistically feasible
  - Trial design
    - Launch and advance this currently untested research area
    - Endpoints, trial design

Defining population at risk: Current state

- Clinical factors
  - Large body of evidence supporting clinical cGVHD risk factors
    - Mostly pre-HCT factors
      - Greatest relevance to initial prophylaxis (WG1)
      - Identify population with greater baseline risk (or inform combined risk models)
    - Exception
      - Acute GVHD development post-HCT

- Risk assignment biomarkers
  - Numerous candidate markers (mostly cell or plasma based)
  - Most not adequately validated
  - Insufficient PPV (and NPV) to justify preemptive intervention
    - Inherent risks, patient acceptance

Defining population at risk: Opportunities

- Clinical factors
  - Early/pre-diagnostic clinical features
  - Identified through longitudinal observational studies
  - Selected by high PPV (may form composite model with biomarkers)

- Risk assignment biomarkers
  - Identified, validated through prospective multi-institutional studies
  - Require comprehensive clinical evaluation and documentation of cGVHD
  - Translatable to clinical practice

- Scope
  - Primary focus: Systemic markers of overall cGVHD syndrome
  - Considerations:
    - Organ-specific markers of organ-specific cGVHD development
    - Diverse range of possible candidates (target tissues, metabolome, microbiome)
    - Change in biomarker values from longitudinal sampling

Preemptive interventions: Current state

- Insight into cGVHD biology
  - Growing body of knowledge suggests targets for intervention
  - Challenges:
    - Multiple aberrant immunologic pathways
      - May threaten success of focused interventions
    - Variation
      - Individual subjects
      - Downstream clinical sub-groups

- Available cGVHD therapeutics
  - Multiple targeted agents now available
  - Tested in largely advanced, refractory cGVHD to date
  - Suggest activity in cGVHD therapy, yet untested for preemption
    - Unique challenges in delivering early post-HCT
    - Need durable tolerability (anticipate prolonged therapy)

Preemptive interventions: Opportunities

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Therapeutic targets

- Thymic dysfunction
- Th17/Th1 differentiation
- Tfh differentiation
- Germinal B cell expansion
- Allo-antibody generation
- Tissue M2 macrophage accumulation
- Tissue fibrogenesis

Preemptive interventions: Opportunities

Feature	Considerations
Biologic rationale	- Selection of interventions that target pathways implicated in cGVHD pathogenesis
Safety	- Low toxicity, limited interactions with concurrent post-HCT medications - Risk profile of intervention commensurate with severity of outcome to be prevented - When possible, minimize disruption of graft vs. malignancy effects
Tolerability, Cost	- Assure intervention adherence - Allow prolonged therapy to prevent late occurring cGVHD events - Patient and health care system able to afford treatment
Efficacy	- Prioritization of agents with demonstrated activity in cGVHD therapy or allied human immune mediated disorders
Transportability	- Logistics of delivering therapy permit dissemination - Orally available agents generally preferred

Preemptive trial design: Current state

- Preemptive therapy
  - Has precedent in other areas of medicine (e.g. CMV)
  - Untested post-HCT for cGVHD

- Major questions
  - Required preliminary data
    - Moving an agent tested in advanced cGVHD therapy to preemptive space
  - Trial design considerations
    - Historical benchmark for single-arm trials, comparative studies
  - Eligibility criteria
    - Clinical/biomarker risk assignment
  - Clinical endpoints
    - Local vs. systemic success definitions
    - Short- vs. long-term outcome measures

Preemptive trial design: Opportunities

- Trial design
  - Single arm phase II trials
    - State firm historical benchmark (cGVHD Consortium longitudinal study of IMD)
    - No single PPV (consider risk of intervention/severity of outcome)
    - Topical vs. systemic interventions: Allied with clearly stated outcome measures
    - Feasibility/agility
      - Shorter-term outcome measures (incidence of moderate/severe within 6 months)
      - Secondary outcomes (durable freedom from cGVHD, off IS)
  - Other trial designs
    - Randomized phase II (rationale for testing multiple agents)
  - Alternative designs
    - Allow sequential testing of multiple agents in series
  - Requirements across all potential designs
    - Academic/industry partnership
    - Multicenter collaboration

Priority next steps

- Risk assignment markers
  - Identified and validated through prospective longitudinal studies
  - Foundational for progress in preemptive therapy
- Preemptive therapy trials
  - Early phase trials conducted using safe, tolerable agents with rationale
  - Eligibility based on robust risk assignment markers
  - Clearly stated success metrics
  - Attention to safety and malignancy relapse
- Subsequently
  - Larger, more definitive trials
  - Long-term success metrics

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Critique

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Robert Soiffer, M.D., Dana Farber Cancer Institute

Response to critique

- Defining population at risk
  - Nuances of approach
    - Influence of prevalence on PPV
    - Clinical + biomarkers for risk assignment
  - Currently informative studies
    - CATCH (cGVHD Consortium), ABLE 2.0 / PBMTC 1901
      - Design, sampling, feasibility, cost considerations
- Interventions
  - Targeted interventions to dominant pathways within subjects
  - Systemic cGVHD vs. organ-specific
- Study design
  - Alternative approaches
    - Adaptive platform design
  - Outcomes
    - PRO, return to work, symptom burden

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Audience Discussion