Opportunistic Infections (OIs) in Patients with Hematologic Malignancies (HM) Treated with Bruton’s Tyrosine Kinase (BTK) and Phosphoinositide 3 Kinase (PI3K) Inhibitors: An 8-Year Retrospective Cohort Study

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Accessibility
Background. Lymphodepletion chemotherapy followed by CD19-targeted chimeric antigen receptor-modified T (CAR-T) cell infusion is a novel treatment for refractory B cell malignancies. Infectious complications of CD19 CAR-T cell immunotherapy have not been studied.

Methods. We described infections between 0–28 and 29–90 days after CD19 CAR-T cell infusion in patients with relapsed and/or refractory CD19+ malignancies treated in a phase 1/2 open-label trial (NCT01865617). We used Poisson and Cox regression to evaluate pre- and post-CAR-T cell infusion risk factors for infection, respectively. Patients receiving anti-tumor therapy after CAR-T cell infusion were censored.

Results. The cohort included 133 patients with acute lymphoblastic leukemia (ALL, n = 47), chronic lymphocytic leukemia (CLL, n = 24), and non-Hodgkin lymphoma (NHL, n = 62). There were 63 infections in 30 patients (22.6%) within 28 days after CAR-T cell infusion with a mean of 1.19 infections per 100 days-at-risk (Fig 1). Among 119 patients followed at our center from day 29–90, there were a mean of 0.67 infections per 100 days-at-risk. Six patients (4.5%) developed invasive fungal infections. Infection was a primary or secondary cause of death in 2 patients (1.5%). Pre-CAR-T cell infusion factors that were associated with more infections included a diagnosis of ALL, >3 prior chemotherapeutic regimens, and highest CAR-T cell dose (2 x 10^6 cells/kg) (p values <0.001). After CAR-T cell infusion, severe (grade 4–5) cytokine release syndrome (CRS) was associated with a >3-fold increased hazard for infection (P <0.001) and was the primary risk factor. Patients receiving an optimized lymphodepletion and CAR-T cell dose regimen had a mean of 0.74 and 0.63 infections per 100 days-at-risk between days 0–28 and 29–90 with no fatal infections.

Conclusion. The incidence of infectious complications after CD19 CAR-T cell immunotherapy was similar to that seen in patients with relapsed and/or refractory B cell malignancies receiving salvage chemotherapy. Patients with more prior chemotherapy regimens and severe CRS after CAR-T cell infusion had the highest risk for infection. Fatal infections were rare, and patients receiving optimized regimens had fewer infectious complications.

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2350. Opportunistic Infections (OIs) in Patients with Hematologic Malignancies (HM) Treated with Bruton’s Tyrosine Kinase (BTK) and Phosphoinositide 3 Kinase (PI3K) Inhibitors: An 8-Year Retrospective Cohort Study

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Background. BTK and PI3K inhibitors are increasingly used for treatment in patients with HM. OIs when these agents were used as first line therapy signaled an increased level of immunosuppression beyond what was expected from the mechanism of action of these drugs. The epidemiology of OIs in the setting of BTK and PI3K inhibitor use has not been characterized.

Methods. We retrospectively studied a cohort of patients with HM who received BTK (ibrutinib, acalabrutinib, spebrutinib) or PI3K (idelalisib, duvelisib, TGR-1202) as part of clinical trials at our center between March 2008 and November 2016. Patients were followed up until April 30, 2017. Incident infectious complications were recorded. Cohort baseline characteristics, underlying malignancy, stage of disease, type of therapy and use of antimicrobial prophylaxis were recorded.

Results. 148 patients who received BTK or PI3K inhibitors as first or second line therapy were included in the study. Median age was 64.5 years, 32% were female, 95.9% had chronic lymphocytic leukemia (CLL), 4.1% had Non-Hodgkin Lymphoma (NHL). Thirty-six percent received BTK inhibitors and 37% received PI3K inhibitors as first line therapy. Pneumocystis and HSV/VZV prophylaxis were used in 82.4% and 85.8% of patients, respectively. Twenty-seven OIs occurred in 24 patients. The most common OIs were pneumocystis (7), aspergillus (5) HSV (3), VZV (3), CMV (2), Cryptococcal meningitis (2), candidiasis (2) and other invasive mold infections (3). Seventy-one patients (48%) had infectious episodes not considered OIs. Median time to onset of OIs after start of therapy was 78 days (range, 6–323). Twelve OIs (8.1%) occurred after first line therapy with BTK inhibitors, 11 OIs (7.4%) occurred after first line PI3K inhibitors.

Conclusion. The use of BTK and PI3K inhibitors as first or second line treatment for CLL or NHL are associated with incident OIs. Clinical awareness of these complications and the use of adequate prophylaxis and/or monitoring strategies are essential in preventing serious OIs in this population.

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2351. Change in Clinical Management Associated with Flexible Bronchoscopy and Bronchoalveolar Lavage in Hematopoietic Stem Cell Transplant Recipients with New Pulmonary Infiltrates

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Background. Pulmonary complications occur in 60% of hematopoietic stem cell transplant (HSCT) recipients with significant morbidity and mortality. Bronchoscopy with bronchoalveolar lavage (BAL) is an important diagnostic tool, but yield can be variable. The aim of this study was to investigate the utility of BAL in HSCT patients with new pulmonary infiltrates and determine factors associated with higher BAL yield.

Methods. Retrospective review of BAL results from January 2014 to July 2016. Included first bronchoscopy for HSCT patients over 18 years of age. Positive BAL was defined by positive culture (bacterial, fungal, mycobacteria), viral PCR, elevated cytologic galactomannan antigen (AGA), and cytologic. Logistic regression analysis was performed.

Results. 54 HSCT recipients were included: 93% allogeneic, 34% neutropenic, 39% on predniisons, 59% on supplemental oxygen, 8% receiving mechanical ventilation. 45% with multilobar infiltrates, 92% on antimicrobials (antibacterial 83%, antifungal 92%, antiviral 13%). 65% had positive BAL (23/54 bacterial, 16/54 elevated AGA, 6/54 fungal, 14/54 viral PCR, 1/54 mycobacteria). Median time to BAL from HSCT was 7.5 months. Not on levofloxacin prophylaxis (P = 0.004), not on MV (P = 0.037), duration donor were positive associated with positive BAL results. Positive bacterial BAL culture was predictive of antibacterial escalation (P = 0.001). Elevated BAL AGA was associated with antifungal escalation and antibacterial de-escalation (P = 0.012). Antiviral initiation was more likely with positive BAL (P = 0.002). Antifungal de-escalation (P = 0.047) and antiviral initiation (P = 0.010) were more likely with negative BAL. 6 month mortality was 41%, and more likely with positive bacterial BAL culture (P = 0.046). Overall positive BAL was not predictive of mortality.

Conclusion. Bronchoscopy with BAL assisted in making critical management changes, elevated AGA with antifungal escalation and antibacterial de-escalation; and negative BAL with prednisone initiation and antifungal de-escalation. Unrelated donors, patients not on levofloxacin, or not on MV were more likely to have a positive BAL. Antimicrobial use likely reduced diagnostic yield for bacterial pathogens. Overall 6 month mortality was high, especially among those with bacterial infections.