HAEMATOLOGICAL CANCER

REACH2: ruxolitinib for refractory aGvHD

Graft-versus-host disease (GvHD) occurs in ~50% of patients who undergo allogeneic haematopoietic stem cell transplantation and results in considerable morbidity and mortality. In May 2019, the FDA approved the JAK1/2 inhibitor ruxolitinib for patients ≥12 years of age with glucocorticoid-refractory acute GvHD (aGvHD) based on the results of the single-arm phase II REACH1 trial. Now, a year later, data from the phase III REACH2 trial confirm the benefits of ruxolitinib in this setting.

In REACH2, 309 patients were assigned (1:1) to receive ruxolitinib or investigator's choice of one of nine commonly used treatments for steroid-refractory aGvHD. The objective response rate (ORR) at day 28 was 62% with ruxolitinib versus 39% in the control group (P<0.001), with complete response rates of 34% versus 19%. The percentage difference in ORR between the treatment groups was fairly consistent across aGvHD grades (18–30%) and was greatest for grade IV disease. The durable ORR at day 56 was 40% versus 22% (P<0.001). The proportion of patients with loss of response at 6 months (10% versus 39%), failure-free survival (median 5 months versus 1 month; HR 0.46, 95% CI 0.35–0.60) and overall survival (median 11.1 months versus 6.5 months; HR 0.83, 95% CI 0.60–1.15) also favoured ruxolitinib.

With regard to toxicity, increased day-28 rates of any-grade thrombocytopenia and cytomegalovirus infection with ruxolitinib were the most obvious differences (33% and 26%, respectively, compared with 18% and 21% in the control group). However, more patients in the ruxolitinib group required dose modifications (38% versus 9%) or discontinued treatment (11% versus 5%).

Ruxolitinib is the only new treatment for aGvHD to be approved in the past 30 years, despite trials of numerous agents. REACH2, the first phase III trial demonstrating the superiority of any aGvHD treatment, corroborates the results of REACH1 and the use of ruxolitinib in the ~60% of patients with aGvHD that is unresponsive to steroids.

David Killock

ORIGINAL ARTICLE Zeiser, R. et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1917635 (2020)

GASTROINTESTINAL CANCER

Activity of regorafenib plus nivolumab

The multi-kinase inhibitor regorafenib has shown immunomodulatory activity when combined with immune-checkpoint inhibition (ICI) in mouse models of colorectal cancer (CRC); in humans, this synergistic activity could help to overcome lack of response to ICI. Now, data from a phase I trial provide early evidence of the efficacy of regorafenib in combination with nivolumab in patients with advanced-stage gastric cancer or CRC.

All patients (25 with gastric cancer and 25 with CRC) had previously received ≥2 lines of treatment (96% of them with anti-angiogenic agents other than regorafenib), and all had microsatellite stable or mismatch repair-proficient tumours, except one with microsatellite instability (MSI)-high CRC. These patients received regorafenib 80–160 mg plus nivolumab 3 mg/kg.

The maximum-tolerated and optimal doses of regorafenib were established as 120 mg and 80 mg, respectively. The incidence of grade ≥3 adverse events was 44% and 27% at these dose levels, respectively, including rash in 20% and 0% of patients. One patient with gastric cancer died from treatment-related diabetic ketoacidosis.

The objective response rate was 44% in patients with gastric cancer and 36% in those with CRC (including the patient with MSI-high CRC). Median progression-free survival and overall survival durations were 5.6 months and 12.3 months, respectively, for patients with gastric cancer, and 7.9 months and not reached in those with CRC.

The survival durations with combination therapy in this trial are longer than those reported with nivolumab or regorafenib monotherapy for gastric cancer or CRC in other trials. Nevertheless, direct comparisons can only be made in large randomized controlled trials, the results of which are awaited to determine whether regorafenib plus nivolumab could be a new treatment option for patients with advanced-stage gastric cancer or CRC.

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ORIGINAL ARTICLE Fukuoka, S. et al. Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase Ib trial (REGONIVO, EPOC1603). *J. Clin. Oncol.* https://doi.org/10.1200/JCO.19.03296 (2020)

EPIDEMIOLOGY

COVID-19: more evidence emerges

Emerging reports suggest that patients with cancer are more vulnerable to SARS-CoV-2 infection and have more severe coronavirus disease 2019 (COVID-19) symptoms. Nonetheless, and perhaps understandably, many of these reports have notable limitations, including small cohort sizes and/or a lack of age and comorbidity-matched control groups. Now, a retrospective analysis of data from 105 patients with cancer and COVID-19 plus 536 age and comorbidity-matched individuals without cancer with COVID-19 provides new evidence in this area.

Patients with cancer included those with lung cancer (22), gastro-intestinal cancers (13), breast cancer, thyroid cancer (11 for both groups) and haematological malignancies (9). Of these patients, 54.3% were diagnosed with cancer within the 12 months prior to admission with COVID-19, and 16.2% had metastatic (stage IV) disease. Patients with cancer and those without were matched in terms of median age and age distribution and incidence of common comorbidities, including, among others, hypertension (28.6% versus 24.3%), cardiovascular disease (11.4% versus 7.3%) and diabetes (6.7% versus 5.4%).

Patients with cancer and those without had similar COVID-19 symptom profiles at initial presentation, albeit with a lower prevalence of fever (64.8% versus 74.8%; P = 0.04) and a higher prevalence of chest distress (14.3% versus 6.2%; P = 0.02). Nonetheless, patients with cancer had a higher risk of death (OR 2.34, 95% CI 1.15– 4.77; P = 0.03), intensive care unit admission (OR 2.84, 95% CI 1.59–5.08; P < 0.01) or having at least one severe or critical COVID-19 symptom (OR 2.79, 95% CI 1.74–4.41; P < 0.01). Patients with stage IV disease had a notably higher risk of death from COVID-19 (OR 5.58, 95% CI 1.71–18.23; P = 0.01), and when data from these patients were removed from the analysis, this difference in risk became statistically insignificant.

In conclusion, these data provide further evidence that patients with cancer have worse COVID-19 outcomes, and the inclusion of a control group strengthens this evidence. Nonetheless, larger datasets are needed to determine how these risks apply to each patient with cancer.

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ORIGINAL ARTICLE Dai, M. et al. Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID-19 outbreak. *Cancer Discov.* https://doi.org/10.1158/2159-8290.CD-20-0422 (2020)