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General AML

Nivolumab as an addition to frontline therapy of AML in younger patients

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T cells in the bone marrow of patients with acute myeloid leukemia (AML) over-express PD-1 leading to anti-tumor activity,[1] but checkpoint inhibitors have been shown to overcome this in mouse models.[2] Cytarabine is known to suppress the expression of PD-1 allowing cytotoxic T lymphocytes (CTLs) to attack AML cells more efficiently, while idarubicin causes the release of antigens which prime CTLs to further promote anti-tumor activity. The combination of both idarubicin and cytarabine has resulted in remission rates of 80%, but despite this high initial response, only 30–50% of patients with AML are disease-free long-term[2]. Alterations of dosing and treatment schedules of this standard induction method have had a limited effect on this outcome.

Professor Farhad Ravandi, The University of Texas MD Anderson Cancer Center, Houston, TX, US, and colleagues conducted a phase II trial to assess nivolumab in combination with idarubicin and cytarabine as a frontline treatment for patients with newly diagnosed AML. They hypothesised that the addition of a further anti-PD-1 agent may improve remission duration by enhancing the anti-tumor activity of CTLs[2]. Professor Ravandi previously presented this data at the 59th American Society of Hematology (ASH) Annual Meeting and Exposition in 2017 in Atlanta (our interview with him can be found here).

Study design

In this single-arm phase II part of the phase I/II study (NCT02464657), 44 patients aged 18–60 years (>60 years if eligible for intensive chemotherapy) with newly diagnosed AML (n=42) or high-risk myelodysplastic syndrome (n=2) who had an Eastern Cooperative Oncology Group Performance (ECOG) status of 0–2 were eligible for inclusion induction treatment.

Induction treatment included a 1.5g/m^2, 24-hour infusion of cytarabine daily on Days 1–4 (three days only for patients >60 years), alongside 12mg/m^2 daily on days 1–3 of idarubicin. Nivolumab was then given on Day 24 at a dose of 3mg/kg which was repeated every two weeks for a year in responders. Initially, a run-in phase was performed with patients with relapsed AML (n=3) who received 1mg/kg nivolumab with idarubicin and cytarabine and no toxicity was observed.

Responders were given consolidation cycles of attenuated doses of idarubicin and cytarabine (up to five) or allogeneic hematopoietic stem cell transplantation (allo-HSCT). The primary endpoint was event-free survival (EFS), with relapse-free survival (RFS) and overall survival (OS) as secondary outcomes. The trial would have stopped if the median EFS was less than seven months or if there was significant toxicity associated with nivolumab use (>10%) at one year.

Key findings

- Twenty-two (50%) patients had an adverse genetic risk, as defined by the European Leukemia Network classification (ELN)[3], of more than one mutation. The most common mutations were *RAS, IDH2, TP53, DNMT3A* and
- Nine (20%) patients were older than 60 years
- Thirty-five (80%) of patients achieved an objective response

  - Twenty-eight (64%) had a complete response (CR), five (12%) had CR with platelet recovery, one (2%) had CR with incomplete platelet recovery, and one (2%) had a partial response (PR)
  - In the 12 patients defined as having a 'poor risk mutation profile' (as defined by the ELN), 67% achieved CR
  - *TP53* mutations seemed to be associated with significantly lower responses, whereas cytogenetics, ELN genetic risk, and secondary or therapy-related AML were not predictors for response
- At the median follow up of 17.25 months, 55% of patients were alive
- Median EFS was not reached at median follow up of 17.25 months
- Median RFS of responders was 18.54 months (95% CI, 8.20–23.22)
- Median OS was 18.54 months (95% CI, 10.81–81)
- A total of 19 (43%) patients with response went on to receive allo-HSCT
  - Median OS was 25 months
  - EFS had not been reached
  - Thirteen (68%) had graft-*versus*-host disease (GvHD), eight responded to treatment when compared with patients who continued on the consolidation cycles of idarubicin, cytarabine and nivolumab
  - OS and EFS were similar with a trend for worse RFS
- There were no nivolumab treatment-associated deaths (there were three deaths, one from pneumonia, one from intracranial haemorrhage and one from early disease progression, all not considered to be related to the study drug)
- Bone marrow immune marker analysis found that non-responders had a significantly higher percentage of PD-1 and TIM-3 expressing CD4-positive T effector cells ($P = 0.042$)
- Adverse events are detailed in Table 1

Table 1: Adverse events regardless of causality

	Grade 1–2 **n (%)**	**Grade 3** **n (%)**	**Grade 4** **n (%)**
Nausea	1 (2)	1 (2)	0
Diarrhea	3 (7)	7 (16)	0
Mucositis or stomatitis	1 (2)	0	0
Muscle weakness	0	1 (2)	0

Syncope	0	1 (2)	0
Elevated transaminases	3 (5)	1 (2)	0
Elevated bilirubin	0	1 (2)	0
Febrile Neutropenia	1 (2)	13 (30)	1 (2)
Rash	1 (2)	2 (5)	0
Pneumonitis	1 (2)	0	0
Colitis	1 (2)	1 (2)	1 (2)
Pancreatitis	1 (2)	1 (2)	0
Cholecystitis	0	1 (2)	0
Small bowel obstruction	0	1 (2)	0
Thrombosis or embolism	1 (2)	0	0

Despite a small sample size, short follow-up and a lack of comparator population, the study demonstrates that the use of nivolumab alongside idarubicin and cytarabine as an intensified induction therapy in patients with AML (including those over 60 years old) is safe and feasible. Patients undergoing subsequent allo-HSCT showed promising responses and no increase in complications such as severe GvHD. Whether this combination produces similar outcomes compared to standard induction therapy with or without allo-HSCT needs to be confirmed in larger, randomized trials.

References

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3. Döhner H. *et al.,* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017 Jan 26;129(4):424-47. DOI: 1041182/blood-2016-08-733196