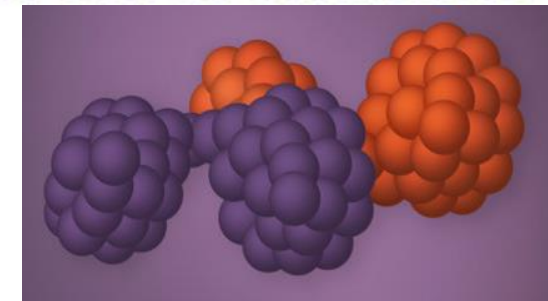# #44: The hematologic toxicities of chemo-immunotherapy compared to chemotherapy alone: a systematic review and meta-analysis

D. Eiger[1], E. Agostinetto[1,2], R. Caparica[1], M.A. Franzoi[1], M. Brandão[1], L. Buisseret[1], A. de Caluwé[1], D. Gimenes[3], S.D. Simon[3,4], N.F. Pondé[5], E. de Azambuja[1]

1 – Academic Trials Promoting Team, Institut Jules Bordet et l'Université Libre de Bruxelles (ULB), Brussels, Belgium; 2 – Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center – IRCCS, Rozzano (Milan), Italy; 3 – Grupo Oncoclinicas do Brasil e Centro Paulista de Oncologia, Sao Paulo, Brazil; 4 – Hospital Israelita Albert Einstein, Sao Paulo, Brazil; 5 – AC Camargo Cancer Center, Sao Paulo, Brazil.

Background

- The association of **immune checkpoint inhibitors (ICI)** with **chemotherapy (I-ChT)** has been shown to be more effective than chemotherapy (ChT) alone for patients with various solid tumours, thus becoming a standard treatment option in multiple settings (1).
- It remains to be determined whether a detrimental interaction between ChT-induced myelotoxicity (2) and ICI-immune-mediated cytopenias (3) occurs, with the potential for **I-ChT to elicit a worse hematologic toxicity profile than ChT alone.**
- In this sense, the aim of this systematic review and meta-analysis is to address this question.

Methods & Objectives

- The **primary objective** was to assess whether I-ChT compared to ChT alone increases the odds of **all-grade (G) anemia, neutropenia, febrile neutropenia (FN) and thrombocytopenia**.
- The **secondary objective** was to assess whether I-ChT compared to ChT alone increases the odds of the same cytopenias grouped by grades (**G1-2, G3-4, and G5**).
- A systematic review using MEDLINE, Cochrane, and conference proceedings (manual selection of studies presented at ASCO and ESMO annual congresses) up to 5 June 2020, with restriction to English language, was performed in accordance with PRISMA guidelines (4).
- All randomized clinical trials comparing I-ChT vs. ChT alone in patients with solid tumors, reporting hematologic toxicities, were selected.
- Subgroup analysis according to **class of ICI** (anti-PD(L)1: pembrolizumab, durvalumab, atezolizumab; anti-CTLA4: ipilimumab), and a **sensitivity analysis excluding trials with a different number of cycles of ChT between arms** were done.
- Pooled odds ratios (pOR) with 95% confidence intervals (95% CI) were calculated using **random effect models**.
- Heterogeneity was assessed with the I² test (substantial heterogeneity whenever I²≥50%).
- Publication bias was ascertained by visual inspection of funnel plots.
- All reported p-values are two-sided, with significance set at p<0.05.

Results

- Following the retrieval of 10201 studies, **19 publications (14 testing an anti-PD(L)1-based I-ChT and 5 an anti-CTLA4-based I-ChT)** were included, with 5254 patients in the I-ChT group and 4316 patients in the ChT alone group **(Table 1)**.
- **Table 2** shows the pooled incidences per I-ChT and ChT alone groups of all-G anemia, neutropenia, FN, and thrombocytopenia.
- There was neither a significant increase in the odds of **all-G anemia (pOR=1.04; 95% CI=0.90-1.21)(Fig. A), neutropenia (pOR=1.01; 95% CI=0.87-1.16)(Fig. B), FN (pOR=1.24; 95% CI=0.97-1.58)(Fig. C), and thrombocytopenia (pOR=1.14; 95% CI=1.00-1.30)(Fig. D)(Table 2)**, nor by groups of G (data not shown).
- An **increment** in the odds of **all-G thrombocytopenia** was found with **anti-PD(L)1-based I-ChT** vs. ChT alone **(pOR=1.18; 95% CI=1.02-1.36; p=0.03)(Fig. D)**.
- Results were **similar** in the **sensitivity analysis** (all-G anemia pOR: 1.12 [95% CI, 0.95-1.31]; all-G neutropenia pOR: 1.03 [95% CI, 0.85-1.24]; all-G FN pOR: 1.20 [95% CI, 0.95-1.52]; all-G thrombocytopenia pOR: 1.17 [95% CI, 1.00-1.38] with anti-PD(L)1 subgroup pOR: 1.21 [95% CI, 1.02-1.44]).
- Symmetric funnel plots of hematologic endpoints indicates a **low risk of publication bias** (Figs. E-H).

References

1 – C. Robert, *Nat Commun.* 2020; 2 – D. Daniel and J. Crawford, *Semin Oncol.* 2006; 3 – R. Calvo, *Front Pharmacol.* 2019; 4 – D. Moher et al., *PLoS Med* 2009.

Forest Plots for all-G anemia (A), neutropenia (B), FN (C), and thrombocytopenia (D)

Funnel Plots for all-G anemia (E), neutropenia (F), FN (G), and thrombocytopenia (H)

Table 1 – Key features of included publications

Trial name or 1st Author	Study design	Tumour Type	IO major class	IO name	ChT	Trial setting	If advanced setting, line of Rx	Different No. of ChT cycles?
KEYNOTE-522	Phase III	Breast	Anti-PD(L)1	Pembrolizumab	AC or EC - T + carbo	Advanced	1st	No
KEYNOTE-048	Phase III	Head and Neck	Anti-PD(L)1	Pembrolizumab	Platinum + 5-FU	Advanced	1st	No
CASPIAN	Phase III	Lung	Anti-PD(L)1	Durvalumab	Platinum + etoposide	Advanced	1st	Yes
IMpassion-130	Phase III	Breast	Anti-PD(L)1	Atezolizumab	Taxane	Advanced	1st	No
IMpower133	Phase III	Lung	Anti-PD(L)1	Atezolizumab	Platinum + etoposide	Advanced	1st	No
KEYNOTE-407	Phase III	Lung	Anti-PD(L)1	Pembrolizumab	Platinum + taxane	Advanced	1st	No
IMpower150	Phase III	Lung	Anti-PD(L)1	Atezolizumab	Platinum + taxane	Advanced	1st	No
KEYNOTE-189	Phase III	Lung	Anti-PD(L)1	Pembrolizumab	Platinum + pemetrexed	Advanced	1st	Yes
Govindan R et al	Phase III	Lung	Anti-CTLA4	Ipilimumab	Platinum + etoposide	Advanced	1st	Yes
KEYNOTE-021	Phase II	Lung	Anti-PD(L)1	Pembrolizumab	Platinum + pemetrexed	Advanced	1st	Yes
Reck M et al	Phase II	Lung	Anti-CTLA4	Ipilimumab	Platinum + etoposide	Advanced	1st	No
Robert C et al	Phase III	Melanoma	Anti-CTLA4	Ipilimumab	Dacarbazine	Advanced	1st	Yes
Reck M et al	Phase II	Lung	Anti-CTLA4	Ipilimumab	Platinum + taxane	Advanced	1st	Yes
Lynch T et al	Phase II	Lung	Anti-CTLA4	Ipilimumab	Platinum + taxane	Advanced	≥2nd	Yes
KATE-2	Phase II	Breast	Anti-PD(L)1	Atezolizumab	DM-1	Advanced	1st	Yes
IMpower130	Phase III	Lung	Anti-PD(L)1	Atezolizumab	Platinum + taxane	Early	NA	No
GeparNuevo	Phase II	Breast	Anti-PD(L)1	Durvalumab	AC or EC - T	Early	NA	No
I-SPY2	Phase II	Breast	Anti-PD(L)1	Pembrolizumab	AC or EC - T	Advanced	≥2nd	No
Tolaney SM et al	Phase II	Breast	Anti-PD(L)1	Pembrolizumab	Eribulin	Advanced	1st	No

Table 2 – Pooled incidences and pooled Odds Ratio (pOR) with 95% confidence intervals (95% CI) in the I-ChT vs. ChT alone groups and subgroups, according to major ICI classes

Adverse Event	I-ChT events/Total No. of patients	ChT alone events/Total No. of patients	pOR (95% CI)	p-value	I² test
All-grade anemia	1934/4608 (42.0%)	1478/3845 (38.4%)	1.043 (0.898-1.211)	0.583	57.1%
Subgroup anti-PD(L)1	1707/3742 (45.6%)	1250/3008 (41.5%)	1.060 (0.899-1.250)	0.487	55.6%
Subgroup anti-CTLA4	227/866 (26.2%)	228/837 (27.2%)	0.967 (0.606-1.543)	0.888	78.5%
All-grade neutropenia	1534/4652 (33.0%)	1183/3889 (30.4%)	1.006 (0.869-1.164)	0.939	48.7%
Subgroup anti-PD(L)1	1349/3786 (35.6%)	957/3052 (31.4%)	1.068 (0.932-1.224)	0.341	28.9%
Subgroup anti-CTLA4	185/866 (21.4%)	226/837 (27.0)	0.755 (0.541-1.054)	0.099	52.1%
All-grade febrile neutropenia	256/3649 (7.0%)	151/3076 (5.0%)	1.236 (0.965-1.583)	0.093	7.9%
Subgroup anti-PD(L)1	235/2783 (8.4%)	143/2239 (6.4%)	1.166 (0.929-1.464)	0.185	0%
Subgroup anti-CTLA4	21/866 (2.4%)	8/837 (1.0%)	1.236 (0.965-1.583)	0.088	33.4%
All-grade thrombocytopenia	686/3507 (19.6%)	510/3086 (16.5%)	1.136 (0.997-1.296)	0.056	0%
Subgroup anti-PD(L)1	577/2641 (21.9%)	405/2249 (18.0%)	**1.177 (1.016-1.364)**	**0.030**	0%
Subgroup anti-CTLA4	109/866 (12.6%)	105/837 (12.5%)	0.993 (0.744-1.325)	0.961	0%

Conclusions

- To our knowledge, this is the largest meta-analysis focusing on the hematologic toxicity profile of I-ChT compared to ChT alone.
- Overall, **I-ChT does not appear to increase hematologic toxicities** as compared to ChT alone.
- Nonetheless, our data is **suggestive of a small yet statistically significant increase of 18% to 21% in the odds of all-G thrombocytopenia with anti-PD(L)1-based I-ChT**. This finding remained even after excluding trials with a different number of cycles of ChT between I-ChT and ChT alone arms, which could have potentially led to unbalanced myelotoxicity rates and biased results.
- In light of this data, **routine monitoring for hematologic toxicities with serial blood counts during treatment with I-ChT for patients with solid tumours appears sufficient**, albeit physicians familiarity with ICI-induced cytopenias should be encouraged.

Contact details: Daniel Eiger, MD at **danieleiger@gmail.com**