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& WEBINAR

12 Aprile 2023

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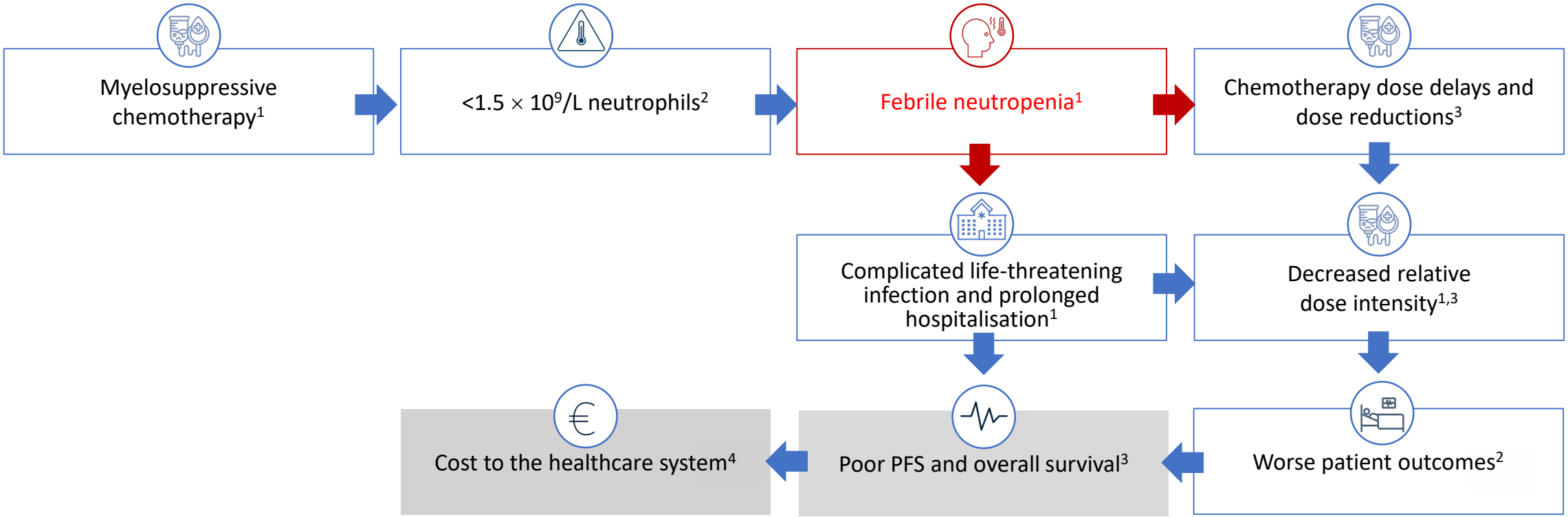
ASST di Pavia e Università LIUC, Castellanza

Un caso di neutropenia grave indotta da inibitori di CDK4/6: da un problema clinico ad un possibile approccio proattivo alla prevenzione dell'esaurimento midollare da chemioterapia antineoplastica

Chemotherapy-induced neutropenia

Potential clinical consequences



CT-induced febrile neutropenia

Patient- and disease-related risk factors for FN

Patient characteristics	Effect on risk
Advanced age 	Risk increases if age ≥65 years
Performance status 	Risk increases if ECOG performance score ≥2
Nutritional status 	Risk increases if albumin <35 g/L
Prior FN episode 	Risk in cycles 2–6 is four-fold greater if FN episode occurs in cycle 1
Comorbidities 	FN odds increase by 27%, 67% and 125% for one, two or three or more comorbidities, respectively

Treatment of malignancy	Effect on risk	
Degree and duration of GI and /or oral mucositis 	Risk is greater if NCI mucositis grade is ≥3 (GI) or if peak score on OMAS is ≥2	
Degree and duration of cytopenia 	Profound, protracted neutropenia	ANC <100/µL for ≥7 days
	Lymphopenia	ALC <700/µL (ANC surrogate)
	Monocytopenia	AMC <150/µL (ANC surrogate)

CT-induced febrile neutropenia

Regimens considered a risk factor for FN

Cytotoxic regimen

Risk is higher with regimens that administer:

- Anthracyclines at doses ≥90 mg/m^2
- Cisplatin at doses ≥100 mg/m^2
- Ifosfamide at doses ≥9 g/m^2
- Cyclophosphamide at doses ≥1 g/m^2
- Etoposide at doses ≥500 mg/m^2
- Cytarabine at doses ≥1 g/m^2

Dose intensity

- Increased risk if >85% of scheduled doses are administered

CT-induced febrile neutropenia and G-CSFs

Guidelines overview

FN can be effectively prevented by the use of G-CSF

- Primary prophylaxis: G-CSF is recommended for:
  - High-risk patients receiving chemotherapy regimens that carry a >20% risk of developing FN
  - Intermediate-risk patients receiving chemotherapy regimens that carry a 10–20% risk, and with additional factors that may increase risk of FN
- Secondary prophylaxis: G-CSF is recommended for patients who have experienced a neutropenic complication in a prior cycle of chemotherapy

Clinical guidelines recognise that the following factors contribute to the risk of FN:[1–4]

Chemotherapy-related factors

Patient-related factors

Disease-related factors

Additional risk factors are instrumental in deciding whether a patient receiving chemotherapy should receive primary prophylaxis to decrease the potential risk of FN[1,4]

Special situations of treatment-associated neutropenia

- Short chemotherapy intervals
- Continuous antineoplastic chemotherapy
- **CDK 6-4 inhibitors**
- Neutropenia in chimeric antigen receptor T Cell Therapy (CAR-T)
- Neutropenia in therapy with immune checkpoint inhibitors

Link HA. Current state and future opportunities in granulocyte colony-stimulating factor
Supp Care Cancer 2022

Clinical case study

62-years-old woman who immigrated from Aegypt. No relevant comorbidities or family history of breast or ovarian cancer

In July 2022, after palpating a right breast mass she was diagnosed with breast cancer. Bilateral mammography revealed on the right breast a 13 mm, firm, spiculated mass with associated calcifications

An ultrasound guided biopsy of the mass yielded an infiltrating moderately differentiated mammary carcinoma with associated low-grade intraductal carcinoma

CT scan was negative for *de novo* disease localization while bone scintigraphy revealed low-burden metastatic disease to left scapula and left iliac bone

After multidisciplinary discussion the patient underwent breast conserving surgery with a positive axillary sentinel lymph node. Hystopathological diagnosis was: invasive ductal carcinoma <2 cm, N1, G3, ER +ve (90%), PgR +ve (60%), HER2 -ve, Ki-67 15%, without lympho-vascular invasion

Clinical case study

Subsequently the patients started breast “adjuvant” Radiotherapy followed by systemic treatment with Palbociclib (125 mg taken orally once daily, for 3 weeks followed by 1 week off), plus Letrozole 2,5 mg once daily

Before treatment a basic blood panel including CBC with differential showed normal values. CBC was planned to be checked after baseline every two weeks for the first two cycles and then prior to each 28-day cycle and as clinically indicated

Prior to start the third cycle the patient had febrile neutropenia (Grade 3 ANC ,700/mm3 and fever >38.5°C) without clinical or laboratory signs of infection. Institutional fever and neutropenia guidelines were started and the initiation of Palbociclib was deferred in order to be subsequently resumed at a lower dose

Clinical case study

Fever and low ANC persist for up two weeks and then patient resumed Palbociclib at 75 mg. After two weeks of retreatment at low dose, febrile neutropenia without documented infections reappeared, togheter with Grade 3 (25.000/mm3), Thrombocytopenia and mild (8.0 g/dL) Anemia

Palbociclib was withheld and after two weeks there was a normalization of hematological parameters, togheter with a complete recovery of the patient clinical conditions

The patient was then treated with standard-dose chemotherapy (AC *q3* weeks followed by weekly paclitaxel), supported in the first 4 courses of AC by prophylactic pegfilgrastim

No further episodes of hematological toxicity occurred, the patient has completed the chemotherapy program, is actually continuing Letrozole and the follow up

CDK4/6 inhibitors in advanced HR+/HER2-breast cancer

There has been a greeat deal of interest in the development of inhibitors of cyclin-dependent kinases (CDKs), more specifically CDK4 and 6, since they were identified as potential regulators of the cell cycle in cancer tissues

They work by blocking the transition form G1 to the S-phase of the cell cycle, thus preventing cancer cell progression and reduce or eliminate endocrine resistance when used in combination with endocrine therapy

Palbociclib, Ribociclib and Abemaciclib combined with endocrine therapy are now considered standard-of-care for first-line therapy of patients with hormone receptor-positive, HER2-negative ABC

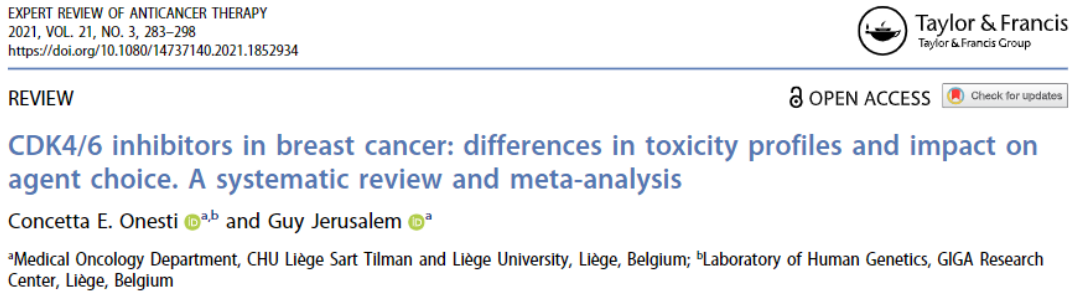
CDK4/6 inhibitors in advanced HR+/HER2-breast cancer

Toxicity overview

Palbociclib - The most common adverse events reported for Palbociclib are fatigue, nausea and mild, rapidly reversible, neutropenia

Ribociclib – Also for Ribociclib, hematologic adverse events, including neutropenia, fatigue, nausea and diarrhea

Abemaciclib – Abemaciclib is structurally different from palbociclib and Ribociclib with a greater selectivity for CDK4 vs CDK6. Hematologic adverse events, including neutropenia, are less common while GI-related toxicity are predominant


EXPERT REVIEW OF ANTICANCER THERAPY
2021, VOL. 21, NO. 3, 283–298
https://doi.org/10.1080/14737140.2021.1852934

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REVIEW

OPEN ACCESS Check for updates

CDK4/6 inhibitors in breast cancer: differences in toxicity profiles and impact on agent choice. A systematic review and meta-analysis

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Neutropenic toxicity from CDK4/6 inhibitors

Although neutropenia is a common side affect of cyctotoxic chemotherapy, the neutropenia associated with CDK4/6 inhibitors is different in that it is rapidly reversible reflecting a cytostatic effect on bone marrow precursors

While mild neutropenia is common, the incidence of febrile neutropenia is very low (from 0% to 1.4%)

Neutropenia is proportional to exposure and ofted declines with subsequent cycles, suggesting a lack of cumulative toxicity

Complete blood count with differential needs to be monitored for all patients on treatment with effective early dose reductions when indicated

Management of neutropenic toxicity from CDK4/6 inhibitors

Drug		Guidance
Abemaciclib[1]	• FN has been reported in <1% of patients in the Phase III MONARCH studies • 2 deaths due to neutropenic sepsis	• Monitor CBC prior to therapy, every 2 weeks for the first 2 months, monthly for the next 2 months and as clinically indicated • Dose interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia
Palbociclib[2]	• FN has been reported in 1.4% of patients in Phase III studies 1 and 2 • One death due to neutropenic sepsis	• Monitor CBC prior to therapy and at beginning of each cycle, as well as on Day 15 of the first 2 cycles and as clinically indicated • Dose interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia
Ribociclib[3]	• FN was reported in 1.4% of patients in Phase III MONALEESA studies • Treatment discontinuation due to neutropenia was 0.8%	• Perform CBC before initiating therapy and monitor every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically indicated

Review > Bull Cancer. 2021 May;108(5):544-552. doi: 10.1016/j.bulcan.2021.01.007.
Epub 2021 Apr 2.

[Patients treated with palbociclib and endocrine therapy for metastatic breast cancer: Can we predict the occurrence of severe early hematological toxicity?]

[Article in French]

Léa Vazquez [1], Antoine Arnaud [2], Julien Grenier [2], Philippe Debourdeau [2]

Affiliations + expand

PMID: 33820647 DOI: 10.1016/j.bulcan.2021.01.007

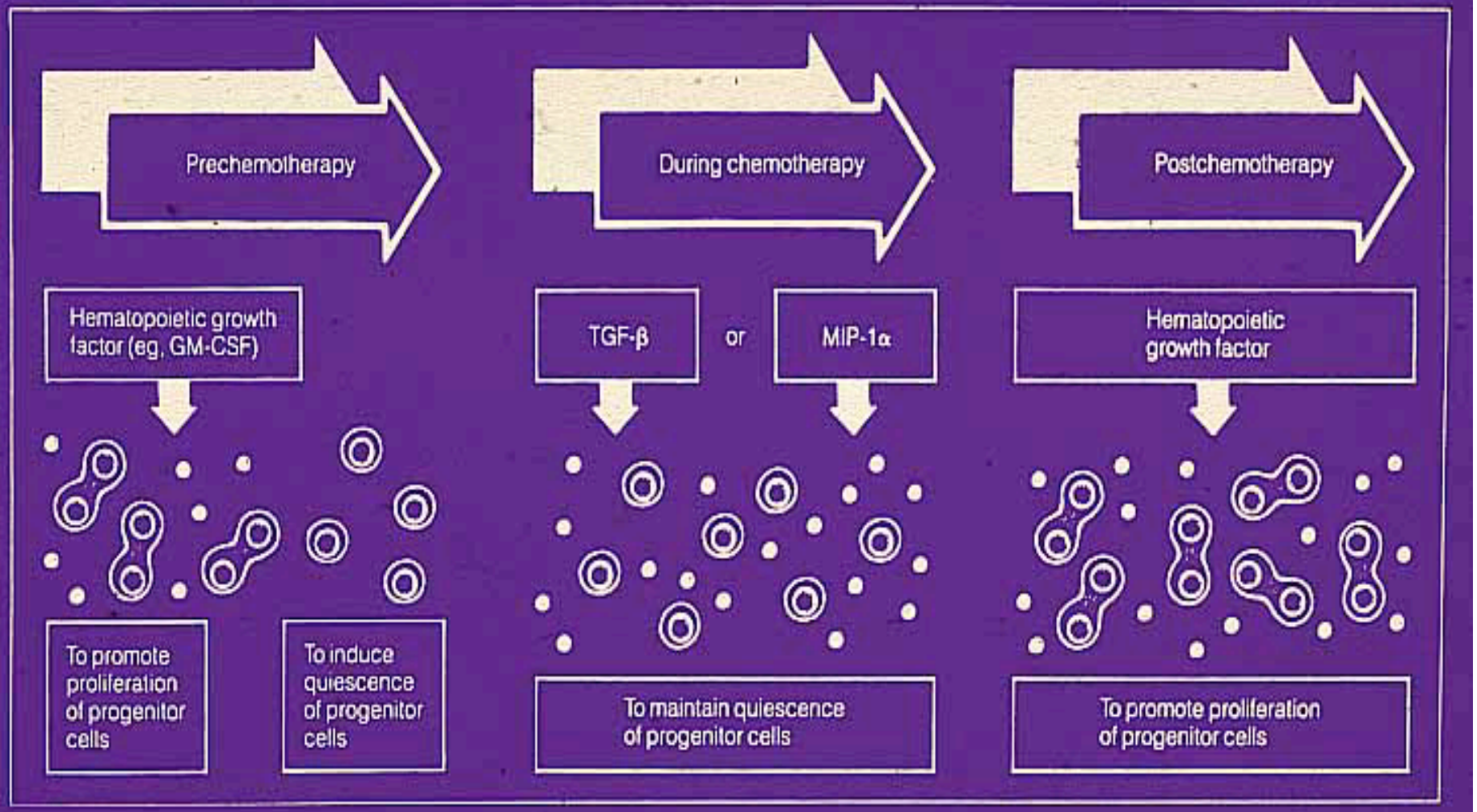
Supportive Care in Cancer
https://doi.org/10.1007/s00520-022-07084-5

COMMENTARY

Cytokinetic-driven myeloprotection after cytotoxic chemotherapy: from an old idea to a new clinical approach

Andrea Sbrana[1,2] · Andrea Antonuzzo[3] · Marco Danova[4,5]

Received: 19 November 2021 / Accepted: 21 April 2022



Danova M, Rosti V, Mazzini G et al.

Cell kinetics of CD34-positive hematopoietic cells following chemotherapy plus CSFs in advanced breast cancer

Int J Cancer **1995;63:646-51**

IJC
International Journal of Cancer

Drugs & Aging (2023) 40:263–272
https://doi.org/10.1007/s40266-022-01005-1

REVIEW ARTICLE

A Proactive Approach to Prevent Hematopoietic Exhaustion During Cancer Chemotherapy in Older Patients: Temporary Cell-Cycle Arrest

Lodovico Balducci[1] · Claire Falandry[2,3] · Alan List[4]

Accepted: 27 December 2022 / Published online: 30 January 2023

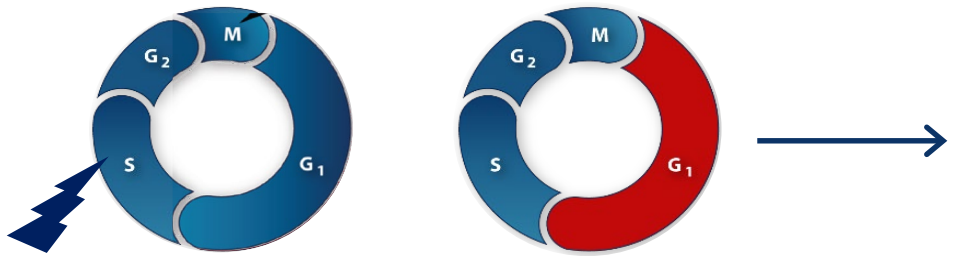
Trilaciclib: competitive inhibitor of CDK4/6

In 2021, Trilaciclib, a new CDK4/6 inhibitor, was approved by the FDA to decrease the incidence of CT-induced myelosuppression in ES-SCLC patients when administered prior to CT

This agent has now been integrated into the NCCN Hematopoietic Growth Factor guidelines (category 2A/B) for use as a prophylactic option to decrease the incidence of CT-induced myelosuppression

When administered prior to CT, Trilaciclib arrests HSPCs and lymphocytes in the G1 phase of the cell cycle. Transient arrest of these cells in the presence of CT protects them from CT-induced damage (myeloprotection). Following CT, normal hematopoiesis can resume resulting in accelerated hematologic recovery

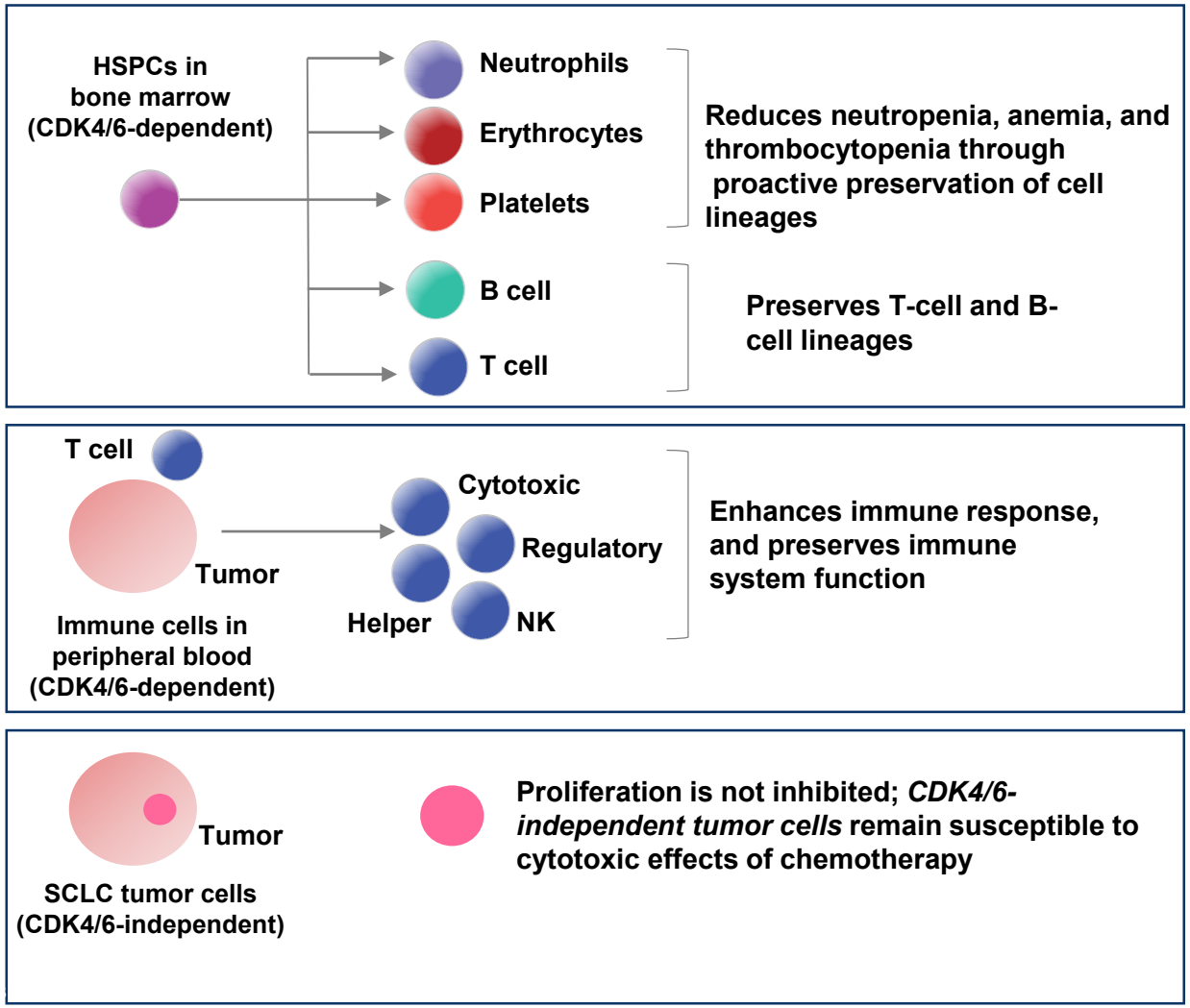
SCLC cells continue to replicate even when treated with a CDK4/6 inhibitor and therefore remain susceptible to the cytotoxic effects of CT



Chemotherapy

Trilaciclib (IV myelopreservation therapy)

- Given prior to chemotherapy on each day chemotherapy is administered
- Arrests HSPCs in the G1 phase of the cell cycle during chemotherapy exposure
- Cell cycle arrest is transient due to daily dosing and short half-life of trilaciclib
- Preserved HSPCs resume activity after chemotherapy



Trilaciclib: competitive inhibitor of CDK4/6

Reduces the incidence of CIM in adult patients with extensive-stage SCLC receiving CT by:

- Protecting haematopoietic lineages from DNA damage caused by CT
- Reversibly inducing cell cycle arrest at the G1 stage
- Facilitating myelopreservation and T-cell activation in CDK4/6-dependent cells

Trilaciclib is administered as 30-minute IV infusions at a dose of 240 mg/m^2 within 4 hours prior to the start of each CT treatment

Myelosuppressive benefits of Trilaciclib administration prior to CT compared with placebo did not impact the anti-tumour efficacy of the CT regimens and led to:

- Supportive care interventions
- CIM or sepsis-related hospitalisation

- HRQoL domains, including fatigue, physical wellbeing and functional wellbeing

frontiers

The efficacy and safety of Trilaciclib in preventing chemotherapyinduced myelosuppression: A systematic review and meta-analysis of randomized controlled trials

Qiu Jingyue[1], Sheng Dandan[1], Lin Fei[2, 3*], Jiang Peng[4], Shi Ning[1*]

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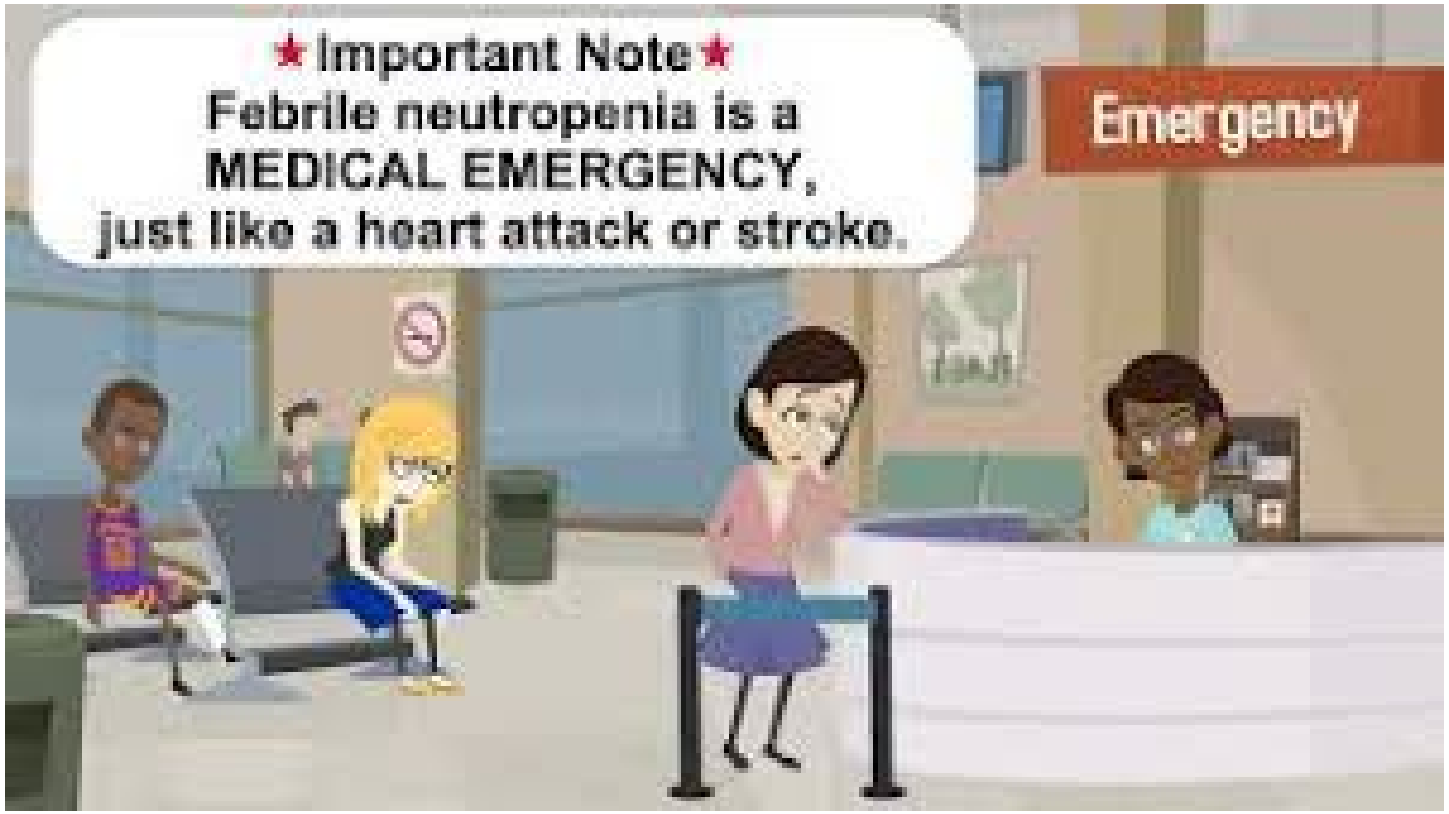
Table 1: Characteristics of selected studies

Study, year published	Intervention		Patient number		Study duration	Study population
	Control	Experimental	Control	Experimental		
J. M. Weiss, 2019	E/P plus placebo	E/P plus Trilaciclib	37	38	between June 2015 and February 2019	≥ 18 years, histologically or cytologically confirmed ES-SCLC.
Davey Daniel, 2020	Placebo prior to E/P/A	Trilaciclib prior to E/P/A	53	54	between June 2017 and February 2018	≥ 18 years, with confirmed ES-SCLC.
Lowell L. Hart, 2021	Placebo prior to topotecan	Trilaciclib prior to topotecan	29	32	between October 2015 and October 2021	≥ 18 years, with confirmed diagnosis of ES-SCLC.
Antoinette R Tan,2019	G/P plus placebo	G/P plus Trilaciclib (D1+D8)	34	33	between February 2017 and May 2018	≥ 18 years, recurrent or metastatic triple-negative breast cancer who had no more than two previous lines of chemotherapy
		G/P plus Trilaciclib (D2+D9)		35		


★Important Note★
Febrile neutropenia is a
MEDICAL EMERGENCY,
just like a heart attack or stroke.
Emergency