Optimizing G-CSF schedules during chemotherapy: supplement material

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Table S1. Data sets. We present data sets used for model development and validation

Disease	**Cyctotoxic drugs modelled**	**Chemotherapy schemes**	**G-CSF**	**Reference**
Breast cancer	Doxorubicin, Docetaxel, Epirubicin, Paclitaxel, Cyclophosphamid	TA, EC-T , E-T-C	Filgrastim, Pegfilgrastim	(Moebus et al. 2010; Holmes et al. 2002; Yowell and Blackwell 2002; Zamboni 2003)
NSCLC	Carboplatin, Paclitaxel	CP	Filgrastim, Pegfilgrastim	
DLBCL	Cyclophosphamid, Doxorubicin, Prednison, Vincristine	R CHOP-14	Pegfilgrastim	(Brusamolino et al. 2006; Mey et al. 2007)
NHL	Cyclophosphamid, Doxorubicin, Etoposide, Prednison, Vincristine	high-CHOEP-14, high-CHOEP-21, CHOP-14, CHOEP-14, CHOP-21, CHOEP-21, R-CHOP-14	Filgrastim	(George et al. 2003; Pfreundschuh et al. 2008; Pfreundschuh et al. 2004a; Pfreundschuh et al. 2004b; Trumper et al. 2008; Zwick et al. 2011)
HD	Cyclophosphamid, Doxorubicin, Etoposide, Prednison, Procarbacine, Bleomycin, Vincristine	BEACOPP-14, BEACOPP-21, BEACOPP-21 escalated	Filgrastim	(Diehl et al. 2003; Sieber et al. 2003)
relapsed or persistent HD or NHL	Etoposide, Cisplatin, Cytarabin, Methyl-prednisolon	ESHAP	Filgrastim, Pegfilgrastim	

Table S2. Toxicity parameters. We present estimated toxicity parameters on stem cells (S), progenitors (CG), proliferating precursors (PGB), maturing precursors (MGB) and lymphocytes (LYM). Toxicity parameters are specific for cytotoxic drug concentrations and risk groups. CHOP chemotherapy consists of Cyclophosphamid (750 mg/m²), Doxorubicin (50 mg/m²), and Vincristine (2 mg).

CHOP chemotherapy	S	CG	PGB	MGB	LYM
high risk	0.2161	1.1848	0.6751	0.0002	20.0000
medium risk	0.2161	0.3697	0.2343	0.0002	12.6982
low risk	0.2152	0.1301	0.1197	0.0001	9.8753

Table S3. Outcome values of different simulated G-CSF schedules, chemotherapies and risk groups.

Therapy	risk group	Outcome measure	Optimal start of Fil	Optimal #Injection Fil	Optimal outcome value Fil	Optimal start of Peg	Optimal outcome value Peg	Currently used schedules	Current Outcome Value
CHOP-14 elderly	high	WBCAOC	7	8	50.51	7	57.16	Fil d4-13	72.58
								Fil d6-12	77.92
								Peg d2	112.45
								Peg d4	91.10
		DoL	6	9	27.17	6	29.88	Fil d4-13	34.67
								Fil d6-12	56.17
								Peg d2	47.67
								Peg d4	39.50
		MLC	9	5	0.99	7	1.15	Fil d4-13	0.88
								Fil d6-12	0.82
								Peg d2	0.56
								Peg d4	0.70
	medium	WBCAOC	9	6	2.16	7	2.81	Fil d4-13	10.47
								Fil d6-12	7.55
								Peg d2	38.82
								Peg d4	22.14
		DoL	9	6	2.75	7	7.13	Fil d4-13	15.00
								Fil d6-12	11.50
								Peg d2	28.79
								Peg d4	21.29
		MLC	8	4	2.84	7	3.21	Fil d4-13	2.84
								Fil d6-12	2.84
								Peg d2	1.90
								Peg d4	2.46
	low	WBCAOC	8	4	0.00	7	0.00	Fil d4-13	0.00
								Fil d6-12	0.00
								Peg d2	21.06
								Peg d4	6.94
		DoL	8	4	0.00	7	0.00	Fil d4-13	0.00
								Fil d6-12	0.00
								Peg d2	22.29
								Peg d4	14.29
		MLC	8	5	4.45	7	4.38	Fil d4-13	4.25
								Fil d6-12	4.01

								Peg d2	2.51
								Peg d4	3.21
BEACOPP esc	all	WBCAOC	7	15	62.07	7	52.98	Fil d8-15	145.16
		DoL	7	15	32.17	6	28.17	Fil d8-15	76.04
		MLC	7	13	0.67	7	0.56	Fil d8-15	0.35
ETC	all	WBCAOC	7	8	0.70	6	5.34	Fil d3-10	14.86
		DoL	7	8	3.63	6	5.54	Fil d3-10	11.71
		MLC	7	8	3.53	7	2.51	Fil d3-10	1.80
CHOP-12	all	WBCAOC	7	6	19.12	6	20.50	-	-
		DoL	6	7	17.5	6	15.54	-	-
		MLC	7	6	2.05	6	1.93	-	-

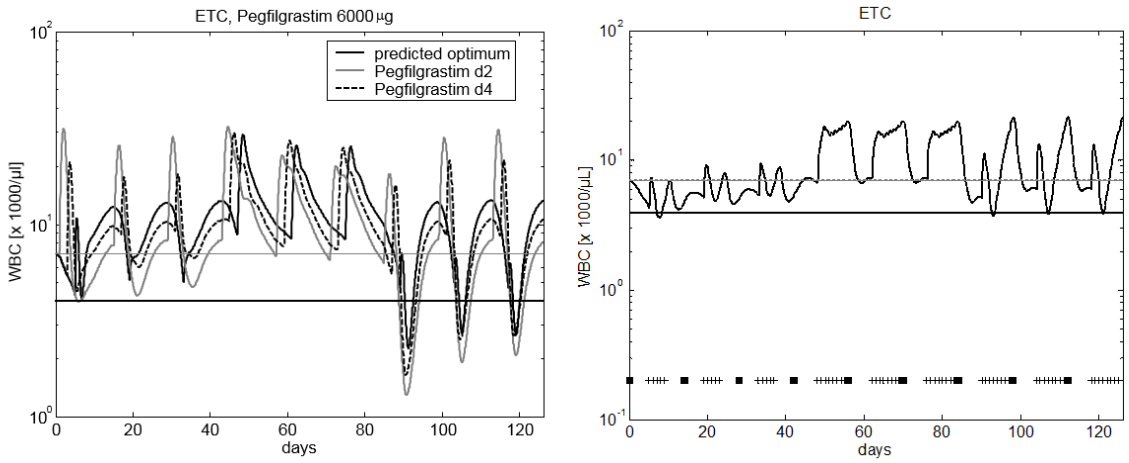

Figure S1. Model predictions of alternative G-CSF schedules for the adjuvant breast cancer therapy ETC. (Left) Pegfilgrastim 6mg d2, d4 and d6 (optimal). (Right) cycle-wise optimization of Filgrastim starting on day 6 with five injections at cycles 1-3 and on day 7 with eight injections at cycles 4-9.

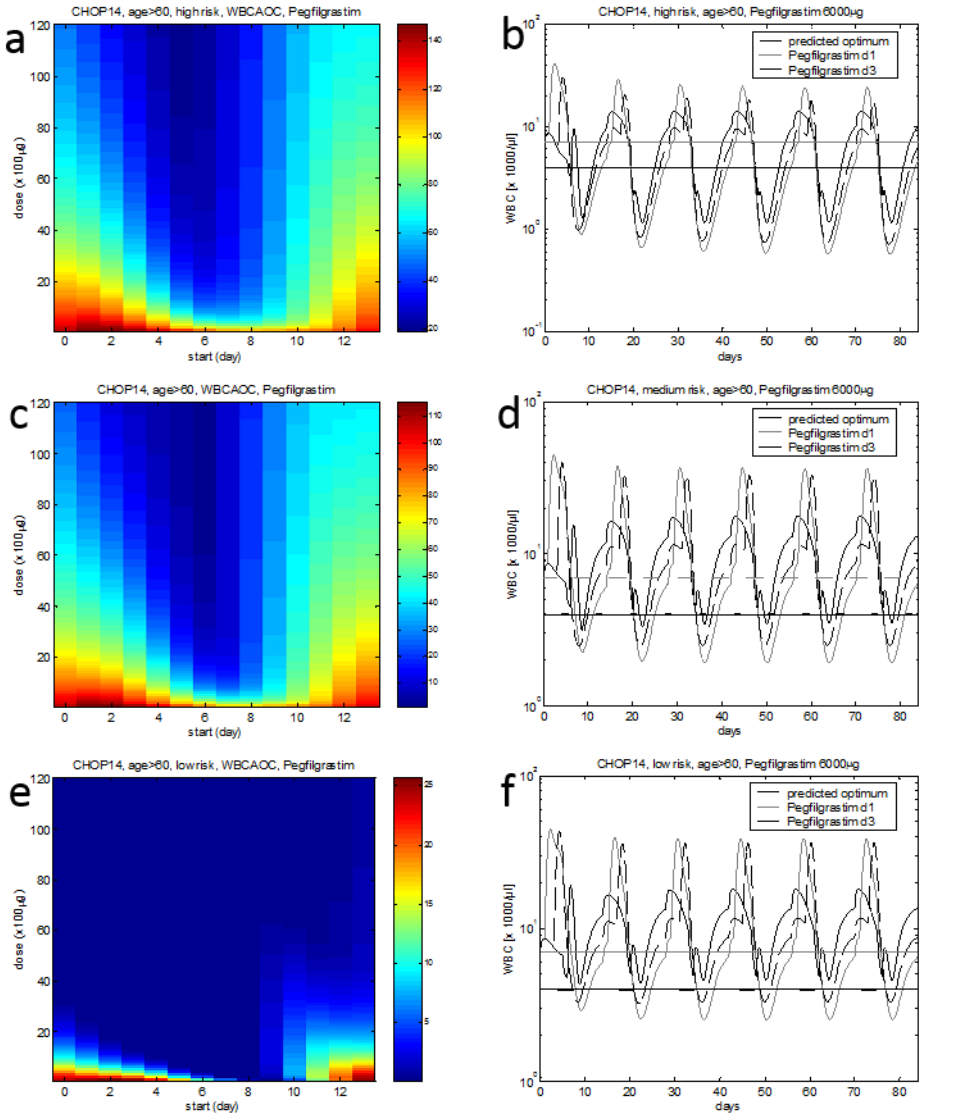

Figure S2. Prediction of leukopenic outcome of modified Pegfilgrastim schedules, dependent on risk group. We analysed 6 cycles of CHOP-14, elderly patients (age>60) for the three risk groups considered. Starting time and dosage of single Pegfilgrastim injections per cycle are varied. Panels on the left present WBCAOC of leukocytes as primary outcome. Panels on the right present the predicted time courses of leukocytes for the optimal timing and the timing day 1 and 3 of 6000µg Pegfilgrastim (a-b) high risk group, (c-d) medium risk group, (e-f) low risk group.

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