

Suppl 3. Details of the dosage regimen and cardiotoxicity outcomes in patients who received 5-FU monotherapy.

No.	Author, year	5-FU administration	Intervention/control			Cumulative dose 5-FU (mg/m ²)	Cardiotoxicity outcomes (N)	CTCAE/WHO grading (N)	Type of cardiotoxicity (reported events) ^a
			Arm A	Arm B	Arm C				
1	Alberto et al, 1988	Rapid IV injection	5-FU 450 mg/m ² rapid intravenous injection	Doxifluridine 4000 mg/m ² rapid intravenous	-	N/A	0/27	-	N/A

			daily for 5 consecutive days every 3 weeks.	injection daily for 5 consecutive days every 3 weeks.					
2	Ansari et al, 2017	IV continuous infusion	- Short-course (SC) group received pelvic radiotherapy 5X5 Gy in 1 week, early surgery - Six monthly cycles of 5-FU 425 mg/m ² and folinic acid 20 mg/m ² given daily for 5 days	- Long-course (LC) was 50.4 Gy administered in 28 fractions during 5.5 weeks with concurrent chemotherapy with continuous infusion 5FU (225 mg/m ² /d), surgery in 4 to 6 weeks - Four monthly cycles of 5-FU 425 mg/m ² and folinic acid 20 mg/m ² given daily for 5 days	-	N/A	17/322	N/A	DVT/VTE (9) Sudden death (1)
3	Bajetta et al, 1993	IV infusion (1 hr)	5-FU (500 mg/m ²) daily for 5 days every 28 days	Doxifluridine 4000 mg/m ² daily for 5 days every 28 days	-	N/A	3/110	3 (1)	N/A
4	Barutca et al, 2004	IV bolus and IV continuous infusion	- Leucovorin 200 mg/m ² i.v. in 2 h - 5-FU 400 mg/m ² i.v. bolus plus 5-FU 600 mg/m ² as a continuous i.v. infusion in 22 h repeated on 2 consecutive days every 2 weeks	-	-	2,000 (0)	0/28	-	N/A
5	Bécouarn et al, 1995	IV bolus then IV infusion 22 hr	FA (200 mg/m ²) in a 2-hour infusion in 5% dextrose followed by 5-FU (400 mg/m ²) intravenous bolus and then 5-FU (600 mg/m ²) in a 22-hour infusion in 5% dextrose. This combination was delivered on days 1 and	-	-	40,000 (4)	4/86	2 (1) 3 (3)	N/A

			2, and therapy was resumed at day 15.						
6	Berenberg et al, 1995	IV continuous infusion and IV bolus	<p>- 5-FU 1000 mg/m²/24 hours administered as a continuous infusion for four days. FA 200/m² was given as a rapid intravenous bolus immediately before the 5-FU and at 24-hour intervals for a total of four doses. Treatment was repeated every 28 days.</p> <p>- 5-FU was given as a 375 mg/m² intravenous bolus immediately after a bolus intravenous injection of FA 200 mg/m² on days 1-5. Treatment was repeated every 28 days.</p>	-	-	N/A	0/76	-	N/A
7	Bonnetain et al, 2005	IV bolus over 2 hr and then continuous infusion over 22 hr	LV5FU2 arm received LV 200 mg/m ² over 2 hours followed by 5-FU 400 mg/m ² bolus then a 600 mg/m ² continuous infusion of 5-FU over 22 hours on days 1 and 2, repeated every 14 days.	<p>- LV5FU2-cisplatin arm received: cisplatin 50 mg/m² over 1 hour on day 1 or day 2 with LV5FU2.</p> <p>- LV5FU2-irinotecan arm received irinotecan 180 mg/m² IV over 90 minutes on day1 with LV5FU2.</p>	-	N/A	0/45	-	N/A
8	Breton et al, 2021	IV bolus and IV continuous infusion	<p>- LV5FU2 classical</p> <p>- LV5FU2 simplified</p> <p>- FUFOL, bolus fluorouracil and leucovorin monthly; LD 5-FU, continuous</p>	<p>- LV5FU2 classical, fluorouracil and leucovorin bimonthly</p> <p>- LV5FU2 simplified, fluorouracil and leucovorin bimonthly</p>	LV5FU2 simplified, Irinotecan, Oxaliplatin, Bevacizumab, Aflibercept	N/A	7/1068	N/A	N/A

			infusion of 5FU at 600 mg/m ² day 1 and 2 every 2 weeks; HD 5-FU, weekly continuous 5FU (2.6 g/m ² /week) for 6 weeks followed by a rest week	- Irinotecan - Oxaliplatin - Bevacizumab					
9	Brücher et al, 2004	IV continuous infusion	5-fluorouracil continuous infusion for 21 days with a dose of 300 mg/m ² /per day	-	-	N/A	2/76	3-4 (2)	N/A
10	Cascinu et al, 2003	IV bolus	5FU administered by rapid intravenous injection at a dose of 450 mg/m ² , daily for 5 consecutive days, then once weekly beginning on day 29 for 48 weeks	Levamisole 50 mg three times daily for a period of 3 days, every 2 weeks for 1 year, plus 5-FU administered by rapid intravenous injection at a dose of 450 mg/m ² , daily for 5 consecutive days, then once weekly beginning on day 29 for 48 weeks	-	N/A	1/91	3-4 (1)	N/A
11	Cashin et al, 2016	Intraperitoneal via abdominal port-a-cath	Surgery arm - Intraperitoneal chemotherapy within 3 h after completion of surgery (peritonectomy) through an abdominal port-a-cath and continued daily for a total of six infusions (6 d) - The regimen consisted of 5-fluorouracil 550 mg/m ² /d administered in 500 ml 0.9% saline solution via the port-a-cath combined with	Systemic chemotherapy arm - 5-fluorouracil, leucovorin, oxaliplatin regimen (FOLFOX-6) Day 1: 2 h infusion of oxaliplatin 100 mg/m ² administered in a glucose solution, 2 h infusion with l-leucovorin 100 mg/m ² . After 2 h, 5-FU 400 mg/m ² bolus injection was administered and then a continuous 5-FU infusion 2400 mg/m ² /46 h was	-	19,800 (1)	1/24	N/A	N/A

			intravenous leucovorin (Isovorin) 30 mg/m ² /d given as a bolus dose 1 h after start of the intraperitoneal infusion. Further 6-d infusion series was administered with the same dosage every 4-5 weeks for a total of six treatments spanning over a 6-month postoperative period	given. If oxaliplatin was contraindicated, irinotecan (180 mg/m ²) was administered. Treatment was given every fortnight for a planned number of 12 cycles or for about 6 months.					
12	Ceyhan et al, 2005	IV bolus and IV continuous infusion	5-FU monotherapy LV 200 mg/m ² 2 hour infusion, 5-FU 400 mg/m ² bolus and 5-FU 600 mg/m ² 22 hours infusion on day 1 and 2 repeat every 2 weeks	-	-	2,000 (2)	2/37	N/A	Unstable angina (2)
13	Citron et al, 1992	IV infusion	5-FU at 4.5 g/m ² over 24 h diluted in 2 L of 5 % dextrose in water for central infusion or 3 L for peripheral intravenous infusion. Treatment was given every two weeks.	-	-	20,250 (4)	4/86	N/A	N/A
14	Cunningham et al, 2009	Continuous intravenous infusion (CIV) and IV bolus	B1: received 5-FU 300 mg/m ² /day CIV (5-FU CIV) without interruption. B2: received 5-FU (400 mg/m ² bolus + 600mg/m ² 22-h CIV on D1, 2) + LV (200 mg/m ² 2-h i.v. infusion D1, 2) (LV5FU2)	A1: received oxaliplatin once every 2 weeks (85 mg/m ² 2-h i.v. infusion on D1) + 5-FU 250 mg/m ² /day CIV given continuously without interruption for the 2-week duration of the treatment cycle	-	N/A	13/362	Chest pain - Any grade (6) - Grade 3/4 (2) Myocardial ischaemia - Any grade (3) - Grade 3/4 (2)	Chest pain (8) Myocardial infarction (5)

			Cycles were repeated every 2 weeks until disease progression or unacceptable toxicity	(oxaliplatin + 5-FU CIV) A2: received oxaliplatin once every 2 weeks (85 mg/m ² 2-h i.v. infusion on D1) 5-FU (400 mg/m ² bolus + 600 mg/m ² 22-h CIV on D1, 2) + LV (200 mg/m ² 2-h i.v. infusion on D1, 2) (FOLFOX4)					
15	Daniele et al, 2003	IV bolus then IV infusion	L-folinic acid (FA) 100 mg/m ² /d as a 2 hour infusion followed by bolus 5-fluorouracil (FU) 400 mg/m ² /d and a 22-hour infusion of FU 600 mg/m ² /d, repeated for 2 consecutive days every 2 weeks	-	-	2,000 (CHF 1) 4,000 (Left ventricular function failure 1)	2/34	3 (1)	Heart failure (2)
16	de Forni et al, 1992	IV continuous infusion	5-FU dose 600 - 1000 mg/m ² /day for 4 or 5 consecutive days	5-FU with cisplatin or mitomycin or cyclophosphamide and epirubicin	-	N/A	5/65	N/A	N/A
17	Dencausse et al, 2002	IV bolus	- Folinic acid 100 mg/m ² i.v. for 15–30 min followed by 5-FU 450 mg/m ² as an intravenous bolus for 5 consecutive days - Treatment cycles were repeated every 4 weeks (day 28) for 12 months or 6 months.	- 5-FU 450 mg/m ² per day intravenously in 5 min for 5 consecutive days followed by weekly application for 1 year - Levamisole 50 mg 3 times a day p.o. for 3 consecutive days every other week	-	N/A	1/105	1-2	Arrhythmia (1)
18	Dencauss et al, 2001	IV continuous infusion	- Weekly 2-hour infusion of FA 500 mg/m ² - followed by continuous 24-hour	-	-	20,800 (1)	1/21	4 (1)	Myocardial infarction (1)

			infusion of 5-FU 2,600 mg/m ²						
19	Ducreux et al, 2002	Rapid IV infusion (<1 hr)	5-FU was administered alone in a rapid infusion (<1 h) at a dosage of 500 mg/m ² /day for 5 consecutive days. Courses were repeated every 4 weeks.	5-FU was given at a dose of 1000 mg/m ² /day. Cisplatin was given at a dose of 100 mg/m ² on the first or second day of each cycle. Courses of the two drugs were repeated every 4 weeks	-	5,000 (3)	3/100	3-4	N/A
20	Ducreux et al, 2004	IV infusion	Single agent 5-FU repeated every 3 weeks 1000 mg/m ² /day continuous i.v. infusion, days 1-4	single-agent oxaliplatin 130 mg/m ² as a 2-h intravenous (i.v.) infusion every 3 weeks (OXA)	OXA 130 mg/m ² 2h-infusion every 3weeks + combined with 5-FU 1000 mg/m ² /day continuous i.v. infusion, days 1-4 (OXFU)	N/A	0/15	-	N/A
21	Ducreux et al, 2005	IV Infusion	Weekly 5FU alone (HDFU, high-dose 5-fluorouracil) 24-h infusion of 3.0 g/m ² of 5FU for 6 weeks (days 1, 8, 15, 22, 29, 36) followed by a week's rest.	Weekly infusion of 500 mg/m ² of folinic acid followed by a 24-h infusion of 2.0 g/m ² of 5FU for 6 weeks (days 1, 8, 15, 22, 29, 36) followed by a week's rest plus cisplatin 50 mg/m ² every 2 weeks (day 1, 15, 29) for 6 weeks, followed by a week's rest.	-	18,000 (1)	1/29	N/A	Cardiac ischemia (1)
22	Dyhl-Polk et al, 2021	IV bolus and IV continuous infusion	5-FU was administered as a bolus infusion (400 mg/m ²) followed by a	-	-	2,800 (22) 5,600 (3) 8,400(2) 11,200(1)	28/108	N/A	Myocardial infarction (6) Arrhythmia (2)

			46-hour infusion (2,400 mg/m ²).						
23	Francini et al, 1994	IV infusion	12 cycles of FA 200 mg/m ² , intravenously (IV), on days 1-5, plus 5-FU 400 mg/m ² , IV, on days 1-5, at 4-week intervals.	Observation	-	24000 (0)	0/118	-	N/A
24	Garufi et al, 1997	IV infusion	An initial 5-FU dose of 600 mg/m ² /d was chosen. The 5-FU dose was increased by 100 mg/m ² /d until a toxic level was reached.	-	-	N/A	1/34	4 (1)	EKG abnormalities (1)
25	Gradishar et al, 1991	IV bolus and IV continuous infusion	5-FU monotherapy - 5 gm/m ² Day 1 q 14 days 7 cases - 4 gm/m ² Day 1 q 21 days 27 cases	1. CDDP 100mg/m ² with 5-FU 1000 mg/m ² /day 2. MTX 120 mg/m ² , CDDP 100 mg/m ² , 5-FU 1000 mg/m ² /day with leucovorin 25 mg/m ² q 6x6 3. MTX 120 mg/m ² , CDDP 100 mg/m ² , 5-FU 1000 mg/m ² /day with leucovorin 15 mg/m ² q 6x6 or CDDP 20 mg/m ² /day, Bleomycin 10 units/m ² /day, MTX 200 mg/m ² with leucovorin 15 mg/m ² 4. CDDP 20 mg/m ² /day, Bleomycin 10 units /m ² /day, MTX 200 mg/m ² with leucovorin 15 mg/m ² or CDDP 100 mg/m ² , 5-FU 1000 mg/m ² /day with	-	7,700-61,000 (3)	3/34	N/A	Sudden death (3)

				leucovorin 100 mg/m ² q 4 5. CDDP 100 mg/m ² , 5-FU 800 mg/m ² /day, leucovorin 100 mg q 4, MTX 50 mg/m ² with PTX 100 mg/m ² q 12x10 6. HU 300-500 mg, 5-FU 800 mg/m ² /day with daily radiotherapy					
26	Haas et al, 1995	IV continuous infusion	Leucovorin 50 mg/m ² and 5-FU 2300 mg/m ² , administered intravenously over 24 hours. Treatment was repeated weekly.	-	-	2,300 (1) 23,000 (1)	2/37	N/A	Chest pain (2)
27	Hartung et al, 1996	IV infusion	- FA 100 mg/m ² i.v. for 15-30 min followed by 5-FU 450 mg/m ² i.v. for 5 consecutive days. - Treatment cycles were repeated every 4 weeks (day 28) for 6 and 12 months	- 5FU 450 mg/m ² per day as an intravenous bolus for 5 consecutive days followed by a weekly application for 1 year. - LEV was administered at doses of 50 mg 3 times a day p.o. for 3 consecutive days every other week.	-	6,750-15,750 (1) 13,500-31,500 (1)	2/55	1 (1) 4 (1)	N/A
28	Hartung et al, 2001	IV continuous infusion over 24 hr	5-FU 2,600 mg/m ² as intravenous infusion over 24 h (FU24h) weekly for 6 weeks, followed by a 2-week rest period (1 cycle = 8 weeks). The subsequent cycle began on day 1 of week 9. In addition, 500 mg/m ² S-FA (Medac	-	-	5,200 (1) 7,800 (1)	2/51	3 (2)	Chest pain (2)

			GmbH, Wedel, Germany) was mixed to 5-FU in the portable pump system.						
29	Highley et al, 2009	IV continuous infusion	Continuously infused 5-fluorouracil 300 mg/m ² /day	-	-	300 (1)	2/46	2 (1) 4 (1)	N/A
30	Hoff et al, 2001	IV bolus	5-FU/LV rapid IV injection of 20 mg/m ² LV followed by an IV bolus injection of 425 mg/m ² 5-FU daily, days 1 to 5 every 4 weeks	Capecitabine monotherapy - orally at a dose of 1,250 mg/m ² twice daily (total daily dose 2,500 mg/m ²) as an intermittent regimen in 3-week cycles (2 weeks of treatment followed by a 1-week rest period)	-	9,775 (3)	3/294	3 (2) 4 (1)	Chest pain (1) Angina pectoris (1) Myocardial infarction (1)
31	Jack et al, 1995	Intravenous injections	5-Fluorouracil 700 mg/m ² was given intravenously every 4 weeks for 12 injections commencing 4 weeks after completion of radiotherapy.	no adjuvant systemic therapy	-	700-3,500 (5) 4,200-7,700 (4)	9/167	N/A	N/A
32	Jäger et al, 1995	IV infusion	FU 2,600 mg/m ² was administered as a 24-hour infusion after a 2-hour infusion of FA 500 mg/m ² once a week via an intravenous port catheter system	-	-	N/A	0/69	-	N/A
33	Jensen et al, 2006	IV continuous infusion and IV bolus	- Bolus infusion of 5-FU (425 mg/ m ²) and isovorin (10 mg/m ²) for 5 days every 4 weeks for six courses (5-FU Mayo) for adjuvant	- Capecitabine 1,250 mg/m ² /day bid with oxaliplatin 130 mg/m ² /day i.v. each 3 weeks (XELOX) for palliative treatment of colorectal	- Capecitabine 1,250 mg/m ² /day bid for 2 weeks for palliative	1,275-10,625 (17)	17/362	N/A	N/A

			<p>treatment of colorectal cancer.</p> <ul style="list-style-type: none"> - 5-FU (400 mg/m²) 2-hours bolus infusion followed by (2,400 mg/m²) flat continuous infusion for 46 h (de Gramont) for treatment of colorectal cancer 	<ul style="list-style-type: none"> - Cancerx capecitabine (1,000 mg/m² bid for 2 weeks), carboplatin (AUC 5) and docetaxel (60 mg/m²) every 4 weeks for treatment of gastric cancer - 5-FU (400 mg/m²) bolus injection followed by (600 mg /m²) flat continuous infusion for 22 h and oxaliplatin (85 mg/m²), for 2 days (FOLFOX4) for treatment of colorectal cancer 	treatment of colorectal cancer				
34	Kerr et al, 1995	Infusional Hepatic Arterial	<p>HAI chemotherapy administered over 48 hours every 2 weeks. The regimen consisted of FA 200 mg/m² by IV infusion over 2 hours, followed by a loading dose of 5-FU 400 mg/m² administered by HAI infusion over 15 minutes, followed by a 22-hour infusion of 5-FU at a starting dose of 800 mg/m² identical chemotherapy was given on day 2 and the regimen was repeated every 2 weeks.</p>	-	-	1,200 (1) 8,400 (1)	2/43	2 (1) 4 (1)	Chest pain (1) Tachycardia (1)
35	Khan et al, 2012	IV Bolus and IV continuous infusion	<ul style="list-style-type: none"> - 5-FU monotherapy, 2 case - 5-FU with LV, 16 cases 	5-FU based regimen	-	N/A	3/18	N/A	N/A

36	Kim et al, 2003	IV bolus	5-FU 450 mg/m ² of 5-FU and FA at a fixed dosage of 30 mg was administered as an IV Bolus on days 1, 8 and 15 of the 4-week cycle (Received 12 cycles of therapy)	UFT at 300 mg/m ² /day and FA at 30 mg/day were administered alternately every 12 hours (the 4 weeks cycle of therapy was defined as 21 consecutive days of treatment of followed by 7-day rest period. (12 cycles)	-	N/A	0/53	-	N/A
37	Klausner et al, 1987	IV infusion	5-FU 500 mg/m ² IV infusion over 8 hr (normal saline 500 ml) followed by radiotherapy given 8 hr following the completion of the 5-FU drip (time interval between each treatment was 72 h) twice weekly	-	-	3,000 (1)	1/30	N/A	EKG abnormalities (1)
38	Köhne et al, 2005	24-hr IV infusion	The standard AIO schedule of FA 500 mg/m ² administered by intravenous infusion over 2 hours, followed by FU 2.6 g/m ² administered by infusion over 24 hours. Both drugs were administered on days 1, 8, 15, 22, 29, and 36, followed by a 2-week rest. Each treatment cycle consisted of 49 days.	The experimental group received a similar schedule but with FU 2.3 g/m ² , which was subsequently reduced to FU 2.0 g/m ² because of toxicity of therapy. Treatment was preceded on each occasion by irinotecan 80 mg/m ² administered intravenously over 30 minutes	-	N/A	13/213	any grade (9) 3-4 (4)	N/A
39	Kok et al, 1996	IV continuous infusion	Treatment consisted of FA 90 mg, given orally every hour for 4 times,	-	-	7,500 (1)	1/29	2	Chest pain (1)

			followed by a continuous infusion of 5-FU 500 mg/sqm/day for 5 days. During the 5-FU infusion, 60 mg of FA was given orally every 4 hours for a total of 30 doses. Courses were repeated every 4 weeks.						EKG abnormalities (1)
40	Kolarić et al, 1986	IV injection over 5-10 min	5-FU 12 mg/kg/day intravenous injection over 5-10 min on days 1-5, every 3-4 weeks.	4-epi-Doxorubicin 40 mg/m ² /day i.v. rapid injection on days 1 and 2 (80 mg/m ² /cycle), 5-FU was administered in lower dose (10 mg/kg/day i.v. on days 1-5). every 3-4 weeks.	-	N/A	2/56	N/A	EKG abnormalities (2)
41	Kosmas et al, 2008	IV continuous 24 h (CI), or IV short <3-h infusion (SI)	5-FU monotherapy - LV 200 mg/m ² (i.v. bolus) D1-5, followed by 5-FU 700 mg/m ² D1-5 (i.v. 3 h infusion) - LV 200 mg/m ² (i.v. bolus), followed by 5-FU 700 mg/m ² (i.v. 2 h infusion) every week - 5-FU 200 mg/m ² D1-5 (24 h CI)	Polychemotherapy - Mitomycin 10 mg/m ² D1 + LV 500 mg/m ² D1-D5 + 5-FU 1,000 mg/m ² D1-D5 - Cisplatin 100 mg/m ² D1 + 5-FU 1,000 mg/m ² continuous infusion days 2-6 - Mitomycin 10 mg/m ² D1+ 5-FU 1,000 mg/m ² D1-D5	Capecitabine	N/A	11/397	N/A	EKG abnormalities (11)
42	Kuzel et al, 1993	IV continuous infusion	5-FU administered as a continuous intravenous infusion at a dose of 1000 mg/m ² /day for 5 days every 28 days	-	-	5,000 (2)	2/22	3-4	Arrhythmia (1) Heart failure (1)
43	Labianca et al, 1982	IV bolus	5-FU 15 mg/kg IV push weekly	5-FU based - with nitrosoureas group (BCNU, MeCCNU),	-	N/A	7/480	N/A	Chest pain (7)

				<ul style="list-style-type: none"> - with BCNU or CCNU ± vincristine - with methotrexate, cyclophosphamide, vincristine - with peptichemio 					
44	Labianca et al, 1988	IV bolus	5-FU (600 mg/mq/i.v. bolus/weekly)	CDDP (60 mg/mq/i.v. every 3 weeks) + 5FU (600 mg/ mq/i.v. bolus/weekly)	-	N/A	2/28	1-2	Chest pain (2)
45	Leichman et al, 2005	IV continuous infusion	The low-dose continuous infusion (LDCI) treatment arm consisted of 5-FU given at 300 mg/m ² per day for 28 days followed by 1 week rest per cycle.	The intermittent high-dose infusion (HDI) 5-FU given at 2600 mg/m ² over a period of 24 hours weekly.	-	LDCI arm equaled 16,800 mg/m ² (25) HDI arm equaled 26,000 mg/m ² (24)	49/690	3-4 Related death (3)	N/A
46	Lestuzzi et al, 2014	IV infusion	5-FU continuous infusion 130–330 mg/mq/day for weeks or months (up to 9 months)	<ul style="list-style-type: none"> - TPF (48 patients): Docetaxel 75 mg/mq i.v. day 1, Cisplatin (CDDP) 75 mg/mq i.v. day 1, 5-FU 750 mg/mq/day days 1–5 every 3 weeks - Al Sarraf (CF) (100 patients): CDDP or Carboplatinum 100 mg/mq i.v. day 1, 5-FU 1000 mg/mq/day days 1–5 c.i. every 3 weeks - FOLFOX/ FOLFIRI (11 patients): Leucovorin 100 mg/mq i.v. day 1, Oxaliplatin 100 mg/mq i.v. day 1, 5-FU 400 mg/mq bolus i.v. day 1, 5FU 2400 mg/mq/d c.i. days 1–2 (plus Irinotecan 	-	89,100 (5)	5/49	N/A	N/A

				in FOLFIRI) every 4 weeks - Concomitant CT-RT (23 patients): CDDP 20 mg/mq i.v. day 1, 5-FU 750 mg/mq i.v. days 1-5.					
47	Meydan et al, 2005	IV bolus then IV continuous infusion	de Gramont's regimen (DG): LV 200 mg/m ² 2-hour infusion, 5-FU 400 mg/m ² bolus and 5-FU 600 mg/m ² 22 hours infusion on day 1 and 2 repeat every 2 weeks	de Gramont's regimen (DG): LV 200 mg/m ² 2-hour infusion, 5-FU 400 mg/m ² bolus and 5-FU 600 mg/m ² 22 hours infusion on day 1 and 2 repeat every 2 weeks with Gemcitabine or CPT-11 or Epirubicin or Cisplatin or carboplatin	-	1,000 (4)	4/163	N/A	Chest pain (3) Arrhythmia (1)
48	Naredi et al, 2003	Intra-arterial infusion	- Intra-arterial 5-FU 750 mg/m ² in 1000 ml saline for 4 h - Leucovorin 100 mg i.v. was given 30 min after the start of the 5-FU for 2 days every second week	- Hepatic artery occlusion (HAO) for 16 h followed by 5-FU was administered intraportally 1000 mg/m ² daily over a period of 4 h for 5 days - Allopurinol 300 mg daily orally	-	N/A	1/21	N/A	Tachycardia (1)
49	Ngan et al, 2001	IV infusion	The participating institutions had the option at the time of joining the trial of using 5-FU infusion either - 300 mg/m ² /day, 96 h per week, from Monday through Friday throughout the course of radiotherapy, or - 225 mg/m ² /day, 7 days a week, throughout the	-	-	6,270-8,820 (2)	2/82	1	N/A

			course of the radiotherapy. The 5-FU infusion began on the first day of radiation treatment and ceased on the day of the final radiation treatment.						
50	Nobile et al, 1985	IV infusion (15 min)	The treatment consisted of 200 mg/m ² of MTHF (methyltetrahydrofolate) IV bolus, followed by a 15-min infusion with 5-FU 375 mg/m ² for 5 consecutive days. Treatment was repeated every 4 weeks and at least 2 courses for response evaluation.	-	-	375 (1)	1/38	N/A	Acute pericarditis (1)
51	Öman et al, 2005	Intraperitoneal	5-FU 750–1500 mg/m ² body surface was administered intraperitoneally by gravity during 30–60 minutes. Thirty minutes after the start of the 5-FU infusion, Leucovorin 100 mg/m ² body surface was given as a slow intravenous injection. The treatment was administered for 2 consecutive days every third week.	-	-	1,500 (3)	3/68	3 (3)	Chest pain (3)
52	Poorter et al, 1995	Subcutaneous infusion chamber (Port-a-Cath)	Continuous infusion of 5-FU for 14 days every 4 weeks at a dose of 300	-	-	42,000 (1)	1/30	N/A	Myocardial infarction (1)

			mg/m ² /day via a portable infusion pump During the 5-FU infusion, oral leucovorin was administered at a dose of 5 mg/day in the first 6 patients and was then escalated by 5 mg/day in every subsequent group of 6 patients until toxicity.						
53	Regazzoni et al, 1996	IV continuous infusion	(5-FU-LDCI) 5-FU 250 mg/m ² given as an intravenous continuous infusion for 3 weeks, followed by a one-week pause.	-	-	1,000 (3)	3/106	2 (1) 3 (2)	Tachycardia (1) Heart failure (2)
54	Rosso et al, 1994	IV bolus	5-FU 370 mg/m ² administered by i.v. bolus for 5 consecutive days immediately preceded by I-FA 100 mg/m ² i.v. bolus.	-	-	N/A	4/79	1 (3) 3 (1)	Chest pain (1) Tachycardia (2) Arrhythmia (1)
55	Schober et al, 1993	IV bolus	- 5-FU 1400-2100 mg/m ² with folinic 200 mg/m ² - 5-FU 600 -700 mg/m ² with folinic 300 mg/m ² - 5-FU 500-600 mg/m ² with folinic 300 mg/m ²	5-FU 600 mg/m ² with Dipyridamole	5-FU 500 mg/m ² with Etoposide	1,800 (6) 2,100 (3)	9/250	N/A	Chest pain (4) Myocardial infarction (1) Tachycardia (3) Heart failure (1)
56	Schuster et al, 1991	IV infusion (1 hr)	5-Fluorouracil (5-FU) 450 mg/m ² day 1-5	Doxifluridine (5'dFUR) 4,000 mg/m ² day 1-5	-	N/A	0/30	-	N/A
57	Terzoli et al, 2004	IV infusion	Chronomodulated intravenous infusion of 5-FU and FA for 5 consecutive days every 3 weeks.	-	-	4,500 (2) 20,500 (3)	5/80	1 (1) 2 (3) 3 (1)	N/A

			The initial dose of 5-FU was 900 mg/m ² /day with intra-patient dose increases at 1,000 and 1,100 mg/m ² /day, at the second and third courses, respectively, in the absence of G2 toxicity. After the third cycle, the dose of 5-FU was no longer increased; 1-FA was injected simultaneously with 5-FU, at a fixed dose of 150 mg/m ² /day						
58	Tsavaris et al, 1990	IV infusion	- Allopurinol 300 mg, three times per day orally was given for 17 days starting 2 days before the other drugs - Folinic acid 200 mg/m ² per day was given by intravenous infusion before 5-FU infusion 700 mg/m ² per day in 500 ml 5% dextrose water over 1 h for 5 days. The cycle was repeated every 21 days.	-	-	10,500-21,000 (5)	5/74	N/A	5 patients in 9 cycles had tachycardia (6 cycles) and angina (3 cycles)
59	Tsavaris et al, 2005	IV short (<3 hr) infusion and IV continuous infusion	- LV 200 mg/m ² /day (i.v. bolus) days 1-5, followed by 5FU 700 mg/m ² (3 h i.v. infusion) days 1-5 - LV 200 mg/m ² (i.v. bolus), followed by 5FU	- Cisplatin 100 mg/m ² /day, day 1; 5FU 1000 mg/m ² /day, CI days 2 - 6 - Mitomycin (MMC) 10 mg/m ² /day, day 1; LV 500 mg/m ² /day, CI days	-	N/A	9/333	N/A	EKG abnormalities (9)

			700 mg/m ² (2 h i.v. infusion) every week - 5FU 1,200 mg/m ² /day (24 h CI) days 1-5; LV 200 mg/m ² /day, CI days 1-5	1-5; 5FU 1,000 mg/m ² /day, CI days 1-5 - Mitomycin (MMC) 10 mg/m ² /day, day 1; 5FU 1,000 mg/m ² /day, CI days 1-5					
60	Tsuchida et al, 2005	IV continuous infusion	Radiotherapy was delivered at 1.8–2.0 Gy/day, Chemotherapy was administered 5 days/week (Monday to Friday), as a continuous infusion of 5-FU (300mg/m ² /24 h) for at least 5 weeks from the first day of radiotherapy.	-	-	24,000 (1)	1/14	3 (1)	Pericardial effusion (1)
61	Urba et al, 1992	IV infusion	Radiation therapy administered as 350-cGy fractions 5 days a week for 14 fractions. 5-FU 300 mg/m ² /d as a continuous intravenous infusion over 24 hours, for a total of 96 hours each week for 3 weeks.	-	-	2,400 (1) 3,096 (1)	2/24	N/A	Chest pain (1) Myocarditis (1)
62	Van Cutsem et al, 2001	IV bolus	5-FU/LV; LV 20 mg/m ² as a rapid IV injection followed by an IV bolus injection of 5-FU 425 mg/m ² , administered daily for 5 days in 4-week cycles	Capecitabine monotherapy 1,250 mg/m ² , twice daily for 2 weeks followed by 1 week rest	-	N/A	3/301	N/A	Myocardial infarction (1) Heart failure (1) Edema (1)
63	van Groeningen et al, 1989	IV infusion	Leucovorin (200 mg/m ²) was administered as an i.v. bolus injection daily for	-	-	6,700 (1) 12,000 (1)	1/22	N/A	Chest pain (1) EKG abnormalities (1)

			5 days; 1 h later, 5-FU was given at an initial dose of 370 mg/m ² as a 2 h i.v. infusion daily for 5 days This treatment was repeated at 21-day intervals						
64	Wang et al, 1998	IV continuous infusion	5-FU 2600 mg/m ² and LV 100 mg/m ² given concurrently over 24 hours of continuous intravenous infusion with the aid of an infusion pump, the treatment was repeated every week	-	-	20,800 (1)	1/41	3 (1)	Cardiomegaly (1)
65	Weh et al, 1994	IV continuous infusion	6 weekly infusions of high dose 5-FU (2600 mg/m ² as 24-hour infusion) and FA (500 mg/m ² as 1-hour infusion prior to 5-FU)	-	-	N/A	2/48	3 (1) 4 (1)	Chest pain (1) Myocardial infarction (1)
66	Yang et al, 1999	IV continuous infusion	- 5-FU, 2600 mg/m ² , admixed with LV, 100 mg/m ² , in a portable infusion pump administered intravenously over a 24-hour period. - The 5-FU/LV was delivered once a week for 5 consecutive weeks followed by a 1-week recovery period. This 6-week period constituted 1 treatment course.	-	-	N/A	1/36	3 (1)	N/A

67	Yang et al, 2001	Portable infusion pumps and through the subcutaneous port administered intravenously over an 8-h period.	The initial dose of 5-FU was 1200mg/m ² , the dose being escalated by 200 mg/m ² weekly. The 5-FU LV admixture was administered to the patients once per week for five consecutive weeks followed by a 1-week rest period. This 6-week period constituted one treatment course.	-	-	N/A	0/26	-	N/A
68	Yang et al, 2002	IV continuous 24 hr infusion	Weekly 24 h infusion of 5-FU 2600 mg/m ² plus LV 100 mg/m ² was used as salvage therapy	Oral UFT 300 mg/m ² /d plus LV 90 mg/d oral UFT 300 mg/m ² /d plus LV 90 mg/d for 28 days followed by a 7-day rest period from all treatment.	-	N/A	0/26	-	N/A
69	Ychou et al, 2003	IV bolus then IV infusion 22 hr via a battery-operated pump	Folinic acid (200 mg/m ² per day) by i.v. infusion over 2 h followed by a 5-FU bolus (400 mg/m ² per day) and immediately after by continuous 5-FU infusion (600 mg/m ² per day) administered via a battery-operated pump over the next 22 h for two consecutive days, i.e., 2000 mg/m ² per cycle.	-	-	12,000 (4)	4/53	1 (3) 3 (1)	N/A
70	Yilmaz et al, 2007	IV bolus then IV continuous infusion	LV 200 mg/m ² 2-hour infusion, 5-FU 400 mg/m ² bolus and 5-FU 600 mg/m ² 22 hours	-	-	1,000 (21)	21/27	N/A	Chest pain (2) Arrhythmia (19)

			infusion on day 1 and 2 repeat every 2 weeks.						
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*Some included studies may not completely report the number of cardiotoxicity subtypes. 5-FU: 5-fluorouracil, AUC: Area under the curve, BCNU: Carmustine, CDDP: Cisplatin, CHF: Congestive heart failure, CI: Continuous infusion, CIV: Continuous intravenous infusion, CPT-11: Irinotecan, CT: Computed tomography, CTCAE: Common Terminology Criteria for Adverse Events, d: day, DVT: Deep Vein Thrombosis, EKG: Electrocardiogram, FA: Folinic acid, HAI: Infusional Hepatic Arterial, HD: High dose, HDI: The intermittent high-dose infusion, hr/h: hour, HU: Hydroxyurea, IV: Intravenous, LD: Low dose, LDCI: The low-dose continuous infusion, LEV: Levamisole, LV: Leucovorin, MeCCNU: Lomustine, MMC: Mitomycin, MTX: Methotrexate, N/A: Not applicable, OXA: Oxaliplatin, P.O.: Per oral, PTX: Paclitaxel, RT: Radiotherapy, UFT: Tegafur/uracil, VTE: Venous Thromboembolism, WHO: World Health Organization.