Clinical Trials of Low-Dose Metronomic Chemotherapy in Castration-Resistant Prostate Cancer

8

Keemo Delos Santos, Lavarnan Sivanathan, Kelly Lien, and Urban Emmenegger

Abstract

Low-dose metronomic (LDM) chemotherapy is the continuous or near-continuous use of conventional chemotherapeutic agents at doses that do not necessitate cyclic treatment interruptions. Recently, LDM chemotherapy has gained traction for the treatment of castration-resistant prostate cancer (CRPC). Its excellent safety profile and relatively low rate of severe (i.e., grade 3/4) toxicities make it an enviable treatment, especially for elderly and frail CRPC patients. By searching the MEDLINE, EMBASE, and CENTRAL databases, we identified fifteen published prostate cancer LDM chemotherapy trials comprising 471 patients. The trials were stratified and analyzed according to three common types of LDM regimens: (1) cyclophosphamide monotherapy, (2) cyclophosphamide plus corticosteroid, and (3) complex combination regimens. Oral cyclophosphamide was part of all LDM regimens. Collectively, LDM chemotherapy was found to be beneficial in almost 60 % of patients (mean clinical benefit rate of 58.08 ± 20.30). Severe treatment-associated side effects were rarely seen, with anemia being the most commonly reported. One comparative single-center study showed a superior safety profile and comparable benefit of LDM cyclophosphamide therapy compared to conventional, maximum tolerated dose (MTD) docetaxel

Authors K. Delos Santos and L. Sivanathan are contributed equally.

K. Delos Santos • L. Sivanathan • K. Lien
Division of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada

U. Emmenegger (✉)
Division of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada

Biological Sciences Platform, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

Institute of Medical Science, University of Toronto, Toronto, ON, Canada
e-mail: urban.emmenegger@sunnybrook.ca

G. Bocci, G. Francia (eds.), *Metronomic Chemotherapy: Pharmacology and Clinical Applications*, DOI 10.1007/978-3-662-43604-2_8,

chemotherapy. Another study highlights that prior LDM chemotherapy does not negatively impact on the subsequent use of MTD docetaxel chemotherapy. In addition, five studies document the benefit of LDM chemotherapy in CRPC patients that have undergone MTD docetaxel chemotherapy. Randomized phase III trials will be needed to allow definitive conclusions as to the clinical utility of the LDM approach in CRPC. Unfortunately, the metronomic use of off-patent drugs such as cyclophosphamide faces unique commercial and regulatory hurdles that are slowing down the clinical development of LDM chemotherapy in prostate cancer and other malignancies.

Abbreviations

bid	Twice a day
CPA	Cyclophosphamide
CRPC	Castration-resistant prostate cancer
LDM	Low dose metronomic (chemotherapy)
MTD	Maximum tolerated dose (chemotherapy)
N/A	Not applicable
od	Once a day
po	Orally
PSA	Prostate-specific antigen
tid	Thrice a day
TTF	Time to treatment failure
TTPP	Time to PSA progression
UFT	Uracil/tegafur

8.1 Introduction

Prostate cancer is the most common non-skin malignancy diagnosed in men. Its incidence and prevalence are peaking in men over 60 years of age, who often also suffer from a number of comorbidities [1]. Despite screening efforts and curative treatment attempts for localized disease, around 25 % of prostate cancer patients present with metastases at diagnosis or during later disease stages. While androgen-deprivation therapy is almost universally applied as the first-line treatment of choice for metastatic prostate cancer, docetaxel chemotherapy is used in only around one-third of patients with castration-resistant prostate cancer (CRPC) [2, 3]. Old age and comorbidities may account for the latter finding. In fact, the use of docetaxel is negatively associated with increasing age of CRPC patients [2]. On the other hand, docetaxel chemotherapy seems to be well tolerated and beneficial in patients up to the age of 80 [4]. Of note, in octogenarians, an individualized treatment approach should be considered.

A recent systematic review of 80 published phase I/II clinical trials studying low-dose metronomic (LDM) chemotherapy documented that this novel form of chemotherapy administration is not only beneficial but that it also excels with an excellent

safety profile [5]. Mean response and median clinical benefit rates were found to be 26.03 % and 46.50 %, respectively. Furthermore, severe side effects were seen in less than 5 % of patients. Aside from breast cancer (26.25 %; $n=21$ studies), prostate cancer was the second most common tumor type studied in LDM chemotherapy trials (11.25 %; $n=9$ studies).

A number of reasons may explain why LDM chemotherapy has gained so much traction in the prostate cancer field. First, the high prevalence of CRPC in elderly and frail patients emphasizes the need for alternative treatment strategies that are more adjusted to this patient population than conventional, maximum tolerated dose (MTD) chemotherapy and its relatively high rate of severe acute toxicities. In fact, safety aspects and quality of life are of paramount importance when it comes to treatment decisions in these patients. In addition, the usually oral and outpatient way of LDM drug administration is particularly appealing to patients with incurable malignancies and limited life expectancy. Second, in the 1980s and early 1990s, cytotoxic treatment of prostate cancer was dominated by metronomic-like oral regimens of cyclophosphamide, etoposide, or estramustine [6, 7]. However, the dosing of such regimens was oriented towards MTD chemotherapy administration, and thus, planned treatment interruptions were common [8]. Third, prostate cancer tumor models have been commonly used in preclinical studies of LDM chemotherapy [9–11]. Fourth, despite recent unprecedented advances in the treatment of CRPC that have seen the approval of potent second-line hormonal therapies, such as abiraterone and enzalutamide, inherent and acquired therapeutic resistance remains a major obstacle to render CRPC a chronic, manageable condition, not to speak of a curable disease [12]. In other words, there continues to be an unmet need for novel treatment modalities. Finally, the economic burden of off-patent drugs such as cyclophosphamide compares favorably to the costs associated with conventional chemotherapy and recently approved targeted anticancer agents [13, 14].

8.2 Overview of Low-Dose Metronomic Chemotherapy Trial Experience in Prostate Cancer to Date

We identified published prostate cancer LDM chemotherapy trials by searching the MEDLINE, EMBASE, and CENTRAL databases (using the keywords "metronomic" and "chemotherapy" and "prostate cancer" or "prostate neoplasm" or "prostate tumour") and by applying the following working definition of LDM chemotherapy, i.e., the continuous or near-continuous use of conventional chemotherapeutic agents at doses that do not necessitate cyclic treatment interruptions to prevent acute treatment-associated toxicities. Although many of the novel targeted anticancer agents are used in a metronomic-like way (i.e., continuously), we focus herein on classical cytotoxic agents as the major component of LDM regimens. We also excluded studies comprising miscellaneous tumor types, including rare cases of prostate cancer [5]. Fifteen studies fulfilled the search criteria and are discussed in more detail.

The study characteristics are summarized in Table 8.1. Briefly, four studies were retrospective chart reviews (27 %) [15–18], nine were prospective,

Table 8.1 Study demographics

	Study design	CRPC stage	Number of patients (evaluable)	Age median (range)	Baseline PSA median (range) ng/mL	Performance status (ECOG)
Lord et al. [19]	Phase II study	Early	80 (58)	69 (51–86)	43.9 (2.4–789)	≤2 (ECOG)
Jellvert et al. [20]	Phase II study	Early	17 (17)	60 (40–75)	N/A	N/A
Vorob'ev et al. [28][a]	Phase II study	Early	25 (25)	72.8 (56–85)[b]	333.1 (±437.4)[c]	≤3 (ECOG)
Nishimura et al. [21]	Phase II study	*Early*-advanced	21 (21)	70 (50–82)	27 (3.6–2,240)	≤3 (ECOG)[d]
Glode et al. [15]	Retrospective chart review	*Early*-advanced	34 (32)	72.6 (54–88)[b]	43.9 (2.4–789)	N/A
Fontana et al. [16]	Retrospective chart review	*Early*-advanced	29 (29)	83 (78–92)	49.4 (6.7–567.8)	≥0 (ECOG)
Hatano et al. [18]	Retrospective chart review	*Early*-advanced	57 (57)	71 (49–90)	27.7 (1.9–7176.0)	≤2 (ECOG)
Nicolini et al. [22]	Phase II study	Early-*advanced*	8 (8)	72 (62–84)	>4–50	≤2 (ECOG)
Fontana et al. [23]	Phase II study	Early-*advanced*	28 (28)	74.5 (54–91)	63.2 (10–5,000)	≤2 (ECOG)
Dickinson et al. [17]	Retrospective chart review	Early-*advanced*	28 (28)	75	123.5 (16–3,448)	N/A
DiLorenzo et al. [29]	Phase I study	Post-docetaxel	16 (16)	67 (46–75)	180 (110–300)	≥1 (ECOG)[d]
Ladoire et al. [24]	Phase II study	Post-docetaxel	23 (23)	74 (55–88)	411 (30–1,760)	≤3 (ECOG)
Nelius et al. [25]	Phase II study	Post-docetaxel	17 (17)	68 (42–85)	134 (11.89–6,554)	≤2 (ECOG)
Gebbia et al. [26]	Phase II study	Post-docetaxel	60 (58)	72 (56–83)	156 (45–478)	≤2 (ECOG)
Meng et al. [27]	Phase II study	Post-docetaxel	28 (28)	72.8 (69–78)	549.5 (50.8–5075.3)	≤2 (ECOG)

Abbreviations: *CRPC* castration-resistant prostate cancer, *PSA* prostate-specific antigen, *ECOG* Eastern Cooperative Oncology Group, *N/A* not applicable

[a]Low-dose metronomic chemotherapy arm

[b]Mean age

[c]Mean (SD)

[d]Karnofsky performance status converted to ECOG performance status

single-arm phase II trials (60 %) [19–27], one was a nonrandomized comparison of CRPC patients undergoing LDM cyclophosphamide monotherapy with a group of patients from the same institution receiving conventional docetaxel chemotherapy (7 %) [28], and one was a prospective phase I trial (7 %) [29]. As is the case with other tumor types, there is no published phase III data available on the use of LDM chemotherapy in prostate cancer but plans for a randomized phase III trial are in motion [30].

All LDM chemotherapy trials accrued patients with CRPC, but the inclusion criteria were often vague, involving patients with (1) early CRPC, patients that had not undergone extensive second-line hormonal therapy attempts, (2) advanced CRPC, patients that had received ≥1 line of second-line hormonal manipulations and/or non-docetaxel chemotherapy, and (3) patients that had undergone docetaxel chemotherapy. Some of the studies comprised patients across these arbitrary categories. Out of the 471 patients enrolled in all these trials, 445 were considered evaluable for response assessment.

Patient age ranged from 40 to 92 years (median age = 72). The average median baseline prostate-specific antigen (PSA) of 146.4 ng/mL is an indication for mostly advanced CRPC stages. With few exceptions [21, 24, 28], the performance status (according to the Eastern Cooperative Oncology Group scale) of study patients was 2 or less. In comparison, contemporary phase III CRPC trials comprise mainly of men with an ECOG performance status of 1 or less, aged 40–95 (median = 69.5), and presenting with an average median baseline PSA (ng/mL) of 103.9 [31–36]. In sum, CRPC patients in the identified LDM chemotherapy trials tend to be older and have higher baseline PSA levels than the prototypical randomized phase III trial CRPC patient. Nonetheless, the patients receiving LDM chemotherapy appear to be largely representative of European or North American CRPC patients, where the majority of the included studies were conducted.

8.3 LDM Chemotherapy Regimens: Clinical Benefit and Side Effects

Table 8.2 depicts the details of the LDM regimens studied. Of note, cyclophosphamide was the chemotherapy backbone of all 15 trials. In 11 trials, cyclophosphamide was flat-dosed at 50 mg po daily. Only four trials studied higher daily cyclophosphamide doses: 50 mg/m^2 od [19], 50 mg po bid [18, 20], or 100 mg po od alternating with 150 mg po od [22]. Fontana et al. also administered a single intravenous bolus of 500 mg/m^2 on the first day of study treatment [23].

8.3.1 Cyclophosphamide Monotherapy

Three clinical trials assessed the activity of cyclophosphamide monotherapy, albeit applying three different cyclophosphamide schedules [19, 22, 28]. Lord et al.

Table 8.2 Treatment regimens

	Treatment					Median duration of treatment [months (range)]
	Chemotherapy drugs			Targeted agents	Corticosteroids	
Lord et al. [19]	CPA 50 mg/m^2 po od					8
Jellvert et al. [20]	Week 1,3,5: CPA 50 mg po bid[b]; ketoconazole 200 mg po tid	Week 2, 4, 6: etoposide 50 mg po bid; EMP 140 mg po bid			Prednisone 10 mg po od	3.5 (0.75–5.5)
Vorob'ev et al. [28][a]	CPA 50 mg po od					6.7 (1–16)
Nishimura et al. [21]	CPA 50 mg po bid	UFT 200 mg po bid	EMP 280 mg po bid			2 (1–3)
Glode et al. [15]	CPA 50 mg po od				Dexamethasone 1 mg po od	9 (95 % CI: 6–14)
Fontana et al. [16]	CPA 50 mg po od			Celecoxib 200 mg po bid	Dexamethasone 1 mg po od	≥3
Hatano et al. [18]	CPA 50 mg po bid	UFT 200 mg bid			Dexamethasone 0.5 mg po bid	4.5 (0.25–45.75)
Nicolini et al. [22]	CPA alternating 100 or 150 mg po od[c]					N/A
Fontana et al. [23]	CPA 50 mg po od[d]			Celecoxib 200 mg po bid	Dexamethasone 1 mg po od	5.4 (1.4–21.5)
Dickinson et al. [17]	CPA 50 mg po od				Dexamethasone 2 mg po od	N/A
DiLorenzo et al. [29]	CPA 50 mg po od			THD 100 or 200 mg po od[e]		N/A
Ladoire et al. [24]	CPA 50 po od				Prednisolone 10 mg po od	N/A
Nelius et al. [25]	CPA 50 mg po od				Dexamethasone 1 mg po od	N/A
Gebbia et al. [26]	CPA 50 mg po od	MTX 2.4 mg po 2×/week				4.5
Meng et al. [27]	CPA 50 mg po od	Capecitabine 1,000 mg po bid		THD 100 mg od	Prednisone 5 mg po bid	6.3 (1.5–20.5)

Abbreviations: *CPA* cyclophosphamide, *UFT* uracil/tegafur, *EMP* estramustine, *THD* thalidomide, *MTX* methotrexate, *od* once a day, *bid* twice a day, *tid* thrice a day, *po* orally, *N/A* not applicable

[a]metronomic arm

[b]one patient received 5 mg od of Idarubicin 4 days/week instead

[c]plus: uromitexan 400 mg po od during 3 of 4 weeks

[d]plus: cyclophosphamide 500 mg/m^2 single iv bolus day 1

[e]plus: Coumadin 1 or 2 mg po od

prescribed cyclophosphamide at 50 mg/m^2, which would correspond to a daily intake of around 90 mg of cyclophosphamide assuming an average body surface area of 1.8 m^2 [37] or even higher given that androgen-deprivation therapy may be associated with significant weight gain in a sizable number of CRPC patients. The daily cyclophosphamide dosing of >50 mg could explain the grade 3/4 lymphopenia rate of 32.8 %. On the other hand, Nicolini et al., who studied a daily alternating oral cyclophosphamide regimen of 100 or 150 mg, reported no instances of lymphopenia. However, grade 2 or 3 neutropenia was noted in all 8 patients, and, as a result, 4 of them came down with infections [22]. In the phase II study by Vorob'ev et al., 50 mg of daily oral cyclophosphamide was not associated with any grade 3 or 4 toxicities at all.

The PSA response rate in the three LDM cyclophosphamide monotherapy studies ranged from 12 to 34.5 % (Table 8.3), with a positive trend for an increasing PSA response rate with an increased daily cyclophosphamide dose. On the other hand, the composite rate of PSA response and PSA stabilization was the highest in the study by Vorob'ev et al. (84 %), and the median response duration was similar in all three trials (around 7.6 months). Inter-study variability and overall small sample sizes, amongst others, preclude definite conclusions about the nature of the association of cyclophosphamide with significant clinical benefit.

8.3.2 Cyclophosphamide plus Corticosteroid Combinations

Cyclophosphamide plus corticosteroid therapy was studied in four trials involving around 25 patients each [15, 17, 24, 25]. Commonly, 50 mg of cyclophosphamide po od was coadministered with varying dosages of dexamethasone (1 or 2 mg po daily) [15, 17, 25] or with 10 mg of prednisolone po od [24]. Since corticosteroids have been shown to be active agents in CRPC, the PSA response and stabilization rates achieved need to be interpreted carefully. They are found to be in the same range as seen with LDM cyclophosphamide monotherapy, as is the case with the median response duration of 6 or 8 months seen in the Glode and Ladoire studies [15, 24].

While the retrospective chart review by Glode et al. did not provide detailed toxicity profiles, Nelius et al. reported no incidence of severe side effects [15, 25]. On the other hand, Ladoire et al. reported severe cases of lymphopenia (26 %), anemia (8 %), and neutropenia (4 %) [24]. Furthermore, the degree of anemia found in 14 % of patients by Dickinson et al. was not specified [17].

8.3.3 Complex Combination Regimens

In attempts to enhance the antiangiogenic effects, LDM cyclophosphamide was combined with the cyclooxygenase-2 inhibitor, celecoxib, in two trials by Fontana et al. [16, 23]. Whereas concurrent cyclooxygenase-2 inhibition appeared to be well tolerated in CRPC patients undergoing LDM cyclophosphamide therapy, the clinical outcome was similar compared to the aforementioned studies of LDM

Table 8.3 Treatment outcome and response

	PSA response (%)	PSA stabilization (%)	PSA progression (%)	Median TTPP [months] (range)	Tumor response rate [RECIST] (%)	Bone metastasis response (%)	Median response duration/TTF [months] (range)	Clinical benefit (%)
Lord et al. [19]	34.5	17.2	48.3	N/A	N/A	N/A	7.5 (CI 3–18)	45
Jellvert et al. [20]	59	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vorob'ev et al. [28][a]	12	72	16	N/A	N/A	N/A	6.3 (2–13)	84
Nishimura et al. [21]	57	24	19	N/A	N/A	10	7 (2–15)	81
Glode et al. [15]	69	6	25	N/A	N/A	N/A	8 (95 % CI 4–10)	75
Fontana et al. [16]	45	17	38	N/A	7	N/A	8.6 (95 % CI 7.6–9.6)	62.5
Hatano et al. [18]	63	26	11	7.2 (4.1–10.1)	29	N/A	N/A	69
Nicolini et al. [22]	25	37.5	37.5	N/A	N/A	N/A	9 (8–31)	62.5
Fontana et al. [23]	32	18	50	3 (2.2–4.2)	17.86	N/A	9.8 (4.9–19.3)	50
Dickinson et al. [17]	46	15	39	4	N/A	N/A	N/A	14
DiLorenzo et al. [29]	15	8	76.9	N/A	N/A	N/A	N/A	23
Ladoire et al. [24]	26	48	22	N/A	N/A	N/A	6 (95 % CI 4–8)	74
Nelius et al. [25]	24	29	47	3 (1–9)	N/A	N/A	N/A	53
Gebbia et al. [26]	25	38	36	N/A	N/A	N/A	4.2 (2–11.2)	63
Meng et al. [27]	35.7	21.4	42.9	2.8 (1–8.6)	N/A	N/A	N/A	57.1

Abbreviations: *PSA* prostate-specific antigen, *TTPP* time to PSA progression, *TTF* time to treatment failure, *RECIST* response evaluation criteria in solid tumors, *N/A* not applicable

[a]Low-dose metronomic chemotherapy arm

cyclophosphamide monotherapy. The longest median response duration of all trials included in our analysis reported by Fontana et al. (9.8 months) might be at least partially attributed to the fact that patients also received a single 500 mg/m^2 bolus cyclophosphamide infusion on the first day of study treatment.

Two studies combined LDM cyclophosphamide with thalidomide, an agent with pleiotropic antitumor effects that also include antivascular activities [27, 29]. In the absence of a trend for increased PSA response rates in both studies when compared to LDM cyclophosphamide monotherapy, the thalidomide-associated toxicities seen by DiLorenzo et al., such as myelosuppression, constipation, neuropathy, and thromboembolic complications, dampen the enthusiasm to further pursue this type of treatment combination. Interestingly, Meng et al. did not report any severe side effects in their patients that also received 5 mg of prednisone po bid and LDM capecitabine.

Four studies explored combinations of ≥2 chemotherapy agents administered concurrently. Nishimura et al. combined cyclophosphamide with the 5-fluorouracil precursor UFT (uracil/tegafur) and with estramustine phosphate [21]. The latter is an estradiol derivative with a nitrogen mustard-carbamate ester moiety with antimicrotubule activities. Likewise, Hatano et al. administered a regimen of cyclophosphamide with UFT and dexamethasone [18]. Gebbia et al. analyzed the benefit of a cyclophosphamide and methotrexate doublet LDM chemotherapy regimen that is commonly used for the treatment of breast cancer [26]. As previously mentioned, Meng et al. combined cyclophosphamide and capecitabine in a regimen also containing thalidomide and prednisone [27]. Despite the limitations of cross-comparing these doublet or triplet LDM chemotherapy regimens with LDM cyclophosphamide monotherapy, the PSA response and stabilization rates were comparable, as were the side effect profiles.

Conventional chemotherapy regimens often comprise several cytotoxic agents with different mechanisms of action that are either scheduled concurrently or sequentially/alternating in an attempt to delay or overcome chemoresistance. Jellvert et al. describe a similar LDM chemotherapy approach based on cyclophosphamide and ketoconazole (an androgen synthesis inhibitor) administration alternating with the use of the topoisomerase II inhibitor etoposide coadministered with estramustine phosphate [20]. Unfortunately, the limited clinical data provided does not allow definitive conclusions as to the clinical potential of this innovative LDM treatment approach. However, the reported incidences of severe toxicities are disconcerting, even though they are based on small absolute numbers given a sample size of 17 patients: thrombocytopenia (24 %), anemia (18 %), heart failure (12 %), abdominal pain (6 %), repeated infections (6 %), pulmonary embolism (6 %), deep vein thrombosis (6 %), acute cholestasis (6 %), weight loss (6 %), and diarrhea (6 %).

8.4 Conventional Versus LDM Chemotherapy

The phase II trial by Vorob'ev et al. is one of the few in the metronomic field that have compared MTD with LDM chemotherapy [28]. Briefly, it is a recent nonrandomized study that compared the efficacy and safety of LDM cyclophosphamide

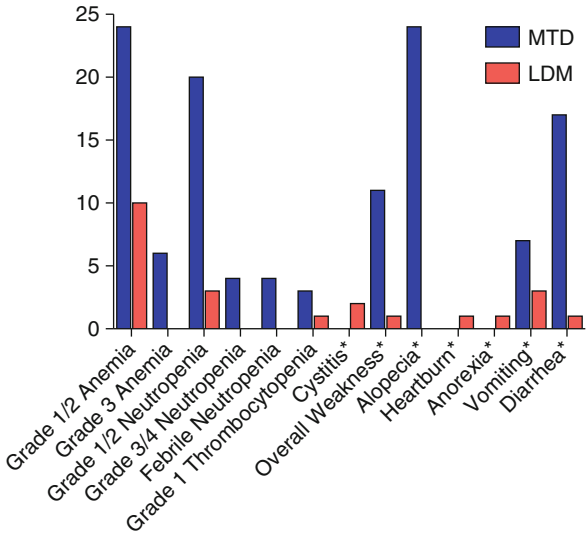

Fig. 8.1 Incidence of adverse side effects in MTD versus LDM treatment arms arising in the study by Vorob'ev et al. [28]: Incidence of adverse side effects, expressed as number of patients affected, between two patient groups treated with either (1) low-dose metronomic chemotherapy (cyclophosphamide) or (2) maximum tolerated dose chemotherapy (docetaxel). *Grade not specified

(50 mg po daily) in 25 early-stage CRPC patients with 30 patients from the same institution that had received MTD docetaxel (75 mg/m^2, every 3 weeks). Vorob'ev et al. did not find significant differences in the median survival time between the LDM and MTD treatment options (15.4 ± 2.2 versus 15.9 ± 1.7 months, respectively). On the other hand, PSA-based parameters, i.e., a PSA response rate of 46.7 % for the MTD arm versus 12 % for LDM cyclophosphamide ($p = 0.02$) with a median PSA stabilization of 6.7 months versus 6.3 months ($p = 0.60$), favored the MTD arm. Likewise, the quality of life assessment using the FACT-P questionnaire (an improvement of 26.7 % in MTD versus 16 % in LDM) and the rate of pain response (according to a visual analogue scale) favored the MTD arm numerically, albeit not statistically significant. While pain reduction occurred in 42.9 % of patients treated with MTD (in contrast to 31.3 % of LDM), the study did not comment on the extent of pain reduction.

With regard to adverse side effects, there is a significant difference between the two treatment options, with consistently lower incidences of side effects occurring in the LDM group (Fig. 8.1). Indeed, no grade 3 or 4 hematologic or non-hematologic toxicities were observed in the LDM group. Overall, Vorob'ev et al. reached the conclusion that, while LDM treatment has some therapeutic significance and is well tolerated, it seemed to be less efficient than standard MTD treatment.

8.5 Low-Dose Metronomic Chemotherapy-Associated Toxicities

Detailed treatment-associated toxicities were reported in 11 LDM chemotherapy trials (Table 8.4). Generally, severe (i.e., grade 3/4) side effects were rarely seen with LDM regimens. This was particularly true for the most commonly used

Table 8.4 Grade 3 and 4 toxicities

	Anemia	Leukopenia	Neutropenia	Thrombocytopenia	Lymphopenia	Hemorrhagic cystitis	Nausea	GI toxicities	Abdominal pain	Acute cholestasis	Peripheral neuropathy	Thromboembolisms	Heart failure	Repeated infections	Weight loss(≥5kg)
Lord et al. [19]	1.7		1.7		32.8										
Jellvert et al. [20]	18			24				6	6	6		12	12	6	6
Vorob'ev et al. [28]															
Nishimura et al. [21]	5	14				5									
Hatano et al. [18]			5												
Fontana et al. [23]															
Dickinson et al. [17]	14														
DiLorenzo et al. [29]	10		37					17			17	17			
Ladoire et al. [24]	8		4		26										
Nelius et al. [25]															
Gebbia et al. [26]		11		3			2								
Meng et al. [27]															

Note: Incidence of grade 3 and 4 side effects (expressed as a percentage of study patients affected)

<5 or not reported
5–10
10–20
>20

cyclophosphamide regimen of 50 mg po daily. Four studies did not report any severe side effects at all [23, 25, 27, 28].

With respect to hematologic toxicities, one needs to consider that cytopenias might also be related to bone-marrow infiltration by prostate cancer cells. On the other hand, it is not unexpected that some of the studies identified patients presenting with severe lymphopenia. In fact, oral cyclophosphamide regimens are used for the treatment of autoimmune disorders, albeit at higher daily doses than 50 mg [38, 39]. Furthermore, total lymphocyte counts may mask the selective depletion of regulatory T lymphocytes by LDM cyclophosphamide, which in turn has been shown to enhance antitumor immunity [40]. While it is not known if immunosuppressive or immunostimulatory cyclophosphamide effects prevail at 50 mg of cyclophosphamide daily, it is reassuring that severe lymphopenias were not accompanied by opportunistic infections [19, 24]. It is similarly reassuring that only 1 out of 471 patients included in the analyses herein developed hemorrhagic cystitis [21].

Compared to LDM cyclophosphamide monotherapy, doublet LDM chemotherapy regimens appear to be similarly well tolerated [21, 26, 27]. However, comedications seem to have contributed to some of the toxicities seen. Specifically, the use of ketoconazole and estramustine likely contributed to the gastrointestinal

and thromboembolic complications reported by Jellvert et al. [20]. In addition, constipation, neuropathy, and thromboembolic events are commonly seen in patients undergoing thalidomide therapy [29]. On the other hand, despite similar thalidomide dosing, no high-grade side effects were seen by Meng et al. [27].

By virtue of its alkylating properties, cyclophosphamide has been shown to increase the risk of secondary malignancies such as leukemia and urothelial cell carcinomas. Dobi et al. recently described a CRPC patient treated with 50 mg of cyclophosphamide daily for 36 months who eventually developed acute myelogenous leukemia characterized by cytogenetic abnormalities frequently observed in alkylating agent-induced leukemias [41]. A cumulative cyclophosphamide dose of >10 g/m^2 (approximate equivalent of 200 days of treatment with 50 mg of cyclophosphamide po daily in a patient with a body surface area of 1.8 m^2) is considered to increase the leukemia risk [42, 43]. While no instances of bladder malignancies were reported, the risk of urothelial cancer doubles for every 10 g cyclophosphamide increment. In addition, treatment duration of more than 1 year was associated with an 8-fold increased risk of bladder cancer [44]. However, no instances of urothelial cell carcinoma were described, admittedly in a patient population with limited life expectancy.

8.6 LDM Chemotherapy for Prostate Cancer: Challenges Ahead

Collectively, LDM chemotherapy was found to be beneficial in almost 60 % of patients (mean clinical benefit rate of 58.08 ± 20.30). In addition, severe treatment-associated side effects were rare. However, there are numerous shortcomings of the evidence published thus far that are worth to be mentioned.

First, our conclusions are based on relatively small and heterogeneous phase I/II trials encompassing 471 patients. While all the trials focused on metastatic CRPC, the extent of pretreatment was highly variable within and between trials. In addition, the study authors used variable endpoint definitions. Second, the term LDM chemotherapy remains vaguely defined. There are no accepted pharmacodynamic surrogate markers to guide proper drug dosing and scheduling. Although cyclophosphamide was the "metronomic backbone" of all LDM regimens, variable cyclophosphamide doses were applied, and cyclophosphamide was combined with a wide array of comedications. Moreover, there is also a lack of detailed knowledge about the benefits of using other drugs than cyclophosphamide in LDM regimens. Third, the limited number of patients studied thus far does not allow definite statements about the rate of rare but potentially clinical significant side effects. Fourth, in the absence of predictive markers of response, all the trials were performed in unselected patients. On the other hand, inherent therapeutic resistance to LDM chemotherapy is common, and acquired resistance develops almost invariably in patients that initially respond to such therapy [11]. While being clearly distinct from resistance to MTD cyclophosphamide [45], the molecular basis of resistance to LDM cyclophosphamide is only poorly understood [11, 46, 47]. In the absence of such molecular information, predictive marker studies performed as part of LDM chemotherapy trials have focused on

angiogenesis-related markers, accounting for the fact that LDM chemotherapy is thought to work primarily via antiangiogenic mechanisms. However, a recent systematic analysis of correlative studies did not reveal consistent results regarding the predictive power of such markers [48]. Interestingly, vascular endothelial growth factor polymorphism analysis of patients of the LDM chemotherapy trial by Fontana et al. discussed herein [23] revealed a highly significant association of the 634CC genotype with treatment outcome [23, 30]. The authors have to be lauded that they plan to validate these findings in a randomized phase III trial.

There are also a number of practical hurdles that slow down the development of LDM chemotherapy towards becoming an accepted treatment modality in prostate cancer. Foremost, there is a lack of phase III trial data. Using cyclophosphamide as an example, it is challenging to obtain industry support for trials with off-patent drugs without commercial interest. On the other hand, studying novel agents combined with LDM chemotherapy is unlikely to result in regulatory approval. Potentially, philanthropic or governmental funding bodies could step in to fill this void. Of note, a pharmacoeconomic evaluation by Bocci et al. suggests that the use of LDM versus MTD chemotherapy may result in cost savings [49]. A "metronomic backbone" may also spare patients the acute side effects typically associated with conventional chemotherapy and may enable the treatment of frail and elderly otherwise not considered for MTD chemotherapy.

It also remains to be seen if there is a role of LDM chemotherapy for earlier stages of prostate cancer. In fact, the beneficial results from randomized phase III trials in early lung and breast cancer applying metronomic-like regimens suggest a role for this treatment modality in the (neo)adjuvant setting, possible also for early prostate cancer [50, 51].

Overseeing the first decade of LDM chemotherapy development in prostate cancer and other malignancies, only history will tell if we are at the end of the beginning or the beginning of the end of rendering this novel use of conventional chemotherapy drugs an accepted treatment modality for prostate cancer. Accounting for the current shift of paradigm towards personalized treatment approaches in cancer therapy, it will be essential to identify pharmacodynamic and predictive markers of response that will provide guidance to use the right chemotherapeutic drug (either alone or in combination) for the right patient with the most suited administration schedule.

Acknowledgments The authors would like to thank Ms. V. Evdokimova for her help with the translation of the article by Vorob'ev et al. (2011). U. Emmenegger was supported by a Clinician Scientist Award from Prostate Cancer Canada and K. Delos Santos by the Joseph and Silvana Melara Cancer Research Fund.

References

1. Droz JP et al (2010) Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults. Crit Rev Oncol Hematol 73(1):68–91
2. Lissbrant IF et al (2013) Population-based study on use of chemotherapy in men with castration resistant prostate cancer. Acta Oncol 52(8):1593–601

3. Cancer System Quality Index (CSQI) Available from: http://www.csqi.on.ca. Accessed Nov 2013
4. Gerritse FL et al (2013) Analysis of docetaxel therapy in elderly (>/=70 years) castration resistant prostate cancer patients enrolled in the Netherlands Prostate Study. Eur J Cancer 49(15): 3176–3183
5. Lien K et al (2013) Low-dose metronomic chemotherapy: a systematic literature analysis. Eur J Cancer 49(16):3387–3395
6. Winquist E et al (2006) Non-hormonal systemic therapy in men with hormone-refractory prostate cancer and metastases: a systematic review from the Cancer Care Ontario Program in Evidence-based Care's Genitourinary Cancer Disease Site Group. BMC Cancer 6(1):112
7. Shelley M et al (2006) Chemotherapy for hormone-refractory prostate cancer. Cochrane Database Syst Rev (4):CD005247
8. Vogelzang NJ (1984) Continuous infusion chemotherapy: a critical review. J Clin Oncol 2(11): 1289–1304
9. Man S et al (2002) Antitumor effects in mice of low-dose (metronomic) cyclophosphamide administered continuously through the drinking water. Cancer Res 62(10):2731–2735
10. Emmenegger U, Kerbel RS (2007) Five years of clinical experience with metronomic chemotherapy: achievements and perspectives. Onkologie 30(12):606–608
11. Chow A et al (2014) Preclinical analysis of resistance and cross-resistance to low-dose metronomic chemotherapy. Invest New Drugs 32(1):47–59
12. Mitsiades N (2013) A road map to comprehensive androgen receptor axis targeting for castration-resistant prostate cancer. Cancer Res 73(15):4599–4605
13. Bocci G et al (2004) Increased plasma vascular endothelial growth factor (VEGF) as a surrogate marker for optimal therapeutic dosing of VEGF receptor-2 monoclonal antibodies. Cancer Res 64(18):6616–6625
14. André N et al (2013) Has the time come for metronomics in low-income and middle-income countries? Lancet Oncol 14(6):e239–e248
15. Glode LM et al (2003) Metronomic therapy with cyclophosphamide and dexamethasone for prostate carcinoma. Cancer 98(8):1643–1648
16. Fontana A et al (2010) Metronomic cyclophosphamide in elderly patients with advanced, castration-resistant prostate cancer. J Am Geriatr Soc 58(5):986–988
17. Dickinson P, Peel D, Sundar S (2012) Metronomic chemotherapy with cyclophosphamide and dexamethasone in patients with metastatic carcinoma of the prostate. Br J Cancer 106(8): 1464–1465
18. Hatano K et al (2011) Retrospective analysis of an oral combination of dexamethasone, uracil plus tegafur and cyclophosphamide for hormone-refractory prostate cancer. Jpn J Clin Oncol 41(2):253–259
19. Lord R et al (2007) Low dose metronomic oral cyclophosphamide for hormone resistant prostate cancer: a phase II study. J Urol 177(6):2136–2140, discussion 2140
20. Jellvert Å et al (2011) Effective oral combination metronomic chemotherapy with low toxicity for the management of castration-resistant prostate cancer. Exp Ther Med 2(4):579–584
21. Nishimura K et al (2001) Oral combination of cyclophosphamide, uracil plus tegafur and estramustine for hormone-refractory prostate cancer. Oncology 60(1):49–54
22. Nicolini A et al (2004) Oral low-dose cyclophosphamide in metastatic hormone refractory prostate cancer (MHRPC). Biomed Pharmacother 58(8):447–450
23. Fontana A et al (2009) Clinical and pharmacodynamic evaluation of metronomic cyclophosphamide, celecoxib, and dexamethasone in advanced hormone-refractory prostate cancer. Clin Cancer Res 15(15):4954–4962
24. Ladoire S et al (2010) Metronomic oral cyclophosphamide prednisolone chemotherapy is an effective treatment for metastatic hormone-refractory prostate cancer after docetaxel failure. Anticancer Res 30(10):4317–4323
25. Nelius T et al (2010) Clinical outcome of patients with docetaxel-resistant hormone-refractory prostate cancer treated with second-line cyclophosphamide-based metronomic chemotherapy. Med Oncol 27(2):363–367

26. Gebbia V et al (2011) Salvage therapy with oral metronomic cyclophosphamide and methotrexate for castration-refractory metastatic adenocarcinoma of the prostate resistant to docetaxel. Urology 78(5):1125–1130
27. Meng L-J et al (2012) Evaluation of oral chemotherapy with capecitabine and cyclophosphamide plus thalidomide and prednisone in prostate cancer patients. J Cancer Res Clin Oncol 138(2):333–339
28. Vorob'ev N et al (2011) Efficacy of standard docetaxel and metronomic cyclophosphamide chemotherapy in patients with hormone-resistant prostate cancer: comparative analysis. Vopr Onkologii 57(6):753
29. Di Lorenzo G et al (2007) Thalidomide in combination with oral daily cyclophosphamide in patients with pretreated hormone refractory prostate cancer: a phase I clinical trial. Cancer Biol Ther 6(3):313–317
30. Orlandi P et al (2013) VEGF-A polymorphisms predict progression-free survival among advanced castration-resistant prostate cancer patients treated with metronomic cyclophosphamide. Br J Cancer 109(4):957–964
31. de Bono JS et al (2010) Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 376(9747):1147–1154
32. de Bono JS et al (2011) Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364(21):1995–2005
33. Kantoff PW et al (2010) Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363(5):411–422
34. Parker C et al (2013) Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 369(3):213–223
35. Ryan CJ et al (2013) Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368(2):138–148
36. Cabot RC et al (2012) Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367(13):1187–1197
37. Sacco JJ et al (2010) The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PLoS One 5(1):e8933
38. Hoffman GS et al (1992) Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 116(6):488–498
39. Haubitz M et al (1998) Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. Arthritis Rheum 41(10): 1835–1844
40. Ghiringhelli F et al (2007) Metronomic cyclophosphamide regimen selectively depletes CD4(+)CD25 (+) regulatory T cells and restores T and NK effector functions in end stage cancer patients. Cancer Immunol Immunother 56(5):641–648
41. Dobi E et al (2013) Treatment-induced acute leukaemia after major response to cyclophosphamide-based metronomic chemotherapy in refractory heavily pre-treated prostate cancer. J Cancer Ther 4:165–169
42. Mauritzson N et al (2002) Pooled analysis of clinical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976–1993 and on 5098 unselected cases reported in the literature 1974–2001. Leukemia 16(12):2366–2378
43. Xu Y et al (2012) Risk of second malignant neoplasms after cyclophosphamide-based chemotherapy with or without radiotherapy for non-Hodgkin lymphoma. Leuk Lymphoma 54(7):1396–404
44. Knight A et al (2004) Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis 63(10):1307–1311
45. Emmenegger U et al (2011) Tumors that acquire resistance to low-dose metronomic cyclophosphamide retain sensitivity to maximum tolerated dose cyclophosphamide. Neoplasia 13(1):40–48

46. Kubisch R et al (2013) A comprehensive gene expression analysis of resistance formation upon metronomic cyclophosphamide therapy. Transl Oncol 6(1):1–9
47. Thoenes L et al (2010) In vivo chemoresistance of prostate cancer in metronomic cyclophosphamide therapy. J Proteomics 73(7):1342–1354
48. Cramarossa G et al (2013) A systematic analysis of correlative studies in low-dose metronomic chemotherapy trials. Biomarkers Med (in press)
49. Bocci G et al (2005) Cyclophosphamide-methotrexate 'metronomic' chemotherapy for the palliative treatment of metastatic breast cancer. A comparative pharmacoeconomic evaluation. Ann Oncol 16(8):1243–1252
50. Kato H et al (2004) A randomized trial of adjuvant chemotherapy with uracil–tegafur for adenocarcinoma of the lung. N Engl J Med 350(17):1713–1721
51. Watanabe T et al (2009) Oral uracil and tegafur compared with classic cyclophosphamide, methotrexate, fluorouracil as postoperative chemotherapy in patients with node-negative, high-risk breast cancer: National Surgical Adjuvant Study for Breast Cancer 01 Trial. J Clin Oncol 27(9):1368–1374