Review paper

Efficacy and safety of megestrol in the management of hepatocellular carcinoma: a systematic review of the literature

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Introduction: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death worldwide. There is as yet no standard therapy for inoperable HCC. We aimed to systematically review all health-related evidence regarding the effectiveness and safety of megestrol in HCC patients.

Material and methods: We conducted a systematic computerised search in PubMed, Scopus, Web of Science, Embase, and Cochrane CENTRAL. All original human studies reporting the efficacy of megestrol in HCC patients were included in our review.

Results: Six studies including 357 patients were finally eligible. The overall mean survival time of 87 megestrol-treated patients, was 9.187 (95% CI 1.134–17.239) months. Eight patients had tumour size enlargement, and eight patients had tumour size reduction. From three studies including 76 patients, 42 patients reported having improvement of appetite and food intake after receiving megestrol. Diverse adverse events were noticed between studies; however, they were tolerable in most of the studies.

Conclusions: To summarise, no conclusive evidence should be declared regarding the effectiveness of megestrol in patients with inoperable HCC. However, previous studies have shown promising results at the level of prolonging the survival rate, tumour size reduction, and improving the quality of life. Therefore, we recommend that future research studies must examine the role of megestrol in large-population, randomised studies.

Key words: megestrol, Megace, hepatocellular carcinoma, HCC, progestin, oestrogen receptor, hormonal therapy.

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Introduction

Hepatocellular carcinoma (HCC) is the most common of liver cancers and one of the leading causes of cancer death worldwide [1]. HCC is more common in males than females, with a ratio of 2.4 : 1. Liver cancer is predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018, with about 841,000 new cases and 782,000 deaths annually [2, 3]. The incidence of HCC is high in specific regions including Middle and Western Africa and Eastern and Southern Asia, compared to lower rates in developed countries [4]. The prognosis of HCC is poor, and the five-year survival rate in the United States is less than 12%. Also, the incidence of HCC has doubled in recent decades, which makes HCC responsible for a major portion of cancer-related death in the United States [5]. Different risk factors have been associated with the incidence of HCC. For instance, most liver cirrhosis patients (80%) develop HCC, and infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) also increase the risk [6]. Patients with HCC usually experience no specific symptoms other than those of their chronic liver disorder [6]. Therefore, in the West, only 30–40% of HCC patients are diagnosed at an early stage, and they can be treated curatively through surgical resection, liver transplantation, or radiofrequency ablation when appropriately selected. In about 60–70% of those patients, the survival rate is five years, which is the prolonged survival time among all possible therapeutic modalities [7]. On the other hand, it is challenging to find a systematic therapy that can effectively manage the advanced stage of HCC, which has a grievous prognosis [8]. Currently, the European Association for the Study of Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) consider sorafenib as the standard systemic remedy for patients with advanced HCC and well-preserved liver function (i.e. Child-Pugh class A) [9, 10]. However, there are limited data about its role in patients with reduced liver function (i.e. Child-Pugh class B) [11, 12]. Oestrogen influences the growth of HCC; however, treatment with the anti-oestrogen tamoxifen demonstrated no clinical efficacy [13]. The repeated occurrence of oestrogen receptor mutations may explain the lack of tamoxifen effects [14, 15].

Megestrol is a synthetic progestin agent, with efficacious anti-oestrogen activity independent of oestrogen receptors. Zhang *et al.* showed that megestrol acetate inhibited the growth of human HCC (HepG2) cells grown both in vitro and in vivo. Apoptosis following G_1 arrest was seen in megestrol acetate-treated cells and this may be a mechanism through which mege-

strol acetate inhibits HepG2 cells [16]. In a single-arm trial, megestrol acetate (acylated derivative of megestrol) was beneficial in the palliative care of advanced HCC with minimal side effects, while no considerable anti-cancer effect was detected [17]. In another controlled study, the megestrol slowed down the tumour growth and significantly improved the survival rate [18]. However, another double-blinded randomised clinical trial (RCT) reported no increase in the survival time, when megestrol acetate was administered [19]. Due to the contradictory results in the current literature, we aimed to systematically review and analyse all health-related evidence regarding the efficacy and safety of megestrol in patients with HCC.

Material and methods

Literature search strategy and selection criteria

In July 2018, we carried out a systematic electronic search of five major databases: PubMed, Web of Science, Scopus, Cochrane CENTRAL, and Embase. The following search terms: (Megestrol OR Megestrol acetate OR Megace) AND (hepatocellular carcinoma OR hepatocellular cancer OR liver cancer OR liver cancers) were utilised to retrieve all potentially relevant articles. A manual search of the reference list of relevant articles was carried out to provide a comprehensive literature search. The authors independently screened the search results about the inclusion and exclusion criteria.

Our inclusion criteria comprised interventional studies, observational studies, and case reports/series that investigate the role of megestrol or its acylated form (megestrol acetate) in the treatment of patients with HCC. We excluded 1) irrelevant studies, overlapped, or unreliably extracted 2) reviews, book chapters, comments, letters, or posters, 3) studies without available full-text, 4) *in vitro* or animal study. The authors checked the eligibility for article inclusion via two rounds: title/abstract screening of all search results, moving to the full-text reading of potentially eligible papers.

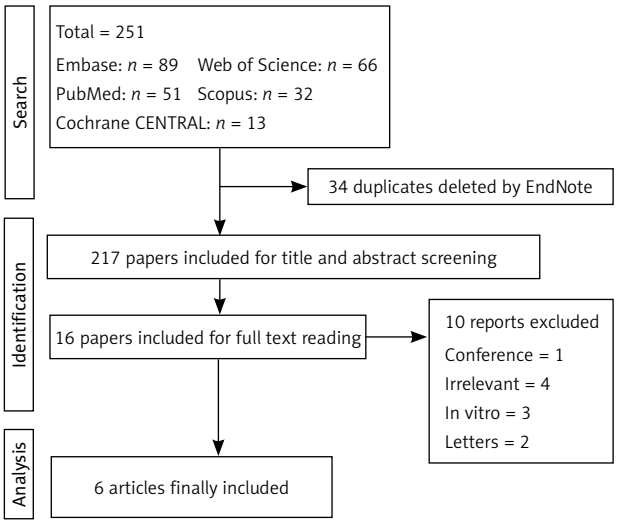


Fig. 1. Flow diagram of the studies' selection and screening

Data extraction and statistical analysis

Three independent authors performed a pilot extraction for two articles to build a standardised data extraction form. We extracted the baseline data including age, gender, country, sample size, and intervention. We also extracted the classification of data according to Child-Pugh system and/or ECOG performance score. The outcomes comprised patients' survival, tumour and AFP alterations following treatment, appetite changes, and adverse events. All data have been refined through discussion and consensus between the three reviewers. We calculated the overall mean survival with the corresponding 95% confidence interval (CI) using Comprehensive Meta-Analysis Software (CMA) version 3.3.070. Studies were eligible for analysis if they provide the mean and standard deviation (SD) or median and range of survival. Median and range were converted to mean and SD through the method of Hozo *et al.* [20].

Results

Literature search

Our systematic electronic search in five databases retrieved 251 articles. The Endnote software cleared 34 duplicated references. Upon the title and abstract screening of the remaining articles, only 16 studies were eligible for full-text reading. Eventually, six studies met our inclusion criteria [12, 17–19, 21, 22]. The flow diagram of study selection and screening is shown in Figure 1.

Study characteristics

Our six included studies consisted of three randomised, controlled trials and three non-randomised, uncontrolled clinical trials. They comprised 357 patients, and most of them were male (83.2%). Two studies used megestrol [18, 21] while the remaining studies utilised megestrol acetate (the acylated derivative of megestrol). The administered dose of megestrol or megestrol acetate was 160 mg in all studies except one study that applied a dose of 320 mg [19]. Baseline characteristics of included studies are detailed in Table 1.

Five studies used the Child-Pugh score to classify their included participants [12, 18, 19, 21, 22]. Out of 228 patients in the megestrol group, 85 (37.28%) were classified as Child-Pugh A, 73 (32.01%) were on Child-Pugh B, and only 21 (9.21%) participants were assessed as Child-Pugh C. In the control group: 57 (44.18%) out of 129 were Child-Pugh A, 55 (42.63%) Child-Pugh B, and only 15 (11.62%) Child-Pugh C. Four trials used the Eastern Cooperative Oncology Group (ECOG) performance score, and most of the patients (282 [93.06%]) scored 0–2. A detailed description of the Child-Pugh score, ECOG score, and tumour staging are shown in Table 2.

Survival

Pooling four studies including 87 megestrol-treated patients, the overall mean survival time was 9.187 (95% CI 1.134–17.239) months (Fig. 2). Two studies were not eligible for meta-analysis. In the first study, the median survival, in

Table 1. Baseline characteristics of included studies

Reference	Country	Study design	Intervention		Sample: *n*		Age: median (range) in years		Male: *n* (%)	
			Case	Control	Case	Control	Case	Control	Case	Control
Chow *et al.* 2011 [19]	Multi-national	RCT	320 mg/day MA	Placebo	123	62	60.9 (31.1–80.9)	56 (20.1–100.3)	108 (87.8)	51 (82.3)
Giacomin *et al.* 2010 [12]	Italy	RCT	160 mg/day MA	Synchro-Levels	18	43	< 65: 0 65–75: 8 > 75: 5	< 65: 5 65–75: 23 > 75: 12	13 (72.2)	30 (69.8)
Cappa *et al.* 2005 [21]	Italy	Clinical trial	5 cases: 160 mg/day MA, 50–300 mg/day thalidomide; 4 cases: as before, plus 1 million U/day IL-2	None	9	None	72 (59–81)	None	6 (66.6)	None
Villa *et al.* 2001 [18]	Italy	RCT	160 mg/day MA	Placebo	21	24	63 ±8*	60 ±11*	14 (67)	22 (92)
Chao *et al.* 1997 [17]	Taiwan	Clinical trial	160 mg/day MA	None	46	None	65 (38–81)	None	44 (95.7)	None
Colleoni *et al.* 1995 [22]	Italy	Clinical trial	160 mg/day MA	None	11	None	68 (54–74)	None	9 (81.8)	None

**Mean (SD); MA – megestrol acetate; RCT – randomised clinical trial; IL-2 – interleukin 2; NA – not applicable*

Table 2. Clinical scores and tumour staging for included participants

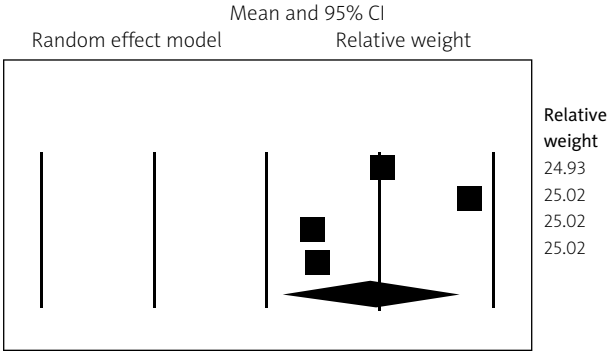
Reference	Child-Pugh class: *n* (%)		ECOG status: *n* (%)		Tumour staging: *n* (%)	
	Case	Control	Case	Control	Case	Control
Chow *et al.* 2011 [19]	A: 59 (48.0) B: 45 (36.6) C: 16 (13.0) unknown: 3 (2.4)	A: 27 (43.5) B: 25 (40.3) C: 8 (12.9) unknown: 2 (3.2)	0: 12 (9.8) 1: 69 (56.1) 2: 30 (24.4) 3: 12 (9.8)	0: 14 (22.6) 1: 33 (53.2) 2: 13 (21.0) 3: 2 (3.2)	TNM staging II: 10 (8.1) IIIA: 33 (26.8) IIIB: 6 (4.9) IVA: 41 (33.3) IVB: 17 (13.8) Unknown: 16 (13.0)	TNM staging II: 12 (19.4) IIIA: 16 (25.8) IIIB: 2 (3.2) IVA: 16 (25.8) IVB: 10 (16.1) Unknown: 6 (9.7)
Giacomin *et al.* 2010 [12]	A: 8 (44.4) B: 10 (55.6)	A: 20 (46.5) B: 23 (53.5)	0–1: 14 (77.7) 2: 4 (22.2)	0–1: 40 (93.0) 2: 3 (7.0)	NA	NA
Cappa *et al.* 2005 [21]	A: 3 (33.3) B: 5 (55.5) C: 1 (11.1)	None	NA	None	CLIP staging 1: 1 (11.1) 2: 5 (55.5) 3: 1 (11.1) 5: 1 (11.1) 6: 1 (11.1)	None
Villa *et al.* 2001 [18]	A: 11 (52.3) B: 6 (28.5) C: 4 (19.0)	A: 10 (41.6) B: 7 (29.1) C: 7 (29.1)	NA	NA	Histological differentiation Well differentiated: 9 (42.9) Moderate: 6 (28.6) Poor: 4 (19.0) Unknown: 2 (9.5)	Histological differentiation Well differentiated: 14 (58.3) Moderate: 5 (20.8) Poor: 2 (8.3) Unknown: 3 (12.5)
Chao *et al.* 1997 [17]	NA	None	0–2: 39 (84.8) 3–4: 7 (15.2)	None	AJCC staging III: 7 (15.2) IV: 39 (84.8)	None
Colleoni *et al.* 1995 [22]	A: 4 (36.3) B: 7 (63.6)	None	0–1: 7(63.6) 2: 4 (36.3)	None	TNM staging III: 2 (18.1) IVA: 7 (63.6) IVB: 2 (18.1)	None

NA – not applicable; AJCC – American Joint Committee on Cancer; TNM – tumour nodes and metastases; ECOG – Eastern Cooperative Oncology Group

Statistics for each study

	Mean	Standard error	Variance	Lower limit	Upper limit	*p*-value	Total
Cappa *et al.* 2005	10.25	0.514	0.264	9.243	11.257	0	9
Villa *et al.* 2001	18	0.125	0.016	17.755	18.245	0	21
Chao *et al.* 1997	4	0.146	0.021	3.715	4.285	0	46
Colleoni *et al.* 1995	4.5	0.157	0.025	4.192	4.808	0	11
	9.187	4.109	16.881	1.134	17.239	0.025	87

Heterogeneity: $I^2 = 99.957\%$, $p = 0$
Test for overall effect: Mean = 9.187, $p = 0.025$



MD – mean difference; CI – confidence interval; *p* – *p*-value

Fig. 2. Forest plot meta-analysis for the overall mean survival of the four included studies

Table 3. Changes in AFP levels in intervention group

Reference	Changes in AFP
Giacomin *et al.* 2010 [12]	AFP level decreased in 40% of the megestrol group compared to 14% in the control group ($p = 0.0444$)
Cappa *et al.* 2005 [21]	AFP progressively increased in six patients while remainingng stable in three
Chao *et al.* 1997 [17]	AFP level was reduced in five patients with a median reduction of 59 ng/ml. Also, one patient had a reduction in AFP of 136,381 ng/ml (from 138,810 to 2429 ng/ml)
Colleoni *et al.* 1995 [22]	No patient had a significant decrease in AFP (> 50%)

Table 4. Adverse events of megestrol versus control group after intervention

Reference	Case: *n* (%)	Control: *n* (%)
Chow *et al.* 2011 [19]	Ascites: 4 (11.4) GI bleeding: 7 (20.0) Jaundice: 6 (17.1) Abdominal pain: 4 (11.4) Anaemia: 3 (8.6) Tumour rupture: 1 (2.9) Pneumonia: 1 (2.9) Admitted for limb pain: 1 (2.9) Chest pain: 1 (2.9) Epistaxis: 1 (2.9) Fall: 1 (2.9) Hypoglycaemia: 1 (2.9)	Ascites: 4 (26.7) Jaundice: 1 (6.7) Abdominal pain: 1 (6.7) Anaemia: 1 (6.7) Tumour rupture: 2 (13.3) Pneumonia: 1 (6.7) Admitted for UTI: 1 (6.7) Cholangitis: 1 (6.7)
Giacomin *et al.* 2010 [12]	Tolerable itching: 1 (5.5)	None
Cappa *et al.* 2005 [21]	Increase in appetite and weight: 7 (77.7) Peritoneal effusion: 2 (22.2) Somnolence: 9 (100)	NA
Villa *et al.* 2001 [18]	Increase in appetite: 15 (71.4) Increase in weight: 13 (61.9) DVT: 1 (4.1) Moderate vaginal spotting: 1 (4.1)	DVT: 1 (4.7)
Chao *et al.* 1997 [17]	Mild congestive cardiac failure: 1 (2.2) Hyperglycaemia: 1 (2.2) Mild oedema: 9 (19.5)	NA
Colleoni *et al.* 1995 [22]	Worsening of concomitant diabetes: 2 (18.2) Gastrointestinal bleeding: 1 (9.1)	NA

UTI – urinary tract infection; DVT – deep vein thrombosis; NA – not applicable

months, for the megestrol-treated group was 1.88 compared to 2.14 for placebo [19]. In the second trial, four patients survived for 12 months or more after receiving megestrol, compared to one patient on the Synchro-Levels ($p = 0.025$) [12].

Tumour size

In the study conducted by Cappa *et al.* five patients had an increase in size/number of nodules, while three patients had tumour enlargement and metastasis [21]. In

contrast, seven patients had a median tumour size reduction of 18%, and one patient had a reduction of tumour size of 40% in the Chao *et al.* trial [17].

Appetite

In three studies including 76 participants, 42 (55.26%) patients reported improvement in appetite and food intake after receiving megestrol [17, 18, 21].

Alpha-fetoprotein

In the study by Giacomin *et al.* and Chao *et al.* there was a significant decrease in alpha-fetoprotein (AFP) levels in the treatment group when compared to the control group. The study by Colleoni *et al.* showed that no patient had a substantial reduction in AFP (> 50%). AFP progressively increased in six patients, while it remained stable in three, in the study by Cappa *et al.* A detailed description of the AFP level is shown in Table 3.

Adverse events

The reported side effects were generally tolerable in most studies. Gastrointestinal bleeding was reported in studies by Chow *et al.* and Colleoni *et al.* [19, 22]. There were no conjoint adverse events between studies except for an increase in weight and appetite in two studies [18, 21]. Itemised characterisation of the reported adverse events are shown in Table 4.

Discussion

HCC is one of the most common tumours worldwide, and it has a dismal prognosis [1]. Due to the associated comorbidities and the liver resistance to systemic chemotherapy, clinical and experimental studies have been examining the role of hormones in patients with HCC [23, 24]. Megestrol is a synthetic progestin agent, with efficacious anti-oestrogen activity independent of oestrogen receptors. Our systematic review of interventional studies showed that megestrol might play a promising role in prolonging the survival, improving performance, and reducing tumour size. Although *in vitro* studies on rat livers showed that MA has high resistance to metabolising enzymes compared to progesterone [25, 26], there were no serious adverse events detected in most of our included studies.

Administering megestrol for HCC patients may have a favourable outcome at the level of patients' quality of life. For instance, previous systematic review and meta-analysis concluded that megestrol is a safe and efficacious remedy for improving appetite in different categories, including oncology patients [27]. The four included studies supported this effect: two controlled studies illustrated improved appetite in the megestrol-treated group compared to placebo [18, 19], whereas two uncontrolled studies reported improvement of appetite and food intake after receiving megestrol [17, 21].

It is evident that megestrol can also improve the performance of HCC patients. In Giacomin *et al.*'s study, more patients in the megestrol group reported improvement of performance status (ECOG) compared to the control group [12]. In a single arm trial by Chao *et al.*, only four patients had an improvement in their performance status [17]. However, it was noted that most of the patients in the two trials were enrolled at moderate ECOG score (0–2). Also, we noted improvement of performance status in the letter of Farinati *et al.*, in which seven patients (18.9%) experienced a slight amelioration of their performance status (Karnowski score) [28].

The contrary results of megestrol effects on tumour size are controversial. Eight patients in the Cappa *et al.* trial [21], had tumour size enlargement versus eight patients who had tumour reduction in the study of Chao *et al.* 1997 [17]. These diverse results may have been influenced by the varied clinical status of the patients at the time of inclusion. Unfortunately, those studies did not employ the same assessment method of performance to underpin our thinking. The finding of the Chao *et al.* trial has been established by two excluded letters. In a letter of the case report, the CT of the patient revealed a significant reduction in tumour bulk from 7 cm × 7.5 cm to 4.9 cm × 3.3 cm [29]. In the second part of the non-randomised study of 37 HCC patients, the tumour mass in one patient decreased by more than 50% [28]. Moreover, when researchers examined the megestrol effect in experimental studies, tumour regression was detected in two out of five included patients [30]. In another pilot study the anti-oestrogen treatment was determined according to the type of liver oestrogen-receptors (ERs) transcript [31]. The patients with wild-type ERs (wtERs) received tamoxifen, while those with variant ER (vERs) received megestrol. Although the sample size was small, all patients on megestrol had considerable slow-down of tumour growth rate [31].

Similar to the study above, the patients of the Villa *et al.* trial had no tumour size reduction, but the megestrol showed remarkable slow-down of growth [17]. The mean tumour mass at baseline was not significantly different between megestrol and placebo groups; however, the median time to first tumour progression was significantly longer in the megestrol group (22 months) compared to placebo group (nine months) [17].

The present systematic review is the first review to assemble the findings from interventional studies regarding the efficacy and safety of megestrol in patients with inoperable HCC. Another strength of the current review is that we searched five major databases, including Embase and Web of Science. Our study has several limitations. Because of the small number of included studies and absence of decisive inference, health-care professionals should cautiously interpret the results displayed in this systematic review in the clinical settings. Another limitation is the lack of homogeneity between included studies and the measurement of outcomes in diverse methods, which hindered us from carrying out a quantitative meta-analysis. Furthermore, lack of randomisation and controlled arms in half of the included trials may inundate the reliability of their inferences. Researchers should take into consideration these limitations in future studies.

Conclusions

In summary, the curative effects of megestrol in HCC are controversial; hence, no conclusive evidence can be drawn

regarding the effectiveness of megestrol in patients with inoperable HCC. However, previous studies have shown promising results at the level of prolonging the survival rate, tumour size reduction, and improving the quality of life. Future trials should consider using megestrol alone or megestrol in addition to chemotherapy in inoperable HCC. Therefore, we recommend that future research studies examine the megestrol role in large-population, randomised studies.

The authors declare no conflict of interest.

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