Endostatin and Cancer Therapy

Subjects: Oncology

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Endostatin constitutes one of the most studied peptides with inhibitory effect on angiogenesis. This peptide is a 20 kDa C-terminal cleavage fragment from the α1 chain of type XVIII collagen, which is an extracellular matrix protein recognized for its anti-atherosclerotic effect as well as a potent inhibitor of angiogenesis. Endostatin has been artificially synthesized in a recombinant human form with the addition of nine extra amino acids that confer greater stability, solubility, and antiangiogenic effect. The endostatin mechanism of action is not completely understood. Evidence shows that this molecule exerts its angiostatic effect through multiple mechanisms involving elements of the extracellular matrix, as well as proteins and signaling cascades related to endothelial cell migration and proliferation.

Keywords: endostatin ; lung cancer ; cell

1. Pulmonary Cancer

Most studies using endostatin have targeted patients with non-small cell lung cancer (NSCLC), which accounts for 85% of all lung cancers. A large portion of this type of cancer is diagnosed in advanced stages (III or IV), where the first line of treatment is platinum-based chemotherapy together with new generation cytotoxic agents, such as etoposide and gemcitabine and/or radiotherapy [1].

Multiple clinical trials have been conducted in recent years demonstrating that the addition of endostatin to the standard treatment of advanced NSCLC significantly increases the overall survival (OS) and the progression-free survival time (PFS) of patients in locally advanced [2][3][4][5][6][7][8][9][10][11][12] or metastatic disease [4][10][11][12][13][14][15]. Trials have also been tested on small cell lung cancer, giving promising results in survival and tolerability of the therapy [16][17][18].

Interestingly enough, the addition of endostatin to these different trials did not increase the incidence of adverse events in a significant manner in comparison to their respective control groups. Among the adverse effects that have been observed in combined treatment schemes of endostatin, in addition to chemotherapy or radiochemotherapy, there are hematological toxicity (neutropenia, thrombocytopenia, and anemia), nausea, vomiting, and fatigue [18]. Fortunately, none of these adverse effects led to discontinuation of therapy.

In addition, other authors have compared the efficacy and safety of using extended endostatin regimes during concomitant chemotherapy [4][12]. The results indicate that the extended endostatin treatment not only is associated with a significant improvement in patient prognosis, but also that it does not lead to a marked increase in the most common adverse effects associated to the therapy. The only exception is represented by cardiac disorders and hypertension, which are increased in patients who received an extended endostatin course, although none of these resulted in discontinuation of therapy [4][12].

2. Gastric Cancer

Gastric cancer accounts for more than 1 million cases diagnosed each year worldwide. Those diagnosed in stage IA or IB have a 5-year survival of between 60–80%. Unfortunately, most of them at the time of diagnosis are already in the metastatic stage, which drastically worsens the prognosis, with a 5-year survival as low as 18% for those diagnosed at stage III [19]. In this context, the first line of treatment is chemotherapy with the FOLFOX (folic acid with 5-Fluorouracil and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) regimens with or without trastuzumab, in cases where HER2 is overexpressed [19]. Recently, clinical guidelines recommend that ramucirumab, a VEGF-R2 monoclonal antibody, can be added to the treatment regimen in the context of disease progression [20]. There are few human studies that have used endostatin for the treatment of gastric cancer. These studies mostly involve patients with locally advanced disease or with distant metastasis.

In a study by Yao J et al. [21] involving 33 patients with advanced gastric cancer with peritoneal carcinomatosis, it was shown that treatment with endostatin plus chemotherapy was superior to chemotherapy alone, with a significantly higher median OS in the group that received endostatin compared to the control group (15.8 vs. 9.8 months).

The main side effects that led to dose decrease and discontinuation of therapy were neutropenia and severe thrombocytopenia. However, they were present in both groups with no significant difference. The adverse events associated with endostatin only correspond to hypertension and bleeding, but they did not translate into discontinuation of therapy.

In another clinical trial conducted by Yang H et al. [22], endostatin plus SOX (S-1 with oxaliplatin) was shown to be effective in the treatment of liver metastases in patients with gastric cancer. The most common adverse effects, such as gastrointestinal reaction, hematological toxicity, and cardiac disorders, were equally present in both groups, but it is interesting to highlight the fact that the severity of these adverse reactions were lower in the group that received endostatin.

One of the most important clinical trials studied the safety and efficacy of molecular targeted therapy in patients with advanced gastric cancer [23]. A total of 200 patients were divided equally into four groups, comparing a control group receiving chemotherapy with others receiving bevacizumab (VEGF-R monoclonal antibody), apatinib (tyrosine kinase inhibitor), and endostatin. The results indicated that molecular therapies were significantly more efficient than chemotherapy in reducing and controlling tumor lesions, and that there were no significant differences between the three experimental groups.

The main adverse effects that occurred in all groups were neutropenia, nausea, vomiting, and rash, but their incidence was significantly higher in the control group. The results of this research lead to the conclusion that molecular targeted therapies represent the treatment of choice for patients with advanced gastric cancer, due to a higher efficacy in the control of tumor lesions and a lower frequency of therapy-related adverse effects.

3. Esophageal Cancer

Esophageal cancer accounts for about 5% of cancer deaths worldwide, with an estimated 570,000 cases diagnosed in 2018, with squamous cell esophageal cancer (SCEC) being the most frequent subtype [24]. It is a cancer with a poor prognosis, given that more than 70% is diagnosed at an advanced stage, with a 5-year survival rate of 25.1% when there is local-regional dissemination and merely 4.8% in the setting of distant metastases [24]. For patients with locally advanced disease, the first line of treatment is surgery accompanied by neoadjuvant chemoradiotherapy prior to surgery, however, for patients with metastases at the time of diagnosis, chemotherapy or chemoradiotherapy is the preferred treatment alternative [25].

The first clinical studies on endostatin in esophageal cancer showed that the endostatin plus DP (docetaxel and cisplatin) regimen did not present a higher rate of the most common adverse effects than the DP regimen alone.

It is noteworthy to point out that three of the ten patients in the group that received endostatin presented ECG changes (T wave changes). However, these changes normalized at the end of the treatment cycles [26].

In the phase II study conducted by Hu Z et al. [27] involving 50 patients who received a regimen of endostatin plus irinotecan/cisplatin, the efficacy and safety of this regimen for the treatment of advanced SCEC was demonstrated. The median PFS was 4.01 months, and the median OS was 12.32 months.

The most frequently reported side effects were leukopenia (18.0%) and neutropenia (16.0%); they presented with severity of grade 3 or higher in five patients (10.0%), leading to the discontinuation of treatment.

Similarly, another phase II clinical trial conducted by Wang Z et al. [28] demonstrated the safety and efficacy of endostatin plus paclitaxel/nedaplatin. The study was conducted on 53 patients with locally advanced or metastatic esophageal squamous cell cancer. The most frequently observed grade 3 or higher adverse effects were neutropenia (17.0%) and anemia (3.8%), and no treatment-related deaths occurred during the entire duration of the study.

Another study worth to be mentioned is the one made by Zhong Z et al. [29], where endostatin therapy plus chemoradiotherapy was shown to be superior to chemoradiotherapy for the treatment of locally advanced but not distant metastatic SCEC. The 1-year and 3-year overall survival rate was significantly higher in the endostatin group than in the radiochemotherapy alone group (72% vs. 50%, 32% vs. 22%, respectively), and the median PFS was 11.3 months for the

endostatin group and 8.1 months for the control. Furthermore, there was no treatment-related toxicity that could be directly attributed to endostatin. Indeed, the most common adverse effects observed were probably associated with chemoradiotherapy.

4. Colorectal Cancer

Colorectal cancer is the third most common cancer worldwide, reporting 1,931,590 new cases in 2020 [30].

The most common treatments for metastatic colorectal cancer correspond to infusions of FOLFIRI (5-Fluorouracil with leucovorin and irinotecan) or FOLFOX (5-Fluorouracil with leucovorin and oxaliplatin) schemes, which have been combined in recent years with anti-VEGF or EGFR antibodies [31].

Bevacizumab is an example of an anti-VEGF antibody, which is approved for first-line use in colorectal cancer.

Although its effectiveness given as a monotherapy has been demonstrated, a meta-analysis reported that there is insufficient evidence to support its use as an adjuvant therapy with other regimens, such as FOLFIRI or FOLFOX.

In addition, its association increased the frequency of adverse events such as hypertension, proteinuria, bleeding, and thromboembolism, along with an increase in treatment interruption [32].

Various studies have tested the use of endostatin in combination with different common chemotherapeutic schemes against colorectal cancer, such as FOLFOX4 [33], modified FOLFOX6 [34], FOLFIRI [35], or including several of them [36].

Li et al. conducted a randomized controlled trial to evaluate the efficacy and safety of the use of endostatin plus FOLFIRI chemotherapy in patients with advanced colorectal cancer, reporting a significantly higher ORR (42.9 vs. 29.4%) and PFS (14.5 vs. 11 months) than the control group [35].

Moreover, Xu et al. evaluated the use of endostatin in combination with FOLFOX4 in patients with non-metastatic colorectal cancer through a retrospective controlled study, reporting a significantly higher ORR (38.9 vs. 22.3%), PFS (6.4 vs. 3.8 months), and OS (12.1 vs. 11.4 months) than the control group [33].

In addition, a pilot study evaluated the efficacy and safety of the use of endostatin in combination with different chemotherapy schemes (CAPIRI, GP, XELOX, DCF, FOLFIRI, or FOLFOX4) in patients with metastatic colorectal and gastric cancer, reporting an OS of 10.3 months (95% CI, 3.9–16.7 months), median time to progression of 2.6 months (95% CI, 2.0–3.2 months), disease control rate of 47.6%, and a ORR of 19.0%, and in patients treated with first-line therapy, the response rate was 57.1%.

Another interesting aspect is that endostatin was also given to a small cohort of patients (n = 5) in addition to previously failed third-line therapies. The results of the study showed disease stability with a maximum TTP of more than 11.0 months. Therefore, the authors indicate that the association of endostatin and chemotherapy could also be able to reverse chemo-resistance. This is an aspect about endostatin treatment that surely needs to be investigated [36].

Regarding the safety of endostatin in patients with colorectal cancer, a phase I clinical trial evaluated the safety, tolerability, and pharmacokinetics of the use of endostatin in combination with the modified chemotherapy regimen FOLFOX6 as a first-line treatment in patients with advanced colorectal cancer using a dose-escalation methodology.

Among the results, it was reported that the most frequent drug-related adverse events were leukopenia, neutropenia, anemia, anorexia, ST-segment/T wave changes, and nausea, but those that presented with a severity grade of 3–4 were only neutropenia, leukopenia, and thrombocytopenia.

There have also been two patients in the endostatin group that stopped therapy after an episode of ventricular arrhythmia [34].

Nonetheless, these results are similar to those reported in controlled clinical trials, where hematological and gastrointestinal adverse events are the most frequent, with no significant differences between the endostatin plus chemotherapy group and the control group [33][35].

Even so, cardiac adverse events vary between studies, where Zhou et al. reported that three patients presented transient sinus bradycardia with spontaneous remission [36]; Xu et al. that 17.7% presented hypertension and 11.1% cardiac ischemia, both in grade 1–2 vs. 5.6% and 0.0%, respectively, in the control group [33]; and Li et al. that three patients

presented grade 1 electrocardiogram abnormalities, reverted by the administration of fructose diphosphate sodium, and two presented grade 1–2 hypertension, which was reversible and manageable [35].

5. Nasopharyngeal Cancer

Nasopharyngeal carcinoma (NPC) is a relatively uncommon cancer in comparison with the others. It had an estimated global incidence of 129,000 cases for the year 2018 [37]. NPC generally responds favorably to radiotherapy, with intensity-modulated radiotherapy (IMRT) the first line of treatment in stage I disease. Patients with locally advanced or metastatic disease (stage II-IV) benefit from adding chemotherapy to IMRT [37]. Existing studies using endostatin in this form of cancer are focused on comparing whether the addition of this agent to conventional therapy represents an improvement in long-term outcomes with an acceptable safety profile, given that the existing first line of treatment to date is very effective in improving short- and medium-term survival.

A study conducted by Guan Y et al. [38] involving 22 patients with stage III-IV NPC, evaluated the safety profile of the endostatin plus IMRT scheme associated with chemotherapy.

The results indicated that this regimen was not associated with a higher rate of adverse effects than those historically reported for standard treatment with IMRT plus chemotherapy. Moreover, endostatin treatment was associated with a lower incidence of nasopharyngeal mucosal necrosis/infection compared to literature reports for the treatment of stage III-IV NPC (31.8% vs. 40.6%, respectively).

A multicenter phase II clinical trial performed by Li Y et al. [39], involved 114 patients with stage III-IV NPC in order to determine the efficacy and safety of endostatin treatment. The experimental group received endostatin plus IMRT with chemotherapy, while the control group received IMRT plus chemotherapy only.

After an average follow-up of 67 months, the results indicated that the experimental group showed a slight but significant improvement in ORR at 3 months after treatment, however, this did not translate into significant differences in the curative effect on nasopharyngeal lesions at long-term follow-up. At 5 years follow-up, there were no significant differences in the OS, PFS, distant metastasis-free survival (DFMS), and locoregional failure-free survival rates between the two groups.

In this research, there was no toxicity associated with endostatin treatment, and the frequency of adverse effects also showed no significant differences.

On the contrary, a retrospective study demonstrated that treatment with endostatin associated with chemoradiotherapy was associated with a significant improvement in PFS and distant metastasis-free survival rates at 3-year follow-up compared to chemoradiotherapy alone (81.4% vs. 63.6% and 88.3% vs. 77.3%, respectively), although no improvement in OS was found [40].

Another retrospective study conducted by Chen W et al. [41] compared the efficacy and long-term adverse reactions between IMRT plus endostatin and IMRT plus chemotherapy. The results indicated that the IMRT plus endostatin group had no significant differences in long-term efficacy at 5-year follow-up in terms of OS, PFS, and DMFS ratios. Nonetheless, the IMRT plus endostatin group was notable for a substantially more favorable long-term adverse effect profile, with a significant decrease in both the incidence and severity of xerostomia, mouth-opening difficulty, and soft tissue fibrosis.

6. Breast Cancer

Currently, breast cancer is the most common cancer worldwide [42]. Although there are different histological types, triple negative breast cancer (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are all negative) stands out for its aggressive biological behavior, low response to treatment, and poor prognosis [43][44]. However, in recent years, the efficacy of treatments and the survival advanced breast cancer patients of the different molecular subtype have improved, mainly due to the deepening of the use of personalized strategies based on anti-VEGF monoclonal antibodies, tyrosine kinase inhibitors, immune checkpoint inhibitors, CDK4/6 inhibitors [45].

The inclusion of anti-VEGF monoclonal antibodies to breast cancer therapy has shown promising results on ORR and PFS, but not on OS [46].

The use of endostatin has shown efficacy and safety when combined with chemotherapy in patients with triple negative breast cancer [47].

Various clinical studies have reported encouraging results when evaluating the efficacy and safety of the use of endostatin in combination with classical therapy in patients with different subtypes or clinical stages of breast cancer, obtaining high overall response rates and overall survival, without increasing the frequency of adverse events [46][48][49][50].

A prospective study evaluated the use of endostatin in combination with taxanes-based chemotherapy in patients with HER-2 negative metastatic breast cancer, reporting an overall response rate of 68.4%, having a greater response in those patients who received the therapy as first line (79.3%) versus those who received it as second and third line or beyond (54.5% and 16.7%, respectively). Additionally, those patients who had not been previously treated with taxanes showed a higher overall response rate. Regarding the PFS, the median was 10.8 months [48].

Moreover, another prospective study evaluated the use of endostatin in combination with platinum-based chemotherapy in patients with triple-negative breast cancer, reporting an ORR of 47.6%, a PFS of 8.8 months (95% CI: 7.2–10.4 months), and a median overall survival of 13.3 months (95% CI: 11.6–15.0 months) [49].

Another study worth mentioning is that of Chen et al. They carried out a phase 3 clinical trial to evaluate the use of endostatin with docetaxel and epirubicin as first-line therapy in patients with stage IIA-IIIC breast cancer [50]. In this research, the authors established the clinical and pathological response as the primary endpoint, defining an objective response as those patients who had a disappearance of all target lesions or at least a 30% decrease in the sum of the longest diameter of target lesions and a pathological response as those patients who had no residual viable invasive tumor. An objective response of 91.0% and pathological response of 10.7% was reported as results in patients who received endostatin plus chemotherapy vs. 77.9% and 7.7%, respectively, in those who received chemotherapy alone [50].

Additionally, there have been studies where endostatin effectiveness was studied as a monotherapy. In a phase II clinical study, the use of endostatin alone for patients with TNM stage III breast cancer was evaluated. Patients were randomized to neoadjuvant therapy consisting of endostatin in combination with docetaxel, epirubicin, and cyclophosphamide or chemotherapy alone.

As major findings, the authors reported significant differences in the ORR, with 81.82% for patients who received endostatin plus chemotherapy vs. 58.14% for those who received only chemotherapy, highlighting that those patients with infiltrating ductal carcinoma showed higher sensitivity to treatment with endostatin. In addition, the median OS was significantly higher in the endostatin group 74.2 months vs. 59.1 months, which was also reflected in the 3- and 5-year OS rates. Finally, the reported median relapse-free survival was 67.3 months vs. 55.0 months in the control group [46].

Finally, regarding the evidence from prospective studies on adverse events by associating endostatin with chemotherapy treatment, Huang et al. reported neutropenia (80.7%), leukopenia (77.2%), liver dysfunction (10.5%), and peripheral neurotoxicity (8.8%) as the most frequent adverse events in grade 3–4, while Tan et al. reported neutropenia (14.3%), anemia (14.3%), leukopenia (9.5%), thrombocytopenia (9.5%), febrile neutropenia (4.8%), and hypertension (4.8%) as grade 3–4 adverse events [48][49].

BC, Breast cancer; CB, Carboplatin; CF, Calcium Folinate; CP, Cisplatin; CPT, Carboplatin; CPC, Capecitabine; CR, Complete Remission; CT, Chemotherapy; CRC, Colorectal cancer; CTX, Cyclophosphamide; DCR, Disease control rate; DTX, Docetaxel; E, Endostatin; EP, Etoposide; EPR, Epirrubicin; FA, Folinic Acid; FU, Fluorouracil; GEM, Gemcitabine; IMRT, Intensity-modulated radiotherapy; INN, Nedaplatin; IR, Irinotecan; m, Months; ORR, Objective response rate; OS, Overall Survival; OX, Oxaliplatin; PEM, Pemetrexed; PFS, Progression-free survival; QOL, Quality of life; NPC, Nasopharyngeal Carcinoma; NSCLC, Non-small cell lung cancer; NVB, Vinorelbine; RCT, Randomized controlled trial; RFS, Relapse free survival; RT, Radiotherapy; SCLC, Small-cell lung cancer; TAX, Paclitaxel; TNBC, Triple negative breast cancer; TTP, Time to progression.

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