Ovarian Cancer

NGR-hTNF plus Doxorubicin in Relapsed Ovarian Carcinoma

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Abstract

Ovarian cancer (OC) is the most deadly gynaecological cancer. Despite surgery and first-line chemotherapy, between 60% and 70% of OC patients will recur with poor prognosis. Several studies suggest anti-tumour activity of tumour necrosis factor (TNF) when given systematically, but the high toxicity of the drug has limited its use. NGR-human TNF ( hTNF) consists of TNF coupled with the peptide NGR that selectively binds to CD13, which is overexpressed on tumour blood vessels. NGR-hTNF is able to increase the intratumoural doxorubicin distribution by altering tumour vasculature. The activity and toxicity profile of NGR-hTNF–doxorubicin combination in recurrent OC will be described.

Keywords

Recurrent ovarian cancer; NGR-hTNF; doxorubicin

Ovarian cancer (OC) is the most lethal gynaecological cancer. In 2010, approximately 21,880 new cases and 13,850 deaths occurred in the US, 1 while in the EU in 2004 the incidence of newly diagnosed cases was 42,700 with a mortality of 12/100,000 women/year. 2 The current treatment of OC involves aggressive cytoreductive surgery followed by platinum- and taxane-based chemotherapy, which produces an objective response rate in approximately 65–80% of patients. 3

Nevertheless, despite surgery and first-line chemotherapy, between 60% and 70% of OC patients will recur and their prognosis and quality of life remain poor. 4 Platinum-based combination therapies represent the standard care for patients recurring more than six months after initial therapy; 5 combination treatment with paclitaxel and gemcitabine have been reported to increase outcome in terms of platinum monotherapy in recurrent platinum-sensitive patients. 6 Recently, the Aarobplatin and Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin and Paclitaxel in Relapsed Platinum-sensitive Ovarian cancer (CALYPSO) trial reported a better therapeutic index for the combination of carboplatin-PLD in comparison with carboplatin-paclitaxel in recurrent, platinum-sensitive OC thus representing, for most clinicians, the preferred option in this setting. 7

The response to platinum retreatment is related to the length of prior response to platinum. 8,9 It has been postulated that patients with partial platinum-sensitive recurrent OC (platinum-free interval [PFI] between six to 12 months) may benefit from a strategy of artificially extending the PFI by using a non-platinum agent followed by platinum at subsequent relapse. 10 In this view, after the publication of An Efficacy and Safety Study for Yondelis (Trabectedin) in Patients With Advanced Relapsed Ovarian Cancer (OVA-301) results, 11 the combination of trabectedin-PLD represent, for several clinicians, an alternative option to platinum-based regimens in this setting.

In general, platinum-resistant patients (who are patients recurring less than six months from last platinum treatment) are treated with sequential single non-platinum agents rather than with combination therapy 9,12 and, currently, the drugs approved in this subset of patients are paclitaxel, PLD, etoposide and topotecan with a short-lasting response rate in 10–25% of patients and a general dismal prognosis. 8,9 Therefore, novel treatment strategies are required to improve outcomes in women with recurrent OC, particularly in resistant disease.

Human NGR-Tumour Necrosis Factor

Tumour necrosis factor (TNF) was first identified by Carswell et al. in the serum of Bacillus Calmette-Guerin-sensitised animals treated with an endotoxin causing the release of a factor able to induce haemorrhagic necrosis of murine tumours. 13 In an in vitro experiment TNF has been shown to have cytostatic and cytotoxic effects against a wide range of human tumour cells and human tumour xenografts in nude mice. 13,14

In addition to the well-known cytostatic/cytotoxic properties, TNF has a broad spectrum of immunomodulatory activities. 15 TNF enhances the expression of class I major histocompatibility antigens on human endothelial cells, dermal fibroblasts and human tumour cell lines 16,17 and the expression of Class II major histocompatibility antigens on human T cells and tumour cells. 18 TNF has also demonstrated multiple actions on natural killer cells, macrophage cells and granulocyte function. 19,20,21 Moreover, evidence suggests that the anti-tumour activity of TNF depends on indirect mechanisms associated with selective obstruction and damage of tumour-associated blood vessels and on activation of immune mechanisms rather than a direct toxic effect on tumour cells. 23

Although numerous preclinical studies have demonstrated that TNF has notable anti-tumour activity 12,14,22,24 early trials in humans showed that its clinical use was limited by severe systemic toxicity. 13,15,25,27

Despite this, loco-regional therapy with TNF high doses in combination with chemotherapy led to elevated response rates in patients with...
melanoma and sarcoma of the extremities\textsuperscript{27–31} and regression of bulky hepatic cancers confined to the liver\textsuperscript{30} and peritoneal carcinomas.\textsuperscript{31}

In vivo screening of peptide-phage libraries has proven to be a powerful tool for the discovery of ligands that selectively home to tumour vessels.\textsuperscript{23} Among the targeting probes, a peptide containing the NGR motif has been coupled to different anticancer compounds, such as doxorubicin, and TNF, thus enabling targeted delivery of these drugs to tumour vessels.\textsuperscript{23,33,34} Based on those observations, the coupling of minute amounts of TNF to tumour vessels represents a novel approach for avoiding negative feedback mechanisms and preserving its ability to alter drug-penetration barriers. Vascular targeting could represent a novel strategy for increasing the therapeutic index of chemotherapeutic drugs.

NGR-Human Tumour Necrosis Factor–Doxorubicin Combination

Anthracyclines are among the most used chemotherapy agents in several solid and haematological tumours: anthracyclines exert claimed anti-tumour activity in OC; nevertheless, the effect on survival was demonstrated only in isolated clinical trials.\textsuperscript{32} In fact, in most studies the addition of doxorubicin had no effect on survival – only affecting the anti-tumour activity of chemotherapy, such as doxorubicin,\textsuperscript{32} cisplatin and melphalan, which indicated a synergistic effect with no evidence of increased toxicity. In particular, NGR-mTNF improved doxorubicin penetration in tumours, as the percentage of cancer cells that can be reached by doxorubicin and the drug intracellular amount suggests that NGR-mTNF improves cytotoxic drug penetration in tumours.\textsuperscript{32,33} The delivery of minute amounts of TNF to tumour vessels represents a novel approach for avoiding negative feedback mechanisms and preserving its ability to alter drug-penetration barriers. Vascular targeting could represent a novel strategy for increasing the therapeutic index of chemotherapeutic drugs.

The relatively poor penetration of doxorubicin in cancer cells is probably related to the structural and functional abnormalities typical of tumour disorganised vasculature and to the complete lack of lymphatics responsible of heterogeneous tumour perfusion, abnormal vascular permeability and increased interstitial pressure. These critical barriers may limit the penetration of drugs into cancer cells distant from tumour vessels and, consequently, the effectiveness of chemotherapy.\textsuperscript{34} Therapeutic strategies that enhance drug penetration have therefore considerable potential to increase cell killing and, consequently, tumour sensitivity.

Preclinical data demonstrated that when administered in combination to doxorubicin, NGR-mTNF exerts a synergic cytotoxic activity probably
fatigue, hypertension, vomiting and pyrexia. As far as anti-tumour events (aEs), reported in at least 10% of patients, were rigors, nausea, based chemotherapy line. Thirty-seven patients with radiologically oc with progressive disease after at least one previous platinum-based regimen were included and 35 were evaluable (54%). Consistently, 9 responses (39%) were recorded. From this viewpoint, the baseline pBLC could be an easily accessible and reproducible predictive biomarker of outcome, which might be exploited for selecting refractory/resistant OC patients who would mostly benefit from the combination of NGR-HTNF and doxorubicin (see Figure 2).

Toxicity profiles of the two drugs apparently did not overlap; most common aEs are those expected when each agent is given alone, consisting of neutropenia for doxorubicin and chills for NGR-HTNF. More importantly, cardiovascular toxicities previously reported for NGR-HTNF and doxorubicin, reported only in immunocompetent mice, being lacking in nude mice depleted of functionally mature T lymphocytes. From this viewpoint, the baseline PBLC could be an easily accessible and reproducible predictive biomarker of outcome, which might be exploited for selecting refractory/resistant OC patients who would mostly benefit from the combination of NGR-HTNF and doxorubicin (see Figure 2).
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