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Current Perspective

The use of bevacizumab in colorectal, lung, breast, renal and ovarian cancer: Where does it fit?

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ABSTRACT

Bevacizumab is approved for the treatment of colorectal cancer, breast cancer, non-small cell lung cancer and renal cell cancer. Before embracing this expensive agent for many other indications, it remains critical to be aware of the evidence upon which oncologists base their day-to-day clinical practice. In this review, we address the results of clinical studies upon which bevacizumab's current use is based and discuss some future perspectives.

1. Introduction

For growth and dissemination, tumours depend on blood supply from adjacent vessels. Angiogenesis is a multi step process primarily initiated through Vascular Endothelial Growth Factor (VEGF). VEGF binds to the endothelial VEGF receptors 1 and 2 (VEGFR-1 or flt-1 and VEGFR-2 or FLK-1/KDR, respectively), which initiates a cascade of intracellular signal transduction pathways, resulting in endothelial cell proliferation and the formation of new blood vessels. Increased VEGF expression is frequently observed in human epithelial cancer and is associated with poor outcome, irrespective of tumour stage or grade. As a consequence, VEGF has been considered a potential treatment target for long.

Bevacizumab (Avastin®) is a humanised monoclonal antibody that binds VEGF prior to its attachment to its natural receptors. After demonstrating anti-angiogenic and anti-tumour activity in preclinical models, bevacizumab produced anti-tumour activity in a number of frequently occurring tumour types in randomised clinical trials. Consequently, bevacizumab obtained regulatory approval for the treatment in first-line metastatic setting of colorectal cancer, non-small cell lung cancer and breast cancer, all in combination with chemotherapy. Apart from these indications, bevacizumab has been extensively tested for numerous other indications such as upper gastrointestinal tumours, mesothelioma, renal cell cancer and ovarian cancer, yielding interesting results. With the rapidly increasing number of established and approved indications for bevacizumab together with the crucial role of VEGF-driven angiogenesis in tumour pathogenesis, one might get the impression that almost all human cancers could or even should be treated with this agent. As it remains critical to be aware of the evidence upon which oncologists base their day-to-day clinical practice, it is crucial to critically appraise the current role of bevacizumab in the treatment of human cancer. In this review, we address the data of the results obtained so far with bevacizumab in colorectal, lung, breast, renal and ovarian cancer and discuss future perspectives.

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2. Metastatic colorectal cancer; first-line treatment

The 'landmark' study that resulted in regulatory approval was a large randomised phase III study in which bevacizumab at a relatively low dose (5 mg/kg every 14 d) was added to the so-called IFL regimen.[1] IFL is a combination regimen consisting of bolus 5-fluorouracil (5-FU), leucovorin and irinotecan that is more efficacious but also more toxic than bolus 5-FU/leucovorin regimens. In this study an increased response rate (RR) and progression free survival (PFS) were observed, which was translated into a significant increase of median overall survival (OS) from 15.6 to 20.3 months (Table 1). In both arms, treatment was given until progression. While the results of this study launched the regular use of bevacizumab, it should be noted that already at the time of publication IFL by many oncologists was no longer considered standard of care in first line.

Apart from this study, two randomised phase II trials comparing the addition of bevacizumab (5 mg/kg every 14 d and 5 or 10 mg/kg every 14 d, respectively) to 5-FU/leucovorin showed improvements in RR, PFS and OS.[2,3] Of note here is that the beneficial effect of bevacizumab in one of these trials was more pronounced in the low dose cohort of bevacizumab, eventhough one might argue that phase II trials are not ultimately meant to describe effects on OS. One has to realise that results from the combination chemotherapy regimens nowadays used in first line (infusional 5-FU/leucovorin or oral capecitabine combined with either oxaliplatin or irinotecan without bevacizumab) seem to exceed the efficacy of bevacizumab with either IFL or 5-FU/leucovorin. Nevertheless, in patients who are not fit enough for such combinations, the addition of bevacizumab to 5-FU/leucovorin 'alone' can be considered. Data on the combination of bevacizumab added to capecitabine monotherapy are not available.

Recently the results of a large randomised trial adding bevacizumab to schedules that are currently widely used, XELOX and FOLFOX-4, were published.[4] The results however, were somewhat disappointing. Although the PFS was significantly improved in the bevacizumab treated groups, RR and, most essential, OS were not improved. In contrast to the studies showing benefit of adding bevacizumab to chemotherapy, it appeared that only a minority of patients were treated until disease progression, which, in view of the authors, could have hampered optimal efficacy of bevacizumab. Another intriguing point from this trial is that two different schedules of administration for bevacizumab were used underscoring the obvious lack of knowledge on optimal dose and treatment duration. Currently, a number of descriptive and observational studies are trying to further 'define' the role of bevacizumab in combination with current first-line chemotherapy schedules such as FOLFOX, XELOX and FOLFIRI. However, these kinds of studies are of course less convincing than appropriately performed prospective randomised trials.

Collectively, bevacizumab can enhance effects of first-line treatment in metastatic colorectal cancer, albeit that the absolute benefit varies considerably, and optimal schedule and duration of bevacizumab treatment are not clear. Despite the disappointing results of the study exploring the combination of bevacizumab and XELOX/FOLFOX-4 and therefore lack of evidence, these regimens are now widely applied in first line. This approach is based on the proven benefits of bevacizumab added to other, less optimal, first-line regimens, the effects of bevacizumab added to FOLFOX-4 in second line (*vide infra*) and the widespread assumption that bevacizumab should be continued until disease progression.

Table 1 – Published randomised trials of chemotherapy + bevacizumab in colorectal cancer

Indication	Study phase	Chemotherapy	Bevacizumab	End-points	References
Palliative First line	3	IFL	5 mg/kg q14 d *versus* placebo	OS 15.6 → 20.3 m PFS 6.2 → 10.6 m RR 34.7 → 44.8%	[1]
Palliative First line	3	Folfox-4	5 mg/kg q14 d *versus* placebo	OS ns PFS ns RR ns	[4]
Palliative First line	3	XELOX	7.5 mg/kg q21 d *versus* placebo	OS ns PFS 7.4 → 9.3 m RR ns	[4]
Palliative First line	2	5-FU leucovorin	5 mg/kg q14 d *versus* placebo	OS 12.9 → 16.6 m PFS 5.5 → 9.2 m RR 15.2 → 26%	[2]
Palliative First line	2	5-FU Leucovorin	5 or 10 mg/kg q14 d *versus* placebo	OS 13.8 → 21.5 → 16.1 m PFS 5.2 → 9 → 7.2 m RR 17 → 40 → 24%	[3]
Palliative Second line	3	Folfox-4	10 mg/kg q14 d *versus* placebo	OS 10.8 → 12.9 m PFS 4.7 → 7.3 m RR 8.6 → 22.7%	[5]

OS denotes overall survival.
PFS denotes progression free survival.
RR denotes response rate.
ns denotes not significant.
M denotes months.

3. Metastatic colorectal cancer; second-line treatment

In contrast to the first-line study of bevacizumab and XELOX/FOLFOX-4, results from a randomised study exploring the role of bevacizumab to FOLFOX-4 as second line have shown a significant effect on OS (Table 1).[5] The dose of bevacizumab (10 mg/kg every 14 d) was higher than used in any of the first-line treatment studies which may explain the contradictory results of bevacizumab with FOLFOX-4 in first and second lines. Additional studies with bevacizumab in various different second-line regimens will more clearly define the role of this agent in this setting.

4. Metastatic colorectal cancer; third-line treatment

While the EGFR targeting antibodies cetuximab and panitumumab have demonstrated clinical benefit in third-line treatment in selected patients, no robust data on meaningful effects of bevacizumab in this line have to date been published. The use of bevacizumab under these circumstances therefore is currently neither proven nor indicated.

5. Adjuvant treatment in colorectal cancer

With the role of angiogenesis inhibiting agents emerging in the metastatic setting, it is likely that their activity will also show in the setting of minimal residual disease. Therefore studies exploring the role of bevacizumab in the adjuvant setting are ongoing. The ongoing AVANT trial randomises high risk stages II and III colorectal cancer patients to either adjuvant FOLFOX-4, FOLFOX-4 in combination with bevacizumab 5 mg/kg every 14 d for 24 weeks followed by bevacizumab monotherapy for another 24 weeks or XELOX with bevacizumab 7.5 mg/kg every 21 d for 24 weeks followed by bevacizumab monotherapy for another 24 weeks. So far only safety data have been presented.[6]

6. Metastatic non-small cell lung cancer; first-line treatment

To date, two randomised phase III studies exploring the role of bevacizumab added to chemotherapy in non-small cell lung cancer (NSCLC) have been performed (Table 2). In the first study, carboplatin/paclitaxel was compared to the same regimen combined with bevacizumab 15 mg/kg every 21 d and continued until progression.[7] Although a significant increase in PFS and OS was observed in this study, 6 and 8 weeks, respectively, the absolute gain remains at best modest. Furthermore, a relatively large number of patients suffered from side-effects attributable to bevacizumab, and some patients even experienced fatal complications, in particular pulmonary haemorrhage.

The second study presented had a comparable design, albeit that chemotherapy here consisted of gemcitabine/cisplatinum and two doses of bevacizumab (7.5 and 15 mg/kg every 21 d) were explored.[8] On PFS, the primary end-point, the lower dose of bevacizumab had a better effect (albeit marginally) than the higher dose, underscoring again the difficulty in assessing the optimal dose of bevacizumab. With regard to side-effects attributable to bevacizumab, no clear dose-relationship could be assessed, but again a number of patients suffered from fatal pulmonary haemorrhage.

While the risk-benefit ratio of the addition of bevacizumab to chemotherapy in NSCLC thus at best should be described as modest, a recently performed subgroup analysis even pointed towards increased toxicity of bevacizumab in the absence of survival benefit in particular groups of patients, most notably the elderly ones.[9] Unfortunately, most patients suffering from NSCLC are in fact of older age, while many of these patients typically are not in an optimal condition due to the occurrence of (most notably cardiovascular) comorbidity. If there is a benefit from adding bevacizumab to first-line chemotherapy in NSCLC, these benefits are likely to be limited to a subset of patients that currently cannot be adequately identified.

7. Metastatic non-small cell lung cancer; second-line treatment

Due to the nature of the underlying disease and the frequent occurrence of comorbidity, usually only a small proportion of patients with NSCLC can be offered second-line treatment in case of disease progression. While chemotherapy under these conditions often is considered too toxic and only has limited activity, less toxic treatment options such as EGFR targeting agents can have a place. Whether the addition of bevacizumab

Table 2 – Published randomised trials of chemotherapy ± bevacizumab in non-small cell lung cancer

Indication	Study phase	Chemotherapy	Bevacizumab	End-points	References
Palliative First line	3	Carboplatin/ Paclitaxel	15 mg/kg q21d Placebo	OS 10.3 → 12.3 m PFS 4.5 → 6.2 m RR 15 → 35%	[7]
Palliative First line	3	Gemcitabine/ Cisplatin	7.5/15 mg/kg q21d Placebo	PFS 6.1 → 6.7 → 6.5 m RR 20 → 34 → 30%	[8]

OS denotes overall survival.
PFS denotes progression free survival.
RR denotes response rate.
ns denotes not significant.
M denotes months.

to such a treatment modality can have activity translating into relevant clinical outcomes is subject of ongoing trials.

8. Adjuvant treatment in non-small cell lung cancer

In an increasing number of patients that have undergone potentially curative resection of NSCLC adjuvant chemotherapy is prescribed. For the same reasons rendering the exploration of bevacizumab in the adjuvant setting worthwhile in other tumour types, such trials are ongoing in NSCLC as well. In these trials there seems to be some kind of agreement on dosing bevacizumab at 15 mg/kg every 21 d.

9. Metastatic breast cancer; first-line treatment

In contrast to trials in colorectal cancer and NSCLC, in breast cancer the first studies with bevacizumab were performed in the second- and third-line metastatic settings (Table 3). It was only recently that mature results from a first-line combination study were published.[10] In this study, having PFS as primary end-point, the addition of bevacizumab at 10 mg/kg every 14 d to weekly paclitaxel significantly improved RR and PFS, the latter from almost 6 to almost 12 months. OS was not improved. Again, bevacizumab was given until progressive disease. Given the relatively favourable toxicity profile, single agent weekly paclitaxel is often administered to relatively frail patients, often those with high age, (cardiovascular) comorbidity or poor condition otherwise. It may be that the risk-benefit ratio of bevacizumab in such a population will be less outspoken than in the pivotal trial.

Docetaxel is another viable first-line treatment option for patients with metastatic breast cancer, and the first data of a randomised study exploring the role of two doses of bevacizumab (7.5 and 15 mg/kg every 21 d) added to docetaxel have meanwhile been presented.[11] Preliminary data reveal dose-dependent and statistically significant improvements in the primary end-point PFS and secondary end-point RR, though seemingly to a lesser extent than when combined with weekly paclitaxel. Data on the secondary end-point OS are not yet available.

Currently a plethora of studies are assessing the role of bevacizumab in various combinations of chemotherapy in both HER-2 expressing and HER-2 negative tumours; as it has been demonstrated that HER-2 expressing tumour cells often produce VEGF, a chemotherapy-free approach with bevacizumab combined with a HER2-targeting compound seems of interest. A small phase II trial of trastuzumab combined with bevacizumab demonstrated clinical feasibility and a 46% RR.[12]

10. Metastatic breast cancer; second-line treatment

The first randomised study with bevacizumab in metastatic breast cancer was performed in second and third-line settings, adding bevacizumab at 15 mg/kg every 21 d to capecitabine.[13] The results of this trial were rather disappointing, with no effects on PFS or OS despite an improved RR. Currently most attention is put on the role of bevacizumab in adjuvant and first-line metastatic treatment settings.

11. Adjuvant and neoadjuvant treatment in breast cancer

Trials exploring the role of bevacizumab as single agent or in combination with either hormonal treatment or chemotherapy in the adjuvant setting for breast cancer have been initiated. While especially patients with HER-2 expressing tumours are becoming familiar with prolonged duration of intravenously administered adjuvant treatment, the issue of treatment duration with bevacizumab is also critical; in ongoing studies up to 52 weeks of treatment, frequently at a dose of 15 mg/kg every 21 d, is most frequently explored. If and how bevacizumab could most optimally be incorporated in neoadjuvant treatment schedules is another field of ongoing research.[14] Bearing in mind the potential increased risk of

Table 3 – Published randomised trials of chemotherapy ± bevacizumab in breast cancer

Indication	Study phase	Chemotherapy	Bevacizumab	End-points	References
Palliative First line	3	Paclitaxel	10 mg/kg q14 d placebo	OS ns PFS 5.9 → 11.8 m RR 21.2 → 36.9%	[10]
Palliative First line	3	Docetaxel	7.5/15 mg/kg q21d placebo	OS ne PFS 8.0 → 8.7→8.8 m RR 44 → 55 → 63%	[11]
Palliative Second line	3	Capecitabine	15 mg/kg q21d placebo	OS ns PFS ns RR 9.1 → 19.8%	[13]

OS denotes overall survival.
PFS denotes progression free survival.
RR denotes response rate.
ns denotes not significant.
ne denotes not evaluable.
M denotes months.

bleeding complications, one of course has to respect a 4 to 6 week period off bevacizumab prior to any planned surgical procedure.

12. Metastatic renal cell cancer; first-line treatment

The rationale to explore inhibitors of the VEGF-VEGFR pathway in the treatment of clear-cell renal cell cancer (RCC) is based upon the frequently decreased function of Von Hippel-Lindau tumour suppressor gene product and the subsequent increased production of VEGF. For long, interferon and/or interleukins were considered the only active drugs, and the role of VEGF inhibition only became clear recently. In second-line setting after immunotherapy, bevacizumab at a dose of 10 mg/kg every 2 weeks yielded a significant prolongation of PFS over placebo, while there was no benefit regarding this end-point from bevacizumab at a dose of 3 mg/kg every 14 d.[15] Recently, two large randomised trials of bevacizumab added to interferon in first-line treatment more convincingly defined its role.[16,17] Compared to interferon alone, PFS was prolonged from almost 6 to more than 10 months, and from 5 to more than 8 months, respectively. Data on OS, however, are still lacking (Table 4).

Meanwhile, sunitinib, a VEGF-receptor tyrosine kinase inhibitor that can be orally administered, has also been shown to be superior compared to interferon in terms of RR, PFS and OS.[18,19] Until now, a head to head comparison of sunitinib *versus* the combination of interferon and bevacizumab in order to demonstrate superiority of any of these regimens is lacking. Combination studies of bevacizumab and compounds such as sunitinib and sorafenib are ongoing while also single-agent high dose schedules of bevacizumab (15 mg/kg every 14 or 7 d) are explored.

13. Metastatic renal cell cancer; second-line treatment

Apparently, not too much focus is currently placed on determining bevacizumab's role in second or subsequent treatment lines, and only one study could be identified likely to be initiated soon.

14. Adjuvant treatment in renal cell cancer

While considering the role of VEGF in the pathogenesis of RCC, a rationale to explore the role of angiogenesis inhibitors in the adjuvant setting can easily be perceived. Although agents such as sunitinib and sorafenib are already being explored in this setting, no such studies with bevacizumab could be identified.

15. Ovarian cancer; first and second-line treatment

With increased expression of *hypoxia-inducible factor-1 alpha* gene and VEGF in ovarian cancer cell lines and the observed negative prognostic impact of increased VEGF expression in the clinical setting, a clear rationale to explore the role of bevacizumab exists. In addition, the frequently obtained clinical situation of minimal residual disease following optimal surgical debulking or following optimal adjuvant chemotherapy even more merits exploration of this agent. Two single-agent phase II trials in recurrent disease showed objective responses and prolongation of PFS when compared to historical controls in one of them.[20] One of these studies was closed prematurely due to an unexpected high number of gastrointestinal perforations, in 7% of patients even fatal.[21] The apparent poor tolerability of bevacizumab was ascribed to the relatively high number of previous chemotherapy lines (most often three). While in two small phase II first-line studies the number of complications was low, the real assessment of safety and efficacy of bevacizumab added to standard chemotherapy in first-line treatment following optimal surgical debulking can only come from large randomised trials that are currently ongoing.[22,23] In addition, the role of bevacizumab as consolidation treatment and in recurrent ovarian cancer in combination with various chemotherapy regimens is currently explored, but mature data are still lacking (Table 5).

Table 4 – Published randomised trials of bevacizumab in renal cancer

Indication	Study phase	Chemotherapy	Bevacizumab	End-points	References
Palliative Second line	2	–	3/10 mg/kgq 14 d Placebo	OS ne PFS 2.5 → 3.0 → 4.8 m	[15]
Palliative First line	3	Interferon-alfa	10 mg/kg q14d Placebo	OS ne PFS 5.4 → 10.2 m RR 39 → 70%	[16]
Palliative First line	3	Interferon-alfa	10 mg/kg q14d Placebo	OS ne PFS 5.2 → 8.5 m RR 13.1 → 25.5%	[17]

OS denotes overall survival.
PFS denotes progression free survival.
RR denotes response rate.
ns denotes not significant.
ne denotes not evaluable.
M denotes months.

Table 5 – Published randomised trials of chemotherapy ± bevacizumab in ovarian cancer

Indication	Study phase	Chemotherapy	Bevacizumab	End-points	References
Second/third line	2	–	15 mg/kg q 21 d	OS 17 m PFS 4.7 m RR 21%	[20]
Third line	2	–	15 mg/kg q 21 d	OS 10.7 m PFS 4.4 m RR 15.9%	[21]
First line	2	Carboplatin/Paclitaxel	15 mg/kg q 21 d	OS ne PFS ne RR 80%	[22]
Second/third line	2	Cyclofosfamide	10 mg/kg q 14 d	OS 16.9 m PFS 7.2 m RR 24%	[23]

OS denotes overall survival.
PFS denotes progression free survival.
RR denotes response rate.
ns denotes not significant.
M denotes months.

16. Discussion

While the role of bevacizumab in several tumour types is now established and is likely to emerge further, in numerous other tumour types its role is still pending. With many clinical studies ongoing, however, it can well be perceived that the number of approved indications for bevacizumab will increase in the coming years.

While assessing current data, some issues seem to stand out; There does not seem to be a clear dose–response relationship, and the choices made for dosing and schedule often seem to be based upon pragmatism and convenience to integrate bevacizumab with chemotherapy regimens given every 2 or 3 weeks. It is unlikely that for all these schedules randomised trials exploring different doses of bevacizumab will ever be performed, and thus the question of truly optimal dosing will likewise never be answered.

Furthermore, in order to avoid over- and undertreatment, there is a great need to identify clinical prognostic and predictive factors for outcome to bevacizumab-based therapies. For some tumour types, this probably means that only a small percentage of patients will actually benefit. NSCLC serves here as an example where in particular elderly male patients with centrally located squamous cell cancer should not be exposed to bevacizumab, given the unfavourable risk-benefit ratio for these patients.

Whether the role of bevacizumab in combination with chemotherapy in first-line metastatic treatment is superior to its role in second and subsequent lines is to date unclear, as some seemingly conflicting data (colorectal *versus* breast cancer) have been observed. Currently, it seems that most emphasis is put on early, i.e. first-line treatment.

Another important point that remains to be elucidated is the optimal treatment duration. Eventhough data in a number of tumour types suggest to continue bevacizumab beyond the duration of first-line chemotherapy, probably until disease progression, the optimal duration of treatment by far has not been established. Whether there is a role for treatment continuation, most likely in combination with second-line chemotherapy following disease progression (the so-called treatment beyond progression strategy), is another question that remains to be answered.

As bevacizumab is increasingly explored in the adjuvant setting, most of the issues discussed for bevacizumab in the advanced setting (in particular the discussion about dose and duration of treatment) will be even more prominent, and here a large area of research is still open.

Finally, but not most unimportantly, the pharmaco-economic analysis or cost-benefit ratio assessment of bevacizumab is an issue. Although the thresholds to accept a drug as economically acceptable and worthwhile can differ from country to country, the acceptable cost per gained life year or Quality Adjusted Life Year (QALY) has been set at approximately €80,000 in several European countries. Based upon any accepted assumption, treatment related costs in relation to gain in clinical outcome can be calculated, and increasingly this is done for new expensive anticancer drugs including bevacizumab.[24,25] Taken as example, this analysis has urged the English National Health Service to conclude that bevacizumab in combination with bolus 5-FU/leucovorin or IFL is not cost effective.[25] Future clinical studies, especially those performed in the adjuvant treatment setting, will have to yield reliable and reproducible clinical outcomes that can serve as a basis for subsequent pharmaco-economic assessments that will ultimately lead to approval or rejection of an agent such as bevacizumab for a particular disease or disease stage.

In conclusion, the introduction in the clinic of bevacizumab almost 10 years ago has resulted in approval, acceptance and regular use for a still increasing number of indications. Nowadays this compound fits in the regular treatment of colorectal cancer, breast cancer and RCC and can be considered in NSCLC.

Although the gain in survival in many instances is at best modest, bevacizumab has been embraced by many treating oncologists as a new and attractive treatment option for many patients. However, before its use is further expanded

to other indications, it is crucial that robust evidence from randomised studies is provided.

Conflict of interest statement

None declared.

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