In this large observational study of first-line mCRC patients

**Study design and treatment**

- **METHODS**

**OBJECTIVES**

- **Echinocardiographic evaluation**

**Data Collection Schedule**

**Table 1.** Hypertension status at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypertension</th>
<th>No Hypertension</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years,</td>
<td>60-64</td>
<td>50.0 (29.3)</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>65-69</td>
<td>46.4 (21.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70-74</td>
<td>49.1 (21.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75-79</td>
<td>51.2 (20.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥80</td>
<td>55.0 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Gender, %</td>
<td>Male</td>
<td>78.9 (81.4)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>74.5 (77.1)</td>
<td></td>
</tr>
</tbody>
</table>
| Hypertension Status at Baseline

- **Table 2.** Type of adjuvant therapy

| Type of adjuvant therapy | Patients, no. (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX (5-FU/leucovorin)</td>
<td>1,023 (56.0)</td>
</tr>
<tr>
<td>FOLFIRI (5-FU/leucovorin)</td>
<td>393 (20.7)</td>
</tr>
<tr>
<td>XELOX (5-FU bolus/LV)</td>
<td>119 (6.3)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>168 (8.8)</td>
</tr>
<tr>
<td>None</td>
<td>82 (4.3)</td>
</tr>
</tbody>
</table>

- **Table 3.** Selected BV-associated adverse events

| Event               | Patients, no. (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>127 (6.3)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>102 (5.2)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>52 (2.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (1.6)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (0.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (0.5)</td>
</tr>
<tr>
<td>Venocclusive</td>
<td>8 (0.4)</td>
</tr>
</tbody>
</table>

**Table 4.** Management of HTN-associated BV adverse effects

<table>
<thead>
<tr>
<th>Event</th>
<th>Management</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Medication</td>
<td>72.5 (73.1)</td>
</tr>
<tr>
<td></td>
<td>Restrict</td>
<td>15.8 (16.4)</td>
</tr>
<tr>
<td></td>
<td>BI 2.5 mg</td>
<td>0.9 (1.0)</td>
</tr>
</tbody>
</table>

**Table 5.** Logistic regression analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.2 (1.8-2.7)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td>Venocclusive</td>
<td>0.6 (0.3-1.2)</td>
</tr>
</tbody>
</table>

**Figure 5.** Patients with comorbidities.

**REFERENCES**

-**K3 SAFETY OF BEVACIZUMAB PLUS CHEMOTHERAPY AS FIRST-LINE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER: UPDATED RESULTS FROM A LARGE OBSERVATIONAL REGISTRY IN THE US (BRITE)**

**INTRODUCTION**

- Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is widely used in the treatment of various cancers. It has shown overall survival and progression-free survival when combined with chemotherapy in metastatic colorectal cancer (mCRC) patients. However, it is associated with serious and uncommon adverse reactions.

- **METHODS**

**DATA COLLECTION**

- **Table 1.** Data Collection Schedule

**SUMMARY AND CONCLUSIONS**

- In this large observational study of first-line CRC patients treated with BV chemotherapy, it is clear that pre-existing hypertension is a risk factor for the development of hypertension associated with BV use.

- The safety profile of BV when used in combination with a variety of chemotherapy regimens, as assessed by the BRITE registry, is consistent with the findings of the pivotal phase III trial (AVF1016G).

- The most common selected BV-associated adverse events are listed in Table 3.

- Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is widely used in the treatment of various cancers. It has shown overall survival and progression-free survival when combined with chemotherapy in metastatic colorectal cancer (mCRC) patients. However, it is associated with serious and uncommon adverse reactions.

- BV is typically used in combination with chemotherapy regimens such as FOLFOX (5-FU/leucovorin), FOLFIRI (5-FU/leucovorin), and XELOX (5-FU bolus/LV), and it is important to monitor for adverse events, including hypertension, which can be managed with antihypertensive medications.

- Bevacizumab (BV) is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF) that is approved for use in the treatment of various cancers, including metastatic colorectal cancer (mCRC).

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- BV is typically used in combination with chemotherapy regimens such as FOLFOX (5-FU/leucovorin), FOLFIRI (5-FU/leucovorin), and XELOX (5-FU bolus/LV), and it is important to monitor for adverse events, including hypertension, which can be managed with antihypertensive medications.
INTRODUCTION
Bevacizumab (BV), an antiangiogenic monoclonal antibody, has established utility in first-line colorectal cancer (mCRC) therapy through its potent antivascular effects. Patients with mCRC who receive BV in the first-line setting experience overall survival and progression-free survival time longer when combined with chemotherapy (21). Bevacizumab chemotherapy regimens are currently used in second-line therapy for mCRC, with significant improvements in survival and quality of life (22). In phase III trials in CRC, BV was associated with relatively uncommon serious but adverse events (SAEs), including gastrointestinal perforation (GP), which occurred in 1.1% of patients receiving BV plus FOLFOX4 (23) or 1.7% of patients receiving FOLFOX4 plus BV who did not have GP (24).

In this large observational study of first-line mCRC patients, the incidence, nature, and management of hypertension requiring new antihypertensive medications associated with the use of BV–GP,姑息性放疗or oral or intravenous 5-FU-based chemotherapy regimens, 42 were evaluated in a large, less-selected community-based population of patients with mCRC. The BRiTE observational study was initiated at the time of FDA approval of BV in order to evaluate the safety and efficacy of BV in a large, less-selected community-based population of patients with mCRC.

The current registry will follow approximately 2000 patients for up to 3 years.

OBJECTIVES
• Assess the incidences of the following selected BV-associated adverse events:
  - GP
  - Pneumonia
  - Cardiac failure
  - Drug toxicity
  - ATE
  - Grade 3 or 4 bleeding events identified by the National Cancer Institute–Common Toxicity Criteria, version 3.0
  - Other adverse events that the physician suspects may be associated with the use of BV in combination with chemotherapy
  - Evaluate the incidence and management of hypertension (HTN) requiring antihypertensive medication

METHODS
Study design and treatment
Observational study, initiated in February 2004
Observational data collected quarterly
Chemotherapy regimen, BV dose, and BV schedule chosen at physician discretion
Eligibility criteria
• Metastatic or locally unresectable CRC
• Receiving BV in combination with any first-line chemotherapy
• Signed informed consent

Data collection
The schedule of data collection, as well as the specific data collected, indicated in column heading unless otherwise indicated; †Local labs (with different references ranges) were used

Table 1. Data Collection Schedule

<table>
<thead>
<tr>
<th>Characteristics*</th>
<th>BV + IFL (n = 131)</th>
<th>BV + IFL (n = 131)</th>
<th>BV + Placebo (n = 1849)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status of primary tumor, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age groups, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
| Characteristics | BRiTE trial | \[IFL + BV and \[5-FU + BV arms (n = 616). \]
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No HTN at baseline</th>
<th>Patients, %</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension requiring new medication was</td>
<td>No HTN at baseline</td>
<td>Patients, %</td>
<td>Patients, %</td>
</tr>
<tr>
<td>BV therapy, %</td>
<td>No HTN at baseline</td>
<td>Patients, %</td>
<td>Patients, %</td>
</tr>
<tr>
<td>No HTN at baseline</td>
<td>Patients, %</td>
<td>Patients, %</td>
<td>Patients, %</td>
</tr>
<tr>
<td>Number of times antihypertensive medication was</td>
<td>No HTN at baseline</td>
<td>Patients, %</td>
<td>Patients, %</td>
</tr>
<tr>
<td>Management of HTN Associated With BV Use: Additions or</td>
<td>No HTN at baseline</td>
<td>Patients, %</td>
<td>Patients, %</td>
</tr>
<tr>
<td>Modifications of Antihypertensive Medications</td>
<td>No HTN at baseline</td>
<td>Patients, %</td>
<td>Patients, %</td>
</tr>
<tr>
<td>Table 5. Management of HTNs Associated With BV Use. Additions or Modifications of Antihypertensive Medications</td>
<td>No HTN at baseline</td>
<td>Patients, %</td>
<td>Patients, %</td>
</tr>
<tr>
<td>Table 6. Selected Adverse Events Associated With the Use of Bevacizumab</td>
<td>No HTN at baseline</td>
<td>Patients, %</td>
<td>Patients, %</td>
</tr>
</tbody>
</table>

REFERENCES
INTRODUCTION

Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has proven to delay overall survival and prolong recurrence-free survival when combined with standard chemotherapy for metastatic colorectal cancer (mCRC). BV has also demonstrated improved outcomes when added to chemotherapy in the treatment of first-line metastatic colorectal cancer. A large, observational study of first-line mCRC patients treated with BV plus chemotherapy was undertaken to provide additional data to support the use of BV in this population.

OBJECTIVES

• Analyses of BRiTE with regard to GIP and efficacy are presented in separate reports (posters K2 and K3, respectively)
• Bevacizumab (Avastin®, BV), a recombinant humanized monoclonal antibody against VEGF, has proven to delay overall survival and prolong recurrence-free survival when combined with standard chemotherapy for metastatic colorectal cancer (mCRC). BV has also demonstrated improved outcomes when added to chemotherapy in the treatment of first-line metastatic colorectal cancer. A large, observational study of first-line mCRC patients treated with BV plus chemotherapy was undertaken to provide additional data to support the use of BV in this population.

METHODS

Study design and treatment

• Observational study, initiated in January 2004
• Observational data collected quarterly
• Chemotherapy regimen, BV dose, and BV schedule chosen at physician discretion

Eligibility criteria

• Metastatic or locally unresectable CRC
• Receiving BV in combination with any first-line chemotherapy

Data collection

• The schedule of data collection, as well as the specific data collected, is detailed in Table 2.

Statistical considerations

• Frequencies and percentages are calculated for the study population as a whole, and for subgroups defined as patients who received BV for a minimum of 1 cycle of BV in the BRiTE study.

RESULTS

Enrollment, follow-up, and site distribution

There were 1960 evaluable patients; 8 patients who never received BV were considered non-evaluable. Median follow-up was 13.2 months at the time of this analysis (March 2008). The majority of affected patients requiring 1 or 2 changes in their antihypertensive regimen (Table 4) were considered non-evaluable because of SAEs related to BV.

SUCCESSS

• Overall, 5% of patients (n = 25) permanently discontinued the use of BV because of SAEs related to BV.

COMMENTS

• There were 1960 evaluable patients; 8 patients who never received BV were considered non-evaluable.

REFERENCES


In this large observational study of first-line mCRC patients
n/a
√
√
n/a
0.2
947 (83.7)
4.3
No
1.0
0.0
0
0.9
√
n/a
13.5
18.7
4.1
101 (54.9)
0
√
0.7
45.8
14 (7.6)
12.2
69 (37.5)
Clinical follow-up of patients in this community-based registry
3.4
63.2
6.4
0.2
0.5
√
1.0
• Signed informed consent
• Receiving BV in combination with any first-line chemotherapy
• Observational study initiated in February 2004
• Analyses of BRiTE with regard to GIP and efficacy are presented in
• This observational registry will follow approximately 2000 patients for
• In phase II trials in CRC, BV was associated with relatively
• Other adverse events that the physician suspects may be
– A T E
requiring antihypertensive medication
Hypertension history:
Cardiac history:
– peptic ulcer
Postoperative bleeding or wound healing
including GIP,
Disease characteristics:
ECOG performance status
Demographics:
• Data for selected adverse events associated with the use of BV—
K3
• Frequency of combined evaluation of HTN at baseline
• The incidence of hypertension requiring antihypertensive
– The safety profile of BV when used in combination with a
– The safety profile of BV when used in combination with a
treatment for metastatic colorectal cancer. BV and placebo were associated with the use of BV—
– The safety profile of BV when used in combination with a
• This observational study of first-line mCRC patients treated with BV—chromotherapy, in which it is selected
– The safety profile of BV when used in combination with a
– The safety profile of BV when used in combination with a
In this large observational study of first-line mCRC patients...
**SAFETY OF BEVACIZUMAB PLUS CHEMOTHERAPY AS FIRST-LINE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER: UPDATED RESULTS FROM A LARGE OBSERVATIONAL REGISTRY IN THE US (BRiTE)**

E. Hedrick, M. Koizumi, J. Hainsworth, S. Badarinaraja, A. Cohn, P. Flynn, W. Dong, S. Suzuki, S. Sarkar, M. Sugrue, A. Grotzhey, and the BRiTE Study Investigators

**INTRODUCTION**

Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is approved for first-line treatment of metastatic colorectal cancer (mCRC) on the basis of overall survival and progression-free survival when combined with fluorouracil (FU) and leucovorin (LV) chemotherapy regimens in colorectal cancer trials (1-3). BV is associated with hypertension (HTN) and an increased risk of serious adverse events (SAEs) (4-6).

**METHODS**

• In this large observational study of first-line mCRC patients receiving BV plus FOLFOX4, the outcomes of 1960 evaluable patients were assessed.
• The incidence and management of hypertension requiring antihypertensive medication were evaluated.
• Clinical follow-up of patients in this community-based registry was 37 months.

**RESULTS**

• The incidences of selected adverse events associated with the use of BV—GPRF placebo-banding or withholding chemotherapy, AVF2107 (n = 616) compared to the pivotal phase III trial AVF2107g (n = 402). Frequencies of grade 3 or 4 bleeding events—were collected on specialized case report forms, which included a risk-factor profile. Other **adverse events** that the physician suspects may be associated with the use of BV in combination with chemotherapy were documented.

**SUMMARY AND CONCLUSIONS**

• In this observational study of first-line mCRC patients treated with BV chemotherapy, which is a selected subset of patients compared to the pivotal phase III trial AVF2107g, the safety profile of BV used in combination with a variety of chemotherapy regimens, as measured by selected adverse events associated with the use of BV, was comparable with the safety profile in the pivotal phase III trial AVF2107g.

• The incidence of HTN requiring antihypertensive treatment was similar to the incidence observed in phase III studies with BV in mCRC. HTN associated with BV use was not dependent on pre-existing HTN. The majority of patients with HTN associated with BV use required 1–3 adjustments to their antihypertensive regimen.

• Discontinuation of BV in patients who developed serious adverse events was associated with improved risk profiles of patients with metastatic colorectal cancer treated with BV in the BRiTE study.
INTRODUCTION

Bevacizumab (BV, Avastin®), a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), is widely used in the treatment of metastatic colorectal cancer (mCRC) due to its potential to slow disease progression.

METHODS

The BRiTE observational study was initiated at the time of FDA approval of BV in order to evaluate the safety and efficacy of BV in a large, unselected community-based population of patients with mCRC.

RESULTS

Enrollment, follow-up, and site distribution

There were 1960 evaluable patients; 8 patients who never received BV were considered non-evaluable.

Table 1. Data Collection Schedule

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Completed</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule A</td>
<td>Yes</td>
<td>1/5/2005</td>
</tr>
<tr>
<td>Schedule B</td>
<td>Yes</td>
<td>2/5/2005</td>
</tr>
</tbody>
</table>

Characteristics

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Female</td>
<td>27.5</td>
<td>0.5</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>42.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>38.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Site(s) of metastatic disease</td>
<td>77.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Site(s) of metastatic disease</td>
<td>38.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Data collection

Surgical complications were assessed, if any, at the time of the surgical procedure. The charts of all patients were reviewed to identify all complications.

Statistical considerations

The incidence of the selected BV-associated adverse events was compared across the BV plus chemotherapy and BV plus placebo groups using the Fisher exact test.

CONCLUSIONS

In this large observational study of first-line mCRC patients treated with BV plus chemotherapy, in which a less-selected community-based population was enrolled, the safety profile of BV when used in combination with a variety of chemotherapy regimens, as measured by selected BV-associated adverse events, is consistent with that observed in phase III trials.

SUMMARY AND CONCLUSIONS

The safety profile of BV when used in combination with a variety of chemotherapy regimens, as measured by selected BV-associated adverse events, is consistent with that observed in phase III trials.

REFERENCES


SUMMARY AND CONCLUSIONS

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SUMMARY AND CONCLUSIONS

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