Critical Reviews in Oncology/Hematology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Review of the current role of targeted therapies as maintenance therapies in first and second line treatment of epithelial ovarian cancer; In the light of completed trials

Taner Korkmaz [a], Selcuk Seber [b,*], Gul Basaran [a]

[a] Acibadem University Hospital, Turkey
[b] Namik Kemal University Hospital, Turkey

Contents

1. Introduction 00
2. First line treatment 00
 2.1. Bevacizumab 00
  2.1.1. GOG-218 00
  2.1.2. Pazopanib 00
  2.1.3. Nintedanib 00
  2.1.4. Erlotinib 00
  2.1.5. Abagovomab 00
3. Targeted therapy in recurrent disease 00
 3.1. Bevacizumab 00
  3.1.1. Platin sensitive patients 00
  3.1.2. Platin resistant patients 00
 3.2. Trabectedin 00
 3.3. PARP inhibitors 00
  3.3.1. Olaparib 00
 3.4. Study 19 00
 3.5. Study 41 00
 3.6. Study 42 00
  3.6.1. Rucaparib 00
 3.7. Trebananib 00
 3.8. Cediranib 00
4. Combination targeted therapy for recurrent ovarian cancer 00
 4.1. Olaparib and cediranib combination treatment 00
5. Conclusion 00
 Conflict of interest 00
 References 00

ARTICLE INFO

Article history:
Received 31 December 2014
Received in revised form 12 August 2015
Accepted 15 October 2015

Keywords:
Ovarian cancer
Maintenance treatment
Targeted therapy

ABSTRACT

Late and recurrent stage ovarian cancer has a high mortality and low response rate to therapy beyond first line treatment. Although first line platinum/taxane based regimens have a satisfactory response rate eventually in most cases disease recurrence is common and second-line treatments are not curative. Delaying progression or recurrence is the main goal of current ongoing clinical studies by means of establishing an effective maintenance regimen with acceptable toxicity profile. Clearly, the persistence of dormant and drug-resistant cells after front-line treatments results in the inability to cure the disease. Over the past several years, the idea of prolongation of therapy for ovarian cancer has garnered clinical attention and academic debate. As a result of a greater understanding of the molecular pathways involved in carcinogenesis and tumor growth, a large number of potential therapeutic targets have been identified and drugs to block receptors, ligands or pathways are being developed. Currently, numerous clinical trials

* Corresponding author.
E-mail address: selcukseber@gmail.com (S. Seber).

http://dx.doi.org/10.1016/j.critrevonc.2015.10.006
1040-8428/© 2015 Elsevier Ireland Ltd. All rights reserved.

Please cite this article in press as: Korkmaz, T., et al., Review of the current role of targeted therapies as maintenance therapies in first and second line treatment of epithelial ovarian cancer; In the light of completed trials. Crit Rev Oncol/Hematol (2015), http://dx.doi.org/10.1016/j.critrevonc.2015.10.006

with targeted agents have just been completed or are ongoing involving patients achieving a complete or durable response after first-line and beyond the first line chemotherapy in order to evaluate the efficacy of different therapeutic approaches in terms of progression-free survival and overall survival.
© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Approximately 22,240 new cases of ovarian cancer will be diagnosed in the United States in 2013 (Ovarian Cancer Key Statistics, 2013). Ovarian cancer remains the leading cause of mortality among women with gynecologic malignancies. More than 70% of women with ovarian cancer will present with advanced disease at diagnosis and while many patients have achieved complete clinical remission at the conclusion of primary treatment with surgical debulking and platinum- and taxane-based chemotherapy up to 80% of them will experience disease recurrence and eventually die from their disease (Martin and Schilder, 2009).

The standard first-line treatment for patients with ovarian cancer is surgery and platinum/taxane-based chemotherapy. Despite the fact that the majority of patients with advanced disease achieve complete remission after first-line treatment, the majority of these cases recur months to years following diagnosis.

The identification of cancer-initiating cells or cancer stem cells as key players in the development of recurrence has opened up a novel field of research aimed at identifying additional innovative therapeutic approaches.

Over the past several years, the idea of maintenance therapy for ovarian cancer has garnered clinical attention and academic debate.

Maintenance therapy is one strategy that has been evaluated in recent years. It has been the focus of considerable debate and many questions remain regarding optimal utilization of this strategy.

Maintenance trials with conventional cytotoxic agents so far has not revealed a clear overall survival advantage and only little benefit in terms of progression free survival but in the face of a significantly increased cumulative toxicity associated with long term chemotherapy (Piccart et al., 2003; De Placido et al., 2004; Pfisterer et al., 2006; Pecorelli et al., 2009; Markman et al., 2003). The concept of switch maintenance relies on the hypothesis that tumors at an advanced stage harbor subpopulations of cancer cells which eventually develop resistance to first line chemotherapy.

In order to inhibit proliferation of these resistant cell clones and delay disease progression, therapeutic agents with different growth inhibiting properties other than conventional chemotherapeutic drugs are increasingly being used immediately after completion of first line therapy. Novel therapies that target specific pathways involved in ovarian tumorigenesis are rapidly emerging. The focus of this review is mainly on targeted therapies, and data presented are from large randomized phase III clinical trials. Main details of the trials assessing effectiveness of targeted therapies in the first line setting (Table 1) and in the setting of recurrent disease (Table 2) are summarized in table format for quick reference.

2. First line treatment

2.1. Bevacizumab

Growth and survival of ovarian cancer cells is mainly dependent upon angiogenesis and therefore inhibition of angiogenesis pathway is important for delaying tumor progression and prolonging survival. In ovarian cancer tissue higher vascular endothelial growth factor (VEGF) expression compared to normal ovaries has been documented and patients who have tumors with high VEGF expression has been shown to have a significantly worse prognosis compared to others with lower VEGF expression (Byrne et al., 2003). In parallel with these results there are several studies who report poor survival to be associated with high serum VEGF levels in patients with advanced disease (Spannuth et al., 2008; Mesiano et al., 1998).

Bevacizumab being a recombinant monoclonal antibody directed against all isoforms of VEGF is a popular targeted agent for investigation in maintenance setting in advanced disease.

2.1.1. GOG-218

Women with newly diagnosed stage III and IV epithelial ovarian cancer who had undergone debulking surgery were randomly assigned to receive one of three treatments: (1) control arm-standard chemotherapy consisting of 3-weekly intravenous paclitaxel plus carboplatin for cycles 1–6 with 3-weekly placebo cycle 2–22; (2) bevacizumab-initiation treatment-chemotherapy with bevacizumab (15 mg/kg) 3-weekly added in cycles 2 through 6 and placebo added in cycles 7–22; (3) bevacizumab-throughout treatment-chemotherapy with bevacizumab continued for cycles 2–22. As expected bevacizumab—throughout arm in which woman continued bevacizumab for a duration of 15 months had a more prolonged PFS compared to control group (10.3 vs 14.1 months; HR = 0.72 and $p < 0.001$, respectively) (Burger et al., 2011).

In the GOG 0218 study protocol disease progression was assessed by two different methods. CA-125 protein levels and imaging techniques. When an analysis of treatment efficacy was done including only progressions determined with the results of imaging reports, women in the maintenance bevacizumab arm had a 6.2 months of improvement compared to control group which translates into a 36% reduction in the risk of cancer progression or death. An important observation is that maximum convergence between PFS survival curves was at 15 months; which is the protocol defined point where bevacizumab therapy was stopped. Prolongation of disease free survival was not reflected to an overall survival advantage between treatment groups (Burger et al., 2011). A possible confounding factor is that 31% of patients in the control arm received bevacizumab after disease progression.

2.1.1.1. ICON 7. Newly diagnosed high risk stage I or II disease along with more advanced patients who have undergone optimal or suboptimal cytoreductive surgery were included in the study group. They were randomized to six cycles of three weekly carboplatin and paclitaxel alone, or the same chemotherapy given concurrently with bevacizumab (7.5 mg/kg) for six cycles and then received bevacizumab alone for 12 additional cycles. The primary endpoint of the study was PFS. Although there was only a 1.7 months of improvement in the bevacizumab group (HR, 0.81; 95% CI, 0.70–0.94), in patients subcategorized as high risk for disease progression (stage III with >1.0 cm residual disease at the end of surgery or stage IV) median PFS improved from 10.5 to 15.9 months with addition of bevacizumab (HR, 0.68; 95% CI, 0.55–0.85; $p < 0.001$) (Perren et al., 2011). Additionally a recently published final analysis of the data revealed 4.8 months of survival advantage (34.5–39.3 months, $p = 0.03$) with bevacizumab compared to standard treatment arm in patients with high risk features however

Please cite this article in press as: Korkmaz, T., et al., Review of the current role of targeted therapies as maintenance therapies in first and second line treatment of epithelial ovarian cancer; In the light of completed trials. Crit Rev Oncol/Hematol (2015), http://dx.doi.org/10.1016/j.critrevonc.2015.10.006

Download English Version:

https://daneshyari.com/en/article/6113480

Download Persian Version:

https://daneshyari.com/article/6113480

Daneshyari.com