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Patterns of palliative care referral in platinum resistant ovarian cancer demonstrate reactive rather than proactive approach

Jennifer G. Haag [a], Alexzandra D. Adler [a], Jeanelle Sheeder [a], Lindsay W. Brubaker [b,*], Carolyn Lefkowits [b]

[a] Department of Obstetrics and Gynecology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

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ABSTRACT

Objective: To evaluate patterns of palliative care (PC) integration in patients with platinum resistant ovarian cancer.

Methods: Single institution retrospective study of patients with ovarian, tubal, or peritoneal high-grade carcinoma treated 2011–2020. Platinum resistance was identified by chemotherapy regimen or provider definition. Data was extracted evaluating treatment regimens, time to progression, PC and hospice referrals, and survival. Descriptive statistics and survival analyses were performed.

Results: We identified 258 patients with platinum resistant ovarian cancer. Median survival from diagnosis of platinum resistance was 15 months (range 0–161). Most (71 %) patients were referred to PC, with 43 % of referrals within 3 months of death. Fourteen percent of patients were referred directly to hospice without PC involvement. Of 46 patients living with platinum resistant disease, 93 % meet criteria for early PC referral, but less than half have seen PC. Median time from platinum resistance to PC referral was 9 months (range 0–157) and from PC referral to death was 3 months (range 0–110). Median time from platinum resistance to hospice referral was 7 months (range 1–57) and from hospice referral to death was < 1 month (range 0–12).

Conclusion: While rates of PC referral in our cohort are high compared with other single institution cohorts, timing of PC referral suggests referral patterns that are reactive to clinical decline rather than proactive as per national recommendations. A significant percentage of patients are directly referred to hospice for end-of-life care, reflecting missed opportunity for concurrent PC and oncology care earlier in the disease course. Diagnosis of platinum resistance should serve as a stimulus for PC involvement.

1. Introduction

Palliative care is defined as "specialized medical care for people living with a serious illness." It focuses on symptom and stress relief for the patient and family, with the ultimate goal of improving quality of life (CAPC, 2020). The provision of palliative care includes symptom management, shared decision-making, spiritual and psychosocial assessment, and advanced care planning. Primary palliative care is provided by the oncology team, whereas specialty palliative care is delivered by a team of palliative care specialists for more complex symptom management, communication, and advanced care planning. Palliative care is appropriate at any point in the course of serious illness, including from time of diagnosis and including when the goal of therapy is cure, distinguishing it from end-of-life care (CAPC, 2020).

At the time of diagnosis of ovarian cancer, 75 % of patients have advanced disease and most will experience a recurrence. Platinum resistance is defined as disease that progresses within six months of treatment with platinum-based chemotherapy (Davis et al., 2014). This includes disease that progresses while actively undergoing platinum-based chemotherapy, specifically referred to as platinum refractory disease (Davis et al., 2014). Platinum resistant ovarian cancer is associated with poor outcomes, including chemotherapy response rates < 15 % (Davis et al., 2014; Pujade-Lauraine et al., 2014), and median survival of 12–16 months (Davis et al., 2014; Pujade-Lauraine et al., 2014; Pujade-Lauraine et al., 2021).

The American Society of Clinical Oncology (ASCO) recommends that patients with advanced cancer should receive dedicated palliative care support early in the disease course, concurrent with active treatment

* Corresponding author at: University of Colorado Anschutz Medical Campus, School of Medicine, 12631 E 17th Ave, B198-6 Aurora, CO 80045.
E-mail address: Lindsay.Brubaker@cuanschutz.edu (L.W. Brubaker).

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(Ferrell et al., 2017). "Advanced cancer" is defined as distant metastases, late-stage disease, cancer that is life-limiting and/or with a prognosis of 6–24 months. "Early palliative care involvement" is defined as within eight weeks of diagnosis of advanced cancer (Ferrell et al., 2017). With a median survival of 12–16 months, all patients with platinum resistant ovarian cancer would be appropriate for referral to palliative care within eight weeks of that diagnosis.

Multiple studies have demonstrated benefits of palliative care, both in symptom control and satisfaction with care (Campion et al., 2015). Literature specific to gynecologic oncology reveals patterns of underutilization of palliative care, despite advanced ovarian cancer diagnoses (Nitecki et al., 2018). We sought to evaluate patterns of specialty palliative care integration in patients with platinum resistant ovarian cancer as a group appropriate for routine early palliative care referral per ASCO guidelines. In this study, reference to palliative care signifies specialty palliative care.

2. Methods

This was a single institution retrospective study. We identified a cohort of patients with ovarian, fallopian tube, and primary peritoneal cancer who received at least one course of chemotherapy or targeted therapy within our hospital system between 2011 and 2020. The project was exempt by the Colorado Multiple Institutional Review Board. The data request was submitted via TriNetX using ICD-9 and ICD-10 codes and a confirmed list of chemotherapy and biologic agents (Supplemental Tables 1 and 2). The data used in this study was collected on May 23, 2020 from the TriNetX Network, which provided access to electronic medical records. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and is certified to the ISO 27001:2013 standard and maintains an Information Security Management System to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX Platform, only contains de-identified data as per the de-identification standard defined in the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources. The Colorado Department of Public Health and the Environment death registry was cross-referenced to confirm vital statistics (Supported by Health Data Compass Data Warehouse Project, HealthDataCompass.org). In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

With a list of medical record numbers of all identified patients, an initial chart review was performed to confirm diagnosis. Platinum resistant patients were identified based on chemotherapy regimen or provider definition, then confirmed with clinical data. Patients were considered platinum refractory if they progressed on first-line platinum-based therapy. Once a cohort of platinum resistant patients was confirmed, a secondary, in-depth chart review was performed. Patients were excluded if data concerning progression and/or therapy was missing, if dates of progression and/or therapy could not be related reliably, or if the patient's primary oncologist was outside our institution. Patients who did not receive a standard platinum-taxane-based regimen as first-line therapy were also excluded. Data was extracted evaluating demographics, disease characteristics, treatment regimens, time to progression, and overall survival (OS). Palliative care and hospice referrals were recorded, as well as indications for referral, including symptom control and goals of care/end of life discussions. Descriptive statistics were calculated, and survival analyses were performed. OS was defined as time from diagnosis of platinum resistance to death.

For this study, a palliative care consult was defined as referral to and subsequent visit with the palliative care service. Consults were classified as "inpatient" if the first contact with palliative care happened during inpatient admission and "outpatient" if the first contact happened at an outpatient clinic visit. Direct hospice referral was defined as a direct referral to hospice with no prior involvement of palliative care. Patients referred to palliative care may have eventually been referred to hospice but were not categorized as such if their initial encounter was with palliative care. Early palliative care referral was defined as referral and subsequent visit with the palliative care service prior to or within eight weeks of diagnosis of platinum resistance, congruent with the ASCO definition (Ferrell et al., 2017). Patients with OS less than eight weeks from diagnosis of platinum resistance were excluded.

3. Results

Initial data request identified approximately 1500 patients with ovarian, fallopian tube, or peritoneal carcinoma treated at our institution between 2011 and 2020. On chart review, 277 patients had platinum resistant disease and 258 patients met our inclusion criteria. Demographics and early disease characteristics are listed in Table 1. Median age at diagnosis of ovarian cancer was 60 (range 16–87). Most patients had stage III/IV disease (96 %) and high-grade serous histology (84 %). 16 % were platinum refractory. Median time from diagnosis of ovarian cancer to platinum resistance was 19 months (range 2–173 months) and median survival from diagnosis of platinum resistance to death was 15 months (range 0–161 months). Excluding the 46 patients still living, there was no difference in OS between patients seen by palliative care (OS 13.3 months), patients referred directly to hospice (OS 9.4 months), and patients with no referral (OS 14.4 months) ($p = 0.11$).

Of 258 patients in the cohort, 184 patients (71 %) were referred to palliative care. At the time of chart review, 212 patients (82 %) were deceased. Of these, 163 patients (77 %) were seen by palliative care, 37 patients (17 %) were referred directly to hospice, and 12 patients (6 %) had no referral. Fig. 1 shows palliative care and hospice referrals stratified by survival time from diagnosis of platinum resistance (<6 months, 6–12 months, >12 months). Notably, even in patients who lived > 12 months from diagnosis of platinum resistance, one third of referrals to palliative care did not happen until within three months of death. Of 46 patients still living at the time of chart review, none have been referred to hospice, 21 patients (46 %) have seen palliative care, and 25 patients (54 %) have no referral.

We investigated timing of palliative care or direct hospice referral. In 163 deceased patients who saw palliative care, median time from diagnosis of platinum resistance to palliative care referral was nine months (range 0–157 months) and from palliative care referral to death was three months (range 0–110 months). In 37 deceased patients referred directly to hospice, median time from diagnosis of platinum resistance to hospice referral was seven months (range 1–57 months) and from hospice referral to death was less than one month (range 0–12 months).

To evaluate early palliative care referrals, two patients were excluded as they had less than two months of follow-up. Of 256 remaining patients, 48 (19 %) had an early palliative care referral prior to or within eight weeks of diagnosis of platinum resistance. Survival from platinum resistance to death was significantly shorter in patients with an early palliative care referral, with median OS 5.7 months (range 0.5–27.6) in those with an early palliative care referral compared to 16.6 months (range 1.8–161.2) in those without early palliative care referral ($p < 0.001$). As described in Table 1, there were no differences in

Table 1
Demographics and disease characteristics (n = 258)[+], n (%) or median (range).

Variable	Early PC referral n = 48; 18.6 % Median (range) or n (%)	No early PC referral n = 208; 81.4 % Median (range) or n (%)	Total n = 258Median (range) or n (%)	p-value
Age (years)	62 (16–87)	59.5 (23–84)	60 (16–87)	0.13
Time (mos) from diagnosis to platinum resistance	21 (2–173)	19 (3–151)	19 (2–173)	0.99
ECOG PS				**<0.001**
0	14 (29)	77 (37)	91 (35)	
1	20 (42)	37 (18)	58 (22)	
2	4 (8)	3 (1)	7 (3)	
3	3 (6)	0 (0)	3 (1)	
Unknown	7 (15)	91 (44)	99 (38)	
Histology				0.70
Serous	41 (85)	174 (84)	217 (84)	
Carcinosarcoma	4 (8)	12 (6)	16 (6)	
Endometrioid	2 (4)	6 (3)	8 (3)	
Clear cell	0 (0)	7 (3)	7 (3)	
Mixed	0 (0)	3 (1)	3 (1)	
Other	1 (2)	6 (3)	7 (3)	
Stage at diagnosis				0.20
I/II	0 (0)	10 (5)	10 (4)	
III	29 (60)	133 (64)	164 (64)	
IV	19 (40)	65 (31)	84 (33)	
Received neoadjuvant chemotherapy	25 (52)	72 (35)	96 (37)	0.09
Optimal debulking	35 (73)	155 (75)	191 (74)	0.82
Platinum sensitivity				0.76
Resistant	41 (85)	174 (84)	217 (84)	
Refractory	7 (15)	34 (16)	41 (16)	
Length of first platinum-free interval				0.85
0 months	7 (15)	34 (16)	41 (16)	
1-6 months	13 (27)	56 (27)	70 (27)	
6-12 months	16 (33)	57 (27)	74 (29)	
>12 months	12 (25)	61 (29)	73 (28)	
Lines of platinum-resistant chemotherapy				**<0.001**
0	10 (21)	5 (2)	15 (6)	
1	26 (54)	37 (18)	64 (25)	
2	9 (19)	50 (24)	60 (23)	
3+	3 (6)	116 (56)	119 (46)	
Treated within				
1 month of death	8 (17)	33 (16)	41 (16)	0.59
3 months of death	25 (52)	114 (55)	139 (54)	0.53
6 months of death	31 (65)	156 (75)	187 (72)	0.70
PC involvement				**<0.001**
Palliative care referral	48 (100)	136 (65)	184 (71)	
Direct hospice referral	0 (0)	35 (17)	37 (14)	
No referral	0 (0)	37 (18)	37 (14)	
Indication for PC referral[*]				0.91
Symptom management	4 (8)	13 (10)	17 (9)	
Goals of care/end of life	14 (29)	34 (25)	48 (26)	
Both	28 (58)	85 (63)	113 (61)	
Not documented	2 (4)	4 (3)	6 (3)	
Clinical events after diagnosis of platinum resistance				
Emergency Department visit	17 (35)	111 (53)	129 (50)	**0.03**
Hospital admission	37 (77)	170 (82)	208 (81)	0.46
Malignant bowel obstruction	16 (33)	81 (39)	97 (38)	0.47
	9 (56)	41 (51)	50 (52)	0.68
Gastric tube placed (n = 97)				
TPN started (n = 97)	8 (50)	30 (37)	38 (39)	0.33
Surgery	8 (17)	74 (36)	82 (32)	**0.01**

Abbreviations: PC palliative care; ECOG Eastern Cooperative Oncology Group; PS performance status; TPN total parenteral nutrition.
[*] Of 184 patients who received palliative care referrals.
[+] Excluding 2 patients with no PC referral and < 2 months of follow-up time.

age, histology, stage, receiving neoadjuvant chemotherapy, optimal debulking, number of lines of platinum sensitive chemotherapy, or length of first platinum-free interval between those with an early palliative care referral and those without. There were no differences in treatment within one, three, and six months of death, hospital admissions after diagnosis of platinum resistance, or malignant bowel obstructions between those with an early palliative care referral and those without. Patients with an early palliative care referral were more likely to receive only zero or one lines of platinum resistant chemotherapy and were more likely to have a worse performance status (ECOG > 0). Patients with an early palliative care referral were also less likely to have emergency department visits (35 % vs 53 %, p = 0.03) or surgery (17 % vs 36 %, p = 0.01) after diagnosis of platinum resistance.

Of all 258 patients, 27 (10 %) saw palliative care before diagnosis of platinum resistance (range 0–108 months prior to diagnosis). These patients had significantly shorter OS from diagnosis of platinum resistance compared to those referred to palliative care after platinum resistance (median survival 8.2 vs 15.5 months, p = 0.03). Patients referred to palliative care prior to platinum resistance were more likely to have received neoadjuvant chemotherapy compared to those referred after platinum resistance (p < 0.0005). There were no differences in histology, stage, optimal debulking, CA-125 levels, presence of liver/lung metastases, platinum sensitivity, ECOG performance status, or receiving treatment within one, three, or six months of death.

Thirty-seven patients (14 %) were referred directly to hospice without prior involvement of palliative care. Compared to patients referred to palliative care, patients referred directly to hospice were more likely to be platinum refractory (32 % vs 13 %, p = 0.002). Median survival from diagnosis of platinum resistance was 9.4 months for patients directly referred to hospice versus 14 months for patients referred to palliative care.

4. Discussion

4.1. Summary of main results

In this single institution retrospective study of palliative care utilization in patients with platinum resistant ovarian cancer, we found an overall referral rate of over 70 %. Despite high rates of referral, presumably reflecting a practice culture supportive of palliative care involvement, we found that timing of referral to palliative care remains late. With a median survival of 12–16 months, patients with platinum resistant ovarian cancer fall within the group recommended by ASCO to have palliative care involvement within eight weeks of diagnosis and yet, in our cohort, median time from platinum resistance to palliative care referral was nine months. Additionally, nearly half of referrals occurred in the last three months of life. Only 16 % of referrals occurred within eight weeks of diagnosis of platinum resistance.

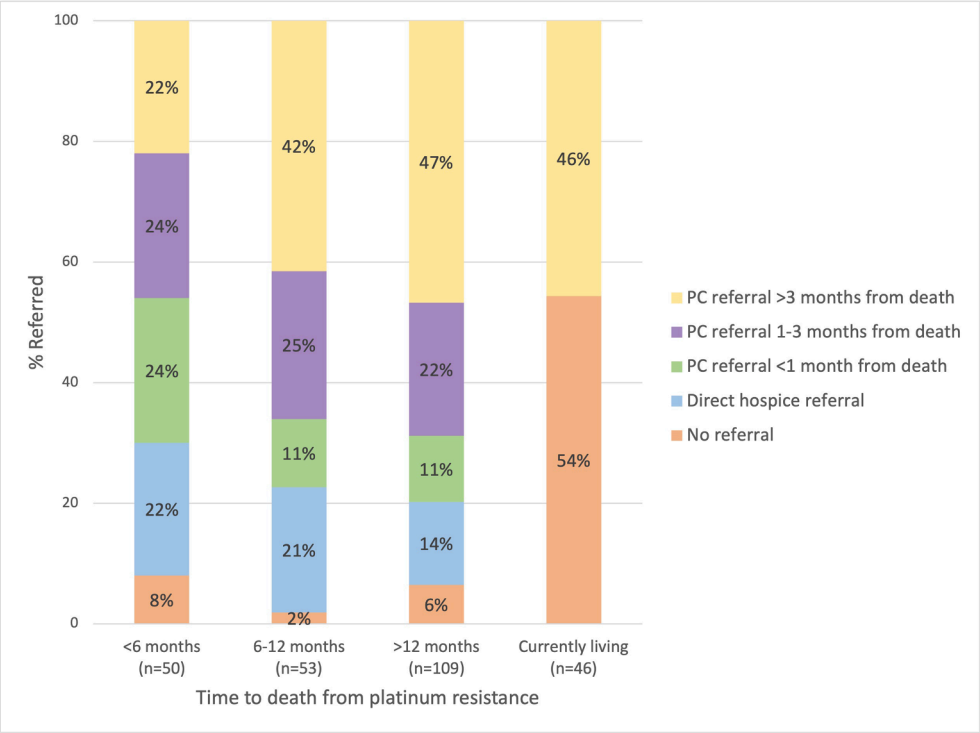

Fig. 1. Palliative Care and Direct Hospice Referrals by Survival Time from Platinum Resistance.

In our cohort, 14 % of patients were directly referred to hospice without any prior palliative care involvement. Compared to patients referred to palliative care, patients referred directly to hospice were more likely to be platinum refractory. In addition, 10 % of patients saw palliative care before diagnosis of platinum resistance and these patients demonstrated shorter OS and were more likely to have received neoadjuvant chemotherapy. These subgroups represent the worst and most aggressive disease processes.

4.2. Results in the context of published literature

The high rates of palliative care referral in our study compare favorably with other single institution cohorts, which describe referral rates < 50 %. (Nitecki et al., 2018; Nevadunsky et al., 2014) Nitecki et al found that only 28 % of their cohort was seen by palliative care and median time from diagnosis to palliative care referral was 1.5 years, a stark comparison to the recommendation of eight weeks from ASCO (Ferrell et al., 2017; Nitecki et al., 2018). Nevadunsky et al conducted a review of 100 patients who died from a primary gynecologic malignancy and found that only 49 % of their cohort received an inpatient palliative care consult and that median time from consult to death was 16 days. Moreover, only 18 % had a "timely" consultation, defined as a consult greater than 30 days from death (Nevadunsky et al., 2014).

4.3. Strengths and weaknesses

To our knowledge, this is the first study to evaluate palliative care referral rates and timing in a cohort of platinum resistant ovarian cancer patients, and the first to evaluate a cohort completely comprised of patients meeting ASCO recommendations for routine early palliative care referral. Additional strengths include a large cohort of patients treated in an academic setting with access to specialized palliative care services. Furthermore, evaluating a practice with high rates of palliative care integration relative to historical controls allowed us to disentangle analysis of underutilization of palliative care overall from suboptimal referral timing. The limitations of our study include retrospective design with information limited to documentation in the medical record. Our study does not capture palliative care provided by the primary oncologist or assess effectiveness of palliative care or hospice services once initiated. We also acknowledge the limited generalizability to patient populations without access to dedicated palliative care services.

4.4. Implications for practice and future research

Taken together, our results show a pattern of *reactive* referral to palliative care in response to adverse clinical indicators, rather than a proactive approach as recommended by national guidelines. In our cohort, patients with early referral to palliative care prior to or within eight weeks of diagnosis of platinum resistance demonstrated significantly shorter survival times, likely because these patients were sicker at baseline. To identify disease characteristics that might be associated with worse disease and therefore prompt earlier referral, we compared patients who received early palliative care referral to those who received later palliative care referral and found no difference in demographics or disease characteristics. We hypothesize that providers who place early referrals may be sensing a worse disease process and subsequently referring to palliative care sooner. Median time from platinum resistance to palliative care referral also suggests a reactive, rather than proactive, pattern of palliative care utilization. Even in the subgroup of patients living > 12 months from diagnosis of platinum resistance, 42 % were referred within the last three months of life, representing a missed opportunity for early palliative care. Furthermore, the patients in our cohort referred directly to hospice without prior palliative care involvement represent the ultimate reactionary referral. By waiting for disease to worsen, we miss an opportunity for timely palliative care involvement.

The benefits of palliative care referral at the time of diagnosis of advanced malignancies are supported by multiple studies and integration of palliative care has been defined as a quality measure (Temel et al., 2010; Zimmermann et al., 2014). For example, in 2006, ASCO developed the Quality Oncology Practice Initiative (QOPI) program, "an oncologist-led, practice-based, quality-improvement program with a

goal of promoting excellence in cancer care through a practice's voluntary self-examination and process improvement system" (Campion et al., 2011). This initiative included measures such as hospice or palliative care involvement and timing prior to death. Furthermore, given the widely recognized value of palliative care, the National Comprehensive Cancer Network Quality and Outcomes Committee endorsed that palliative care consult be offered to patients with metastatic non-small cell lung cancer within eight weeks of diagnosis (D'Amico et al., 2020). Given the reactionary pattern in our cohort, the solution for timely integration of palliative care may be a protocolized approach, as the use of checklists and protocols has been shown to improve patient outcomes in other circumstances, such as reducing catheter-related blood stream infections in intensive care units and reducing morbidity and mortality with surgical safety checklists (American College of Obstetricians and Gynecologists, 2019; Pronovost et al., 2006; Haynes et al., 2009). We therefore advocate for a proactive approach with routine referral to palliative care at the time of diagnosis of platinum resistant ovarian cancer.

5. Conclusions

Diagnosis of platinum resistance is a pivotal point in ovarian cancer treatment as subsequent survival is limited. Though palliative care referral rates in our cohort were relatively high, we found substantial room for improvement in timing. We identified palliative care referral patterns that are reactive to clinical decline, rather than proactive based on disease status, representing a significant missed opportunity. Proactive, routine referral of ovarian cancer patients to palliative care at the time of diagnosis of platinum resistance would help our patients and their families derive the full range of clinical benefits of palliative care integration.

CRediT authorship contribution statement

Jennifer G. Haag: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft. **Alexzandra D. Adler:** Data curation, Writing – review & editing. **Jeanelle Sheeder:** Formal analysis, Writing – review & editing. **Lindsay W. Brubaker:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Carolyn Lefkowits:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2022.101053.

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