

One Year of Procarbazine Lomustine and Vincristine is Poorly Tolerated in Low Grade Glioma: A Real World Experience in a National Neuro-Oncology Centre

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Abstract

Background

Following optimal local therapy, adjuvant Procarbazine, Lomustine and Vincristine (PCV) improves overall survival (OS) in low-grade glioma (LGG). However, one year of PCV is associated with significant toxicities. In the pivotal RTOG 9802 randomised control trial, approximately half of the patients discontinued treatment after six months. As patients on clinical trials may be fitter, we aimed to further explore the tolerability of PCV chemotherapy in routine clinical practice.

Methods

We conducted a retrospective study between 2014 and 2018 at a National Neuro-Oncology centre. Patients who had received PCV during this time period were included. The primary objective was to assess tolerability of treatment. Secondary objectives included evaluation of treatment delays, dose modifications and toxicities.

Results

Overall, 41 patients were included, 24 (58%) were male and 21 (51%) aged ≥ 40 years. Overall, 38 (93%) underwent surgical resection and all patients received adjuvant radiotherapy prior to chemotherapy. The median number of cycles completed was 3,2,4 for procarbazine, lomustine and vincristine respectively. Only 4 (10%) completed all six cycles of PCV without dose modifications. There was a universal decline in dose intensity as cycles of chemotherapy progressed. Dose intensity for cycle 1 versus cycle 6 respectively: procarbazine (98% versus 46%), lomustine (94% versus 48%) and vincristine (93% versus 50%). Haematological toxicities were common. Six (14%) patients experienced Grade III-IV thrombocytopenia and 13 (31%) experienced Grade III-IV neutropenia.

Conclusion

Toxicities are frequently observed with the PCV regimen in clinical practice. It might be preferable to adjust doses from the start of chemotherapy to improve tolerability or consider alternative chemotherapy, particularly in older patients with LGG.

Background

Low grade gliomas (LGGs) account for 17 to 22% of primary brain tumours, diffusely infiltrate the central nervous system and cannot be cured by surgery alone (1). Until recently, the World Health Organisation (WHO) classified LGGs based on histopathological features, and divided them into astrocytoma, oligodendroglioma and oligoastrocytoma, but this was updated in 2019 to include molecular tumour features (2). Patients with LGG typically present at a younger age, with the peak incidence between 35 and 44 years of age and have longer overall survival (OS) than patients with high grade (III-IV) gliomas (3,

4). Given the incurable but indolent nature of these tumours, they pose unique challenges for physicians in terms of treatment decisions and the management of tumour-related and treatment-related sequelae.

In fact, the optimal management of patients with LGG has been one of the most controversial areas in Neuro-Oncology. For some patients with newly diagnosed tumours, watchful waiting has been an accepted strategy (5). Conversely, a high-risk group has been defined, including factors such as age > 40, astrocytoma histology, tumour diameter >6 cm, tumour crossing the midline and the presence of neurological deficit prior to surgery (6). Following the decision to operate, these prognostic variables have also been used historically to select patients for more intensive therapy such as radiotherapy and chemotherapy. Against this background the Radiation Therapy Oncology Group (RTOG) conducted the prospective randomised 9802 trial, which was initiated in 1998 and enrolled patient with high-risk LGG, defined as age >40 years or with subtotal resection (7). Patients were randomised to radiation alone (40 Gy in 30 fractions over six weeks) or radiation plus chemotherapy consisting of CCNU (lomustine), procarbazine and vincristine every 8 weeks for 6 cycles (one year). This study demonstrated a significant improvement with chemotherapy with a median OS of 13.3 years for patients treated with PCV compared to 7.8 years for the radiation alone group. (4). This magnitude of treatment benefit was considerable and established a new standard of care. Despite a planned 6 cycles of treatment in this trial, the median number of cycles completed for procarbazine, lomustine and vincristine was three, four and four respectively (4). The toxicities recorded were significant. The most clinically relevant of these being myelosuppression, most pronounced for neutrophils and platelets. Specifically, the incidence of grade III and IV haematological toxicity with PCV was 51% and 15% respectively (4). It is unknown whether the broader use of this combination in the real world would result in greater toxicity. Therefore, in our study, we aimed to gain a greater understanding of the tolerability of PCV in routine clinical practice.

Methods

This was a retrospective study conducted in a national neuro-oncology centre in Ireland. Approval, including a waiver of informed consent was obtained per institutional guidelines. Patients with LGG who were treated with PCV chemotherapy between November 2014 and November 2018 were identified from a pharmacy database. Patient demographics and treatment data were collected from paper and electronic clinical records. As previously reported, the PCV regimen consisted of procarbazine (60 mg/m² formulated in 50mg capsules) orally day 8-21, lomustine (110 mg/m² in 40mg capsules) orally on day 1, and vincristine (1.4 mg/m², capped at 2 mg) intravenously on day 8 and day 29 of each 56 day cycle (4). Patients underwent dose reductions and delays as per standard of care.

The primary objective of the study was tolerability of treatment, as assessed by the number of patients completing all planned treatment without any dose omissions. Secondary objectives included treatment delays, dose modifications and the evaluation of toxicities graded as per CTCAE version 4 (8). Data were collected for the overall population and using the age 40 as a cut-off as previously reported by Buckner et al (4). For the primary objective, the number of patients who had 1 or more drugs omitted was expressed as a percentage of the total number of patients for each cycle of PCV. Dose intensity was calculated for

each chemotherapeutic agent by cycle as a percentage of the total calculated dose that was actually administered. Dose omissions, dose delays and reductions were recorded for each chemotherapy agent for each cycle of PCV. Data were collected using Microsoft Excel and statistical analysis was performed using Excel and SPSS® version 26 software.

Results

Patient Characteristics:

A total of 45 patients with LGG who received PCV chemotherapy were identified. Four patients were excluded: one had no prior radiotherapy, one had chemotherapy in another institution and two had additional radiotherapy in the preceding five years. Therefore, 41 patients were included in the study. Most (58%) patients were male (table 1). There was a similar number of patients that were aged < 40 (n=20) and ≥ 40 years (n=21). The predominant histopathological subtype was oligodendroglioma (68%). The vast majority (93%) of patients underwent surgical resection (rather than biopsy alone) prior to chemotherapy and all patients underwent adjuvant radiotherapy prior to initiation of chemotherapy. The majority of tumours had some favourable biology, 93% had IDH mutation and 61% 1p19q co-deletion.

Treatment Delivered:

Twenty (48%) patients completed all six cycles of treatment. Only four (10%) patients completed all six cycles without any dose modifications. The median number of cycles completed of procarbazine, lomustine and vincristine was three, two and four respectively. The number of dose omissions increased as patients progressed from cycle 1 to cycle 6 (Figure 1). In cycle 1, at least one dose was omitted in 17% of patients, but this rose to 29% and 34% in cycles 4 and 6 respectively. In addition, 15% and 27% patients had discontinued all treatment doses by cycle 4 and 6 respectively (figure 1).

The dose intensity for each chemotherapy agent decreased from cycle 1 to cycle 6 (figure 2A). The dose intensity for procarbazine dropped from 98% in cycle 1 to 68% in cycle 4 and 46% in cycle 6. Similarly, the dose intensity of lomustine dropped from 94% in cycle 1 to 74% in cycle 4 and 48% in cycle 6. For patients under the age of 40, the dose intensity for procarbazine, lomustine and vincristine was 98%, 92% and 90% respectively in cycle 1. By cycle 6, the dose intensity for these three agents was 62%, 56% and 67% respectively (Figure 2B). This decline was even more evident in patients aged 40 years and above, for whom cycle 6 dose intensity was only 39%, 41% and 50% for the three agents respectively (Figure 2C).

There was a consistent trend towards more dose reductions and omissions with increased cycles (figure 3). The percentage of patients who received the full dose of each drug for Cycle 1 as compared to Cycle 6 was as follows; procarbazine 98% versus 27%, lomustine 98% versus 17%, and vincristine 71% versus 34%. There were no dose reductions in Cycle 1 however by Cycle 6, 34% had a dose reduction of procarbazine, 49% had a dose reduction of lomustine and 5% had a dose reduction of vincristine. Only 2% of patients did not receive procarbazine or lomustine for Cycle 1, but this increased to 39% and 34%

respectively for cycle 6. Overall, 60% of patients did not receive Vincristine for Cycle 6. Patients forty and above received more dose reductions and dose omissions compared to those under 40 years of age for each of the three agents (Figure 3B/3C).

Toxic Effects:

Overall, 21 (51%) patients had treatment discontinued prematurely. The most common reason for this was haematological toxicity, which occurred in 14 (66%) patients. In addition, 5 (24%) patients discontinued treatment due to non-haematological toxicity and two (9%) discontinued due to disease progression. In terms of haematological toxicities, 5 (12%) and 1 (2%) patients had Grade III and IV thrombocytopenia respectively. 10 (24%) and 3 (7%) patients had grade III and IV neutropaenia respectively. Table 2 summarises non-haematological toxicities recorded in our study most notably Grade I/II fatigue which occurred in 59% of cases.

Discussion

This retrospective study conducted over a five-year period in a tertiary neuro-oncology centre provides important 'real-world' data on the tolerability of PCV chemotherapy in routine clinical practice. Our study confirms that frequent toxicities occur with the PCV regimen with implications for treatment tolerability. Less than half of the patients completed all six cycles and 10% of patients completed all six cycles without dose modifications, primarily because of haematological toxicity. Additionally, the number of dose reductions and dose delays increased as treatment progressed highlighting the associated toxicity and poor tolerability of this chemotherapy regimen. Perhaps unsurprisingly, PCV appeared to be less well tolerated in patients aged forty and above, with a higher rate of dose reductions and dose delays seen in this cohort as compared to their younger counterparts, as well as a reduction in dose intensity. This likely reflects the better performance status of patients under the age of forty and age is itself an independent risk factor for poor prognosis in LGG (6).

Patients with LGG have a longer survival than those with high grade tumours with a median survival of 13 years with intensive treatments (4). Therefore, treatment toxicities are a critical consideration when determining the most appropriate therapeutic strategy. Given the relative longevity associated with these tumours, it is essential that treatment toxicities are carefully considered when making treatment decisions and managing tumour-related and treatment-related sequelae. In terms of non-haematological toxicities, we found that there was a higher incidence of Grade III nausea recorded in our study compared to the RTOG 9802 (5% versus 2%) (4). However, Grade III fatigue was reported in 8% of cases in the RTOG 9802 trial compared 2% of cases in our study (4). The RTOG 9802 had higher rates of Grade I/II non-haematological toxicities, which may reflect the fact that often less severe adverse events may be under-reported or not rigorously recorded in routine clinical practice. Although the incidence of peripheral neuropathy was not specifically recorded in the RTOG 9802 trial it should be noted that a high percentage of patients in our study experienced this (32%).

The considerable number of dose reductions and dose omissions, coupled with the fact that just over half of patients had treatment discontinued prematurely, supports the argument for adjusting doses from the outset of chemotherapy to improve tolerability. The impact of this on patient outcomes is unclear. Whether or not such an alternative treatment strategy may be more suitable in patients with LGG remains to be seen. Temozolomide is easier to administer with better patient tolerance and it has improved survival in high grade glioma. It therefore has replaced PCV in more recent trials because of its improved toxicity profile and the expectation that both alkylating-based therapies would prove similarly efficacious. However, a direct comparison of the two regimens in this setting has yet to be completed. The longest ongoing clinical trial in oligodendrogliomas is the Phase III CODEL trial which has reopened as a two-arm comparison of either RT followed by PCV or RT with concurrent and adjuvant temozolomide and the results of this are eagerly awaited (9). As more treatment options for low-grade gliomas become available, quality-of-life measures and outcomes will play key roles in management recommendations. Future therapies will be focused not only on improving survival but also on quality of life. As we move towards molecular profiling of tumours, more targeted and personalised treatments will hopefully be available and our treatment strategies will be altered accordingly.

Some of the limitations of this study should be noted. First, the sample size is relatively small, although this series still represents a large series given the rarity of the tumour. In addition to this, this is a retrospective study, which was unable to assess the impact of treatment on cognition and quality of life. Grade I and Grade II non-haematological toxicities may have been under-reported as we relied on retrospective clinical records for this information, rather than multiple additional data-points, which might have been collected in a clinical trial. Dose reductions may also not have been as rigorously or as consistently applied as in the RTOG 9802 trial. As such, data derived from this analysis should be interpreted cautiously.

In summary, our study confirms the earlier findings of the RTOG 9802 trial that the PCV regimen is poorly tolerated in routine clinical practice and demonstrates that toxicities are frequently observed. Furthermore, there was a notable difference in the treatment tolerability of PCV in those aged greater than forty. It might be preferable to adjust doses from the start of chemotherapy to improve tolerability or consider alternative chemotherapy, particularly in older patients with LGG.

Abbreviations

PCV: procarbazine, lomustine, vincristine; OS: overall survival; RTOG: Radiation Therapy Oncology Group; LGG: low grade glioma; WHO: World Health Organisation; CTCAE: Common Terminology Criteria for Adverse Events; RT: radiation therapy.

Declarations

Ethics approval and consent to participate: The study was approved by the Audit office at Beaumont Hospital, Dublin, Ireland. As a retrospective study, no informed consent was obtained. This is in

compliance with National Guidelines as indicated by the Health Research Consent Declaration Committee on Retrospective Chart Review (Updated August 30th, 2019) (10).

Consent to publish: Not applicable.

Availability of data and materials: The data that support the findings of this study are available from the corresponding author on reasonable request.

Competing Interests:Travel support: Patrick G. Morris, Roche, Novartis, Amgen; **Honoraria:** Patrick G. Morris, Astellas, Novartis, Pfizer, Teva, Nordic 2013, Bristol Meyers Squibb, Astra Zeneca, Genomic health, Roche; **Consultancy or Advisory role:** Patrick G. Morris, Novartis, **Speaker Role:** Patrick G. Morris, Teva; **Research funding:** Patrick G. Morris, Teva, Genomic Health.

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Authors' Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by RJK, RA, and MAH. The first draft was written by RJK and MAH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1: Patient Baseline Characteristics

| | Age <40 | | Age ≥ 40 | | Total | |
|-----------------------------------|---------|----|----------|----|--------|-----|
| | N = 20 | | N = 21 | | N = 41 | |
| | | | | | (%) | |
| | N | % | N | % | N | % |
| Gender: | | | | | | |
| Male | 13 | 65 | 11 | 52 | 24 | 58 |
| Female | 7 | 35 | 10 | 48 | 17 | 41 |
| Recurrent/First Diagnosis: | | | | | | |
| First Diagnosis | 12 | 60 | 10 | 48 | 22 | 54 |
| Recurrent | 8 | 40 | 11 | 52 | 19 | 46 |
| Surgery: | | | | | | |
| Resection | 18 | 90 | 20 | 95 | 38 | 93 |
| Biopsy | 2 | 10 | 1 | 5 | 3 | 7 |
| Histology: | | | | | | |
| Oligodendroglioma | 9 | 45 | 19 | 90 | 28 | 68 |
| Astrocytoma | 11 | 55 | 2 | 9 | 13 | 32 |
| IDH: | | | | | | |
| Mutated | 19 | 95 | 19 | 90 | 38 | 93 |
| Wildtype | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown | 1 | 5 | 2 | 9 | 3 | 7 |
| 1p19q Co-deletion: | | | | | | |
| Present | 7 | 35 | 18 | 86 | 25 | 61 |
| Absent | 10 | 50 | 2 | 9 | 12 | 29 |
| Unknown | 3 | 15 | 1 | 5 | 4 | 10 |
| MGMT | | | | | | |
| Methylated | 8 | 40 | 6 | 29 | 14 | 34 |
| Unmethylated | 1 | 5 | 0 | 0 | 1 | 2.4 |
| Unknown | 11 | 55 | 15 | 71 | 26 | 63 |

| ATRX: | | | | | | |
|---|----|----|----|----|----|----|
| Mutated | 5 | 25 | 1 | 5 | 6 | 15 |
| Wildtype | 3 | 15 | 8 | 38 | 11 | 27 |
| Unknown | 12 | 60 | 12 | 57 | 24 | 58 |
| Each value is represented by number of patients (N) and percentage of patients (%) | | | | | | |

Table 2: Most Common Toxicities:

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--|----------------|----------------|----------------|----------------|
| Haematological | | | | |
| Thrombocytopaenia | 36 | 18 | 5 | 1 |
| Neutropaenia | 27 | 21 | 10 | 3 |
| Non-Haematological: | | | | |
| Fatigue | 17 | 7 | 1 | - |
| Gastrointestinal symptoms (anorexia, nausea) | 15 | 7 | 1 | - |
| Peripheral Neuropathy | 11 | - | 2 | - |
| Each value is represented by the number of patients that experience each toxicity (N) | | | | |

Figures

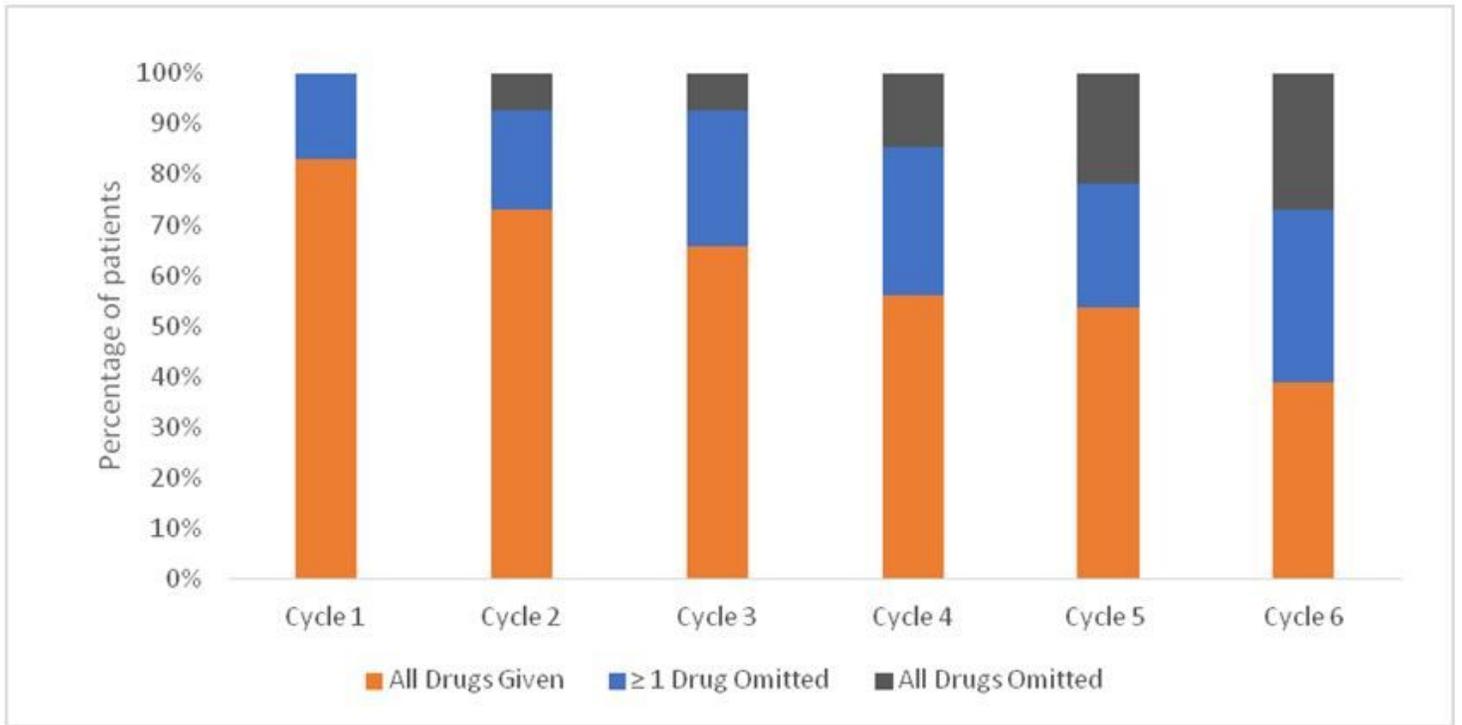


Figure 1

Treatment administered by PCV cycle. Data expressed as a percentage of patients who had all drugs given (orange), ≥ 1 drug omitted (blue), all drugs omitted (grey).

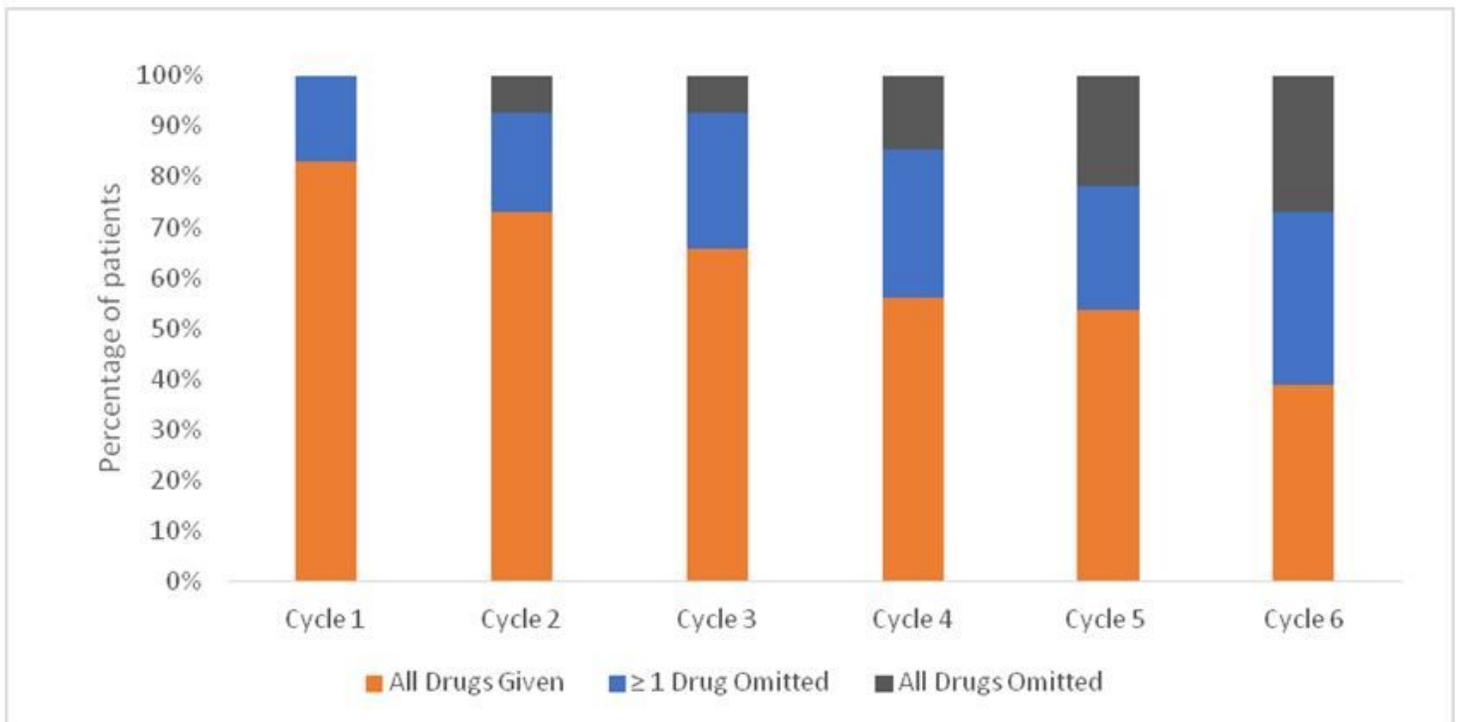


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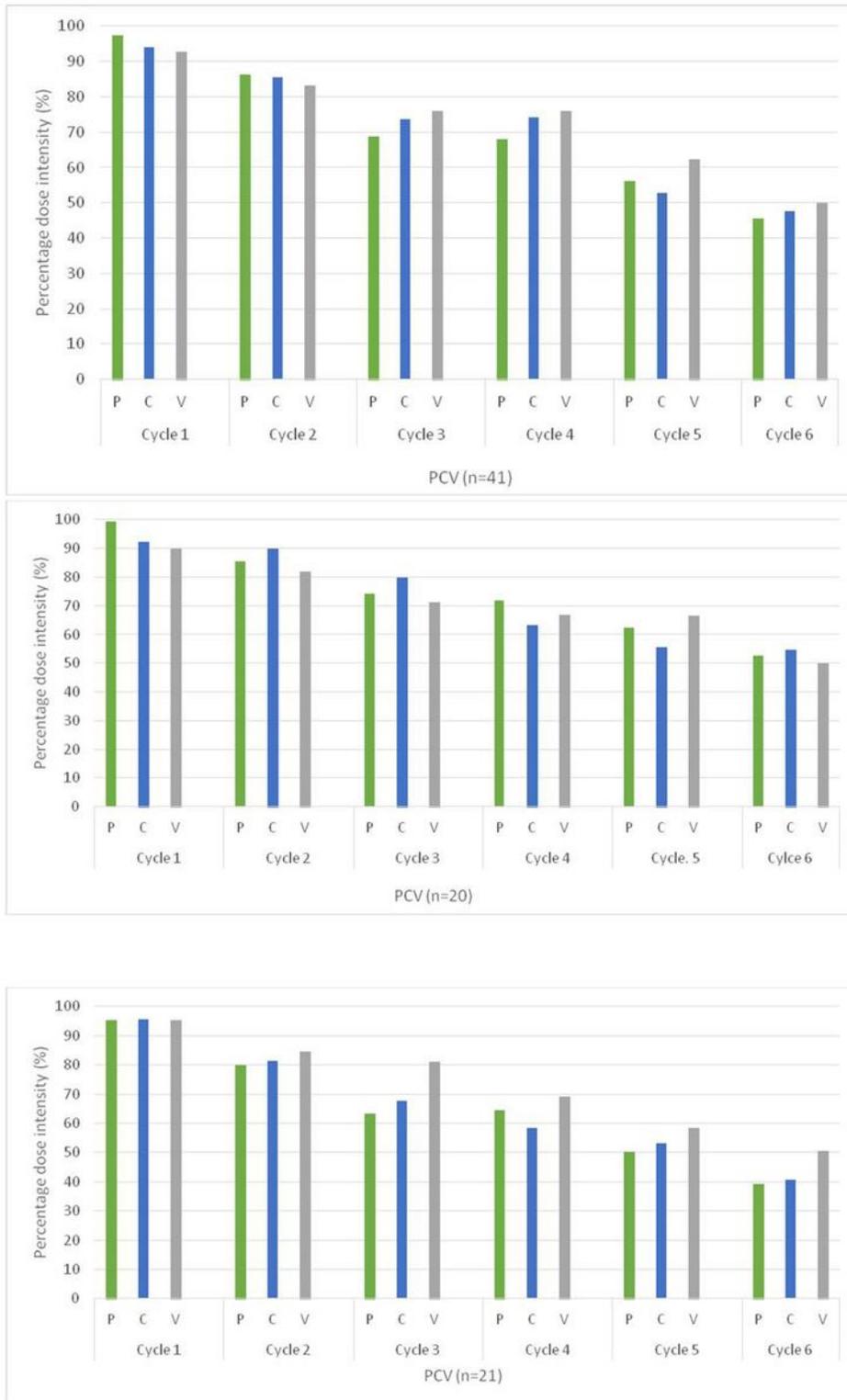


Figure 2

dose intensity by cycle and by cytotoxic agent; 2A: Overall (n=41), 2B: aged <40 years (n=20), 2C: aged ≥ 40 years old (n=21)

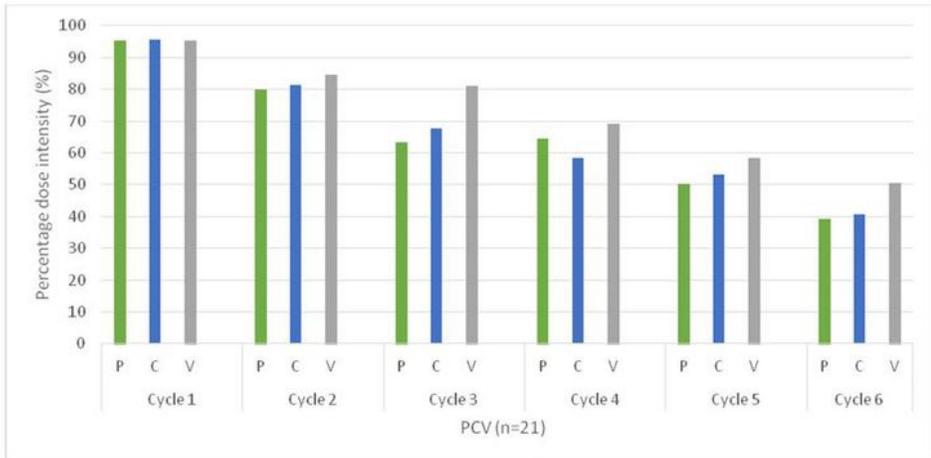
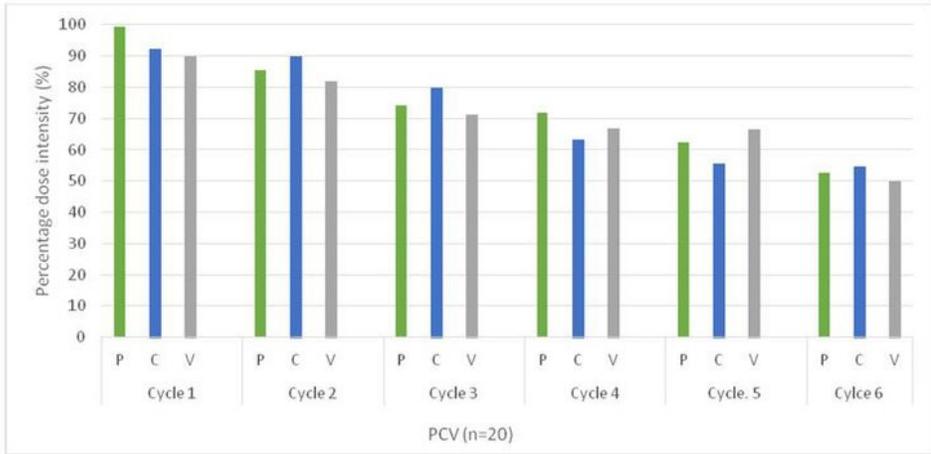
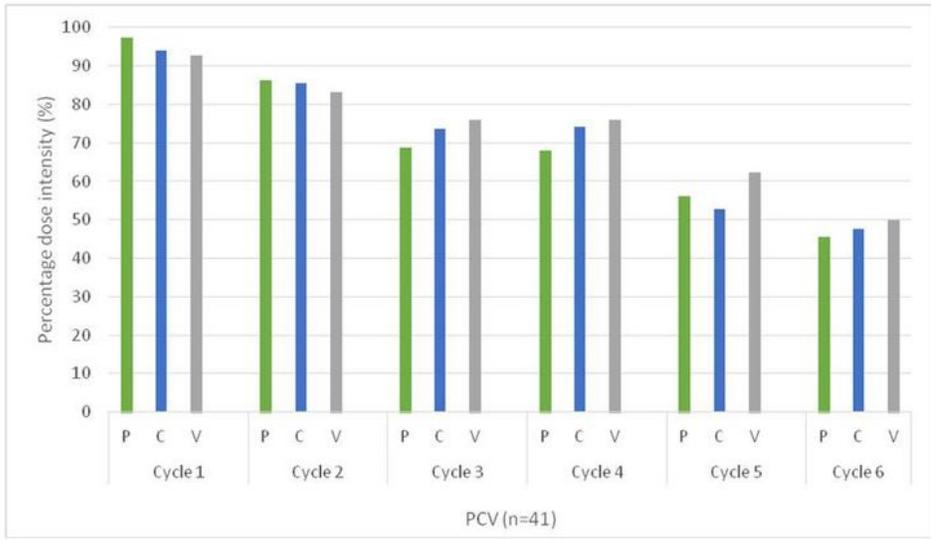


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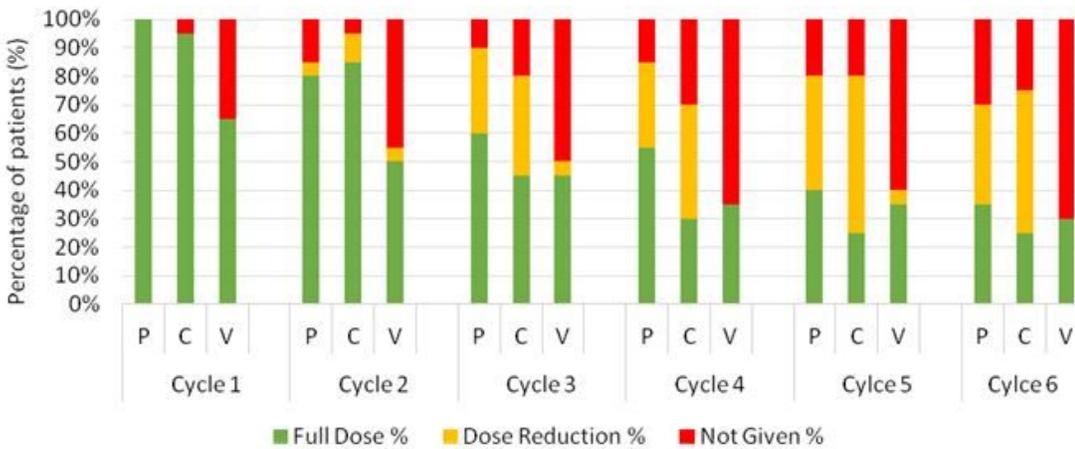
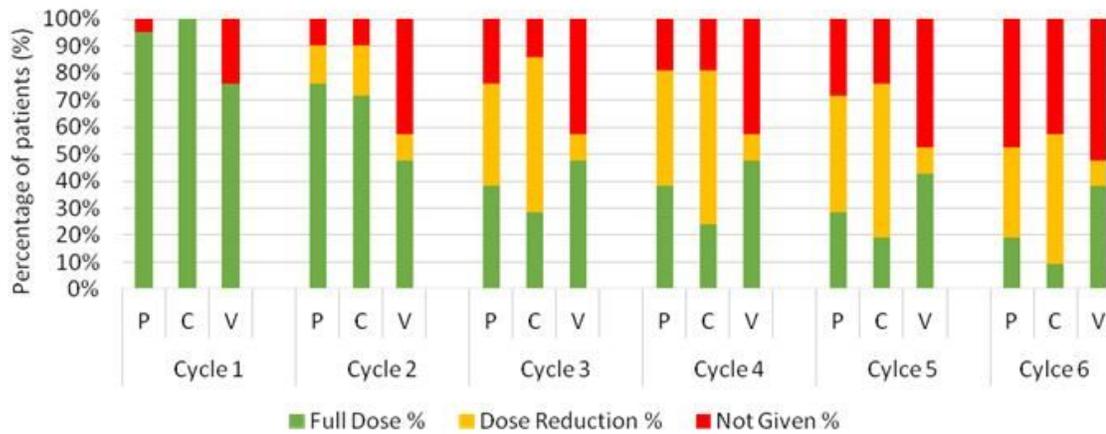
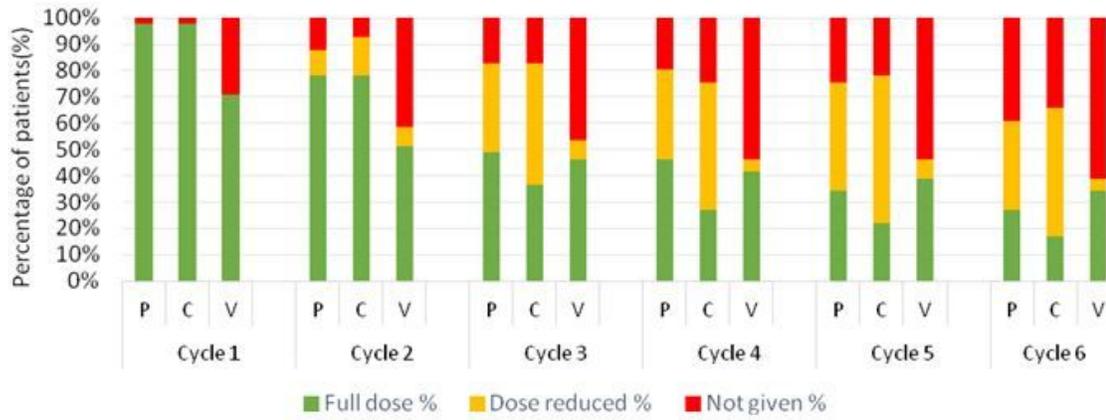


Figure 3

percentage of patients who received full dose (green), dose reduction (yellow) and dose omission or delay (red) for each agent for each cycle of PCV. Figure 3A: overall group (n=41), 3B: < 40 years old (n=20), 3C ≥40 years old (n=21)

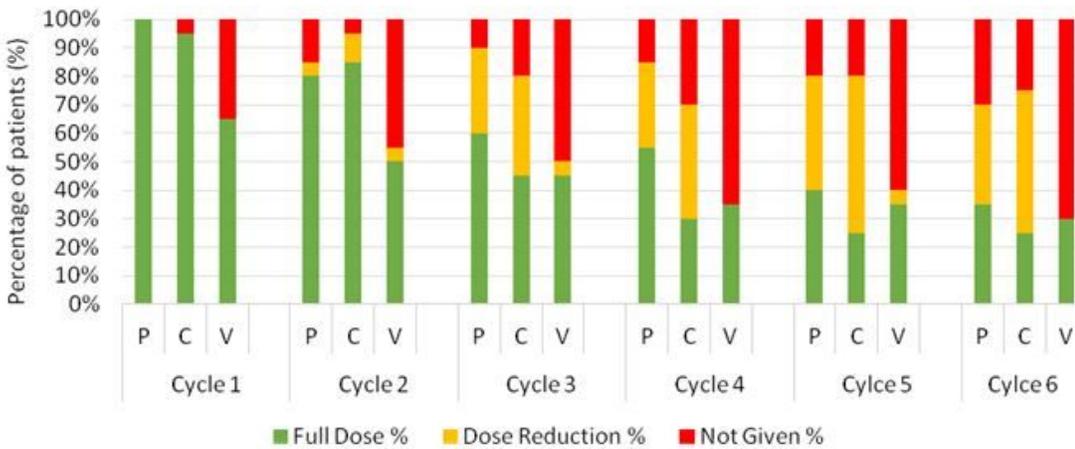
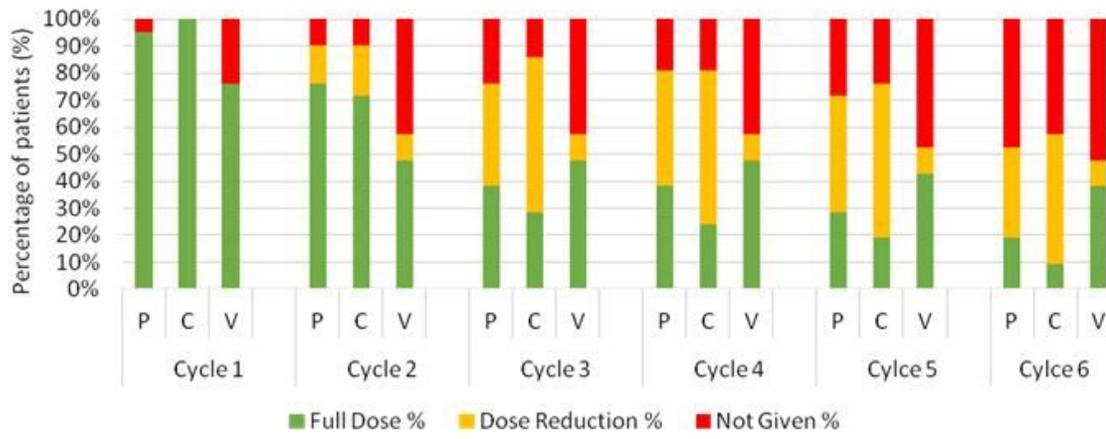
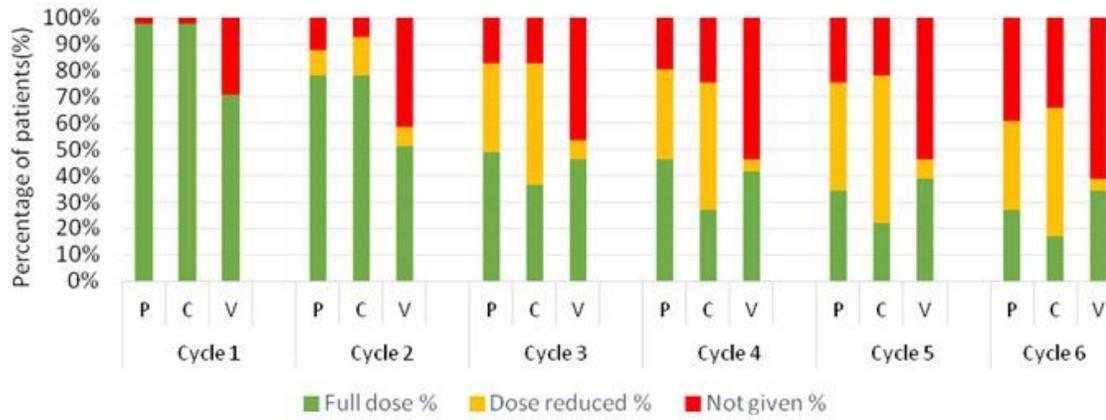


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