VIA MEDICA

REVIEW ARTICLE

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New dosing schedule of pembrolizumab — theoretical basis and scientific evidence

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Oncology in Clinical Practice
2020, Vol. 16, No. 6, 358–363
DOI: 10.5603/OCP.2020.0033
Translation: prof. Ewa Bartnik

ISSN 2450–1654

ABSTRACT

Pembrolizumab among other immunotherapy agents is a breakthrough drug in oncology. Its wide therapeutic index allowed evolution from a dosing schedule based on body mass 2 mg/kg to a fixed-dose 200 mg every 3 weeks. In 2019 the European Medicines Agency approved dosing 400 mg every 6 weeks, despite lack of evidence from clinical trials on safety and efficacy, based only on pharmacokinetic data derived from previous clinical studies. This year, facing the SARS-CoV-2 pandemic, international oncology societies recommended a new dosing schedule in order to minimise patient exposition to health care units. In April 2020 the US Food and Drug Administration also approved a new dosing schedule, based on an interim analysis of clinical trial Keynote-555.
Key words: pembrolizumab, immunotherapy, dosing schedule

Oncol Clin Pract 2020; 16, 6: 358–363

Introduction

Pembrolizumab is a monoclonal humanized antibody against the programmed death 1 receptor (PD-1). This receptor is present on activated T, B and NK lymphocytes and monocytes. Its binding to ligands (PD-L1 and PD-L2) prevents excessive activation of immunological system and the associated inflammatory reaction. It also causes immunological tolerance of own tissues, and in case of neoplasms, it inhibits the effects of immunological system on neoplastic cells.

Blocking the binding of PD-1 receptor with its ligands present on antigen presenting cells (APC) and the cells of some neoplasms favors the cytotoxic reaction and apoptosis of neoplastic cells. At the same time, this reaction may take place in healthy tissues which is responsible for adverse effects on autoimmunological basis [1].

The first clinical trial using pembrolizumab (Keynote-001) in solid tumors was initiated in 2011. On the basis of the results of this trial this drug was acknowledged as a breakthrough in 2013 and in 2014 in an accelerated mode it was registered for melanoma treatment and in 2015 for non-small cell lung cancer [2]. Currently, pembrolizumab is registered for multiple indications (Table 1). It is used in monotherapy or together with chemotherapy or in molecularly targeted treatment.

The effectiveness and safety of pembrolizumab have been confirmed in numerous trials [3]. 2019 brought publication of 5-year observations of patients with advanced melanoma and non-small cell lung cancer, who received pembrolizumab at a dose of 2 mg/kg body mass (b.m.) every 3 weeks (Q3W) or 10 mg/kg b.m. Q3W or every 2 weeks (Q2W) in the Keynote-001 trial. An objective response was reached in 41% of patients with melanoma and 26% with non-small cell lung cancer, whereas the percentage of disease control was 65% and 63%, respectively. After five years the response was maintained in 73% of the patients with melanoma and 54% with non-small cell lung cancer, and in respect to disease control, this percentage was 61% and 23%, respectively [4, 5].

Adverse effects of pembrolizumab concern 63–96% of treated patients (including 10–41% with grade 3–4).

Table 1. Registration indications for pembrolizumab

Registration indications according to EMA	Registration indications according to FDA
Palliative treatment	**Palliative treatment**
Melanoma	Melanoma
Non-small cell lung cancer	Non-small cell lung cancer
Classical Hodgkin lymphoma	Small cell lung cancer
Urothelial cancer	Classical Hodgkin lymphoma
Squamous cell head and neck carcinoma	Mediastinal large B cell lymphona
Renal cell carcinoma	Solid tumors with microsatellite instability Stomach cancer
	Esophageal cancer
	Cervical cancer
	Hepatocellular carcinoma
	Merkel cell cancer
	Endometrial carcinoma
	Urothelial cancer
	Squamous cell head and neck carcinoma
	Renal cell carcinoma
	Skin spinocellular carcinoma
Adjuvant treatment	**Adjuvant treatment**
Stage III melanoma	Stage III melanoma

EMA — European Medicines Agency; FDA — Food and Drug Administration

According to the Keytruda Summary of Product Characteristics in force in Poland, the registered indications for the use of the drug include the following diseases: melanoma, non-small cell lung cancer, classical Hodgkin's lymphoma, urothelial carcinoma, squamous cell carcinoma, head and neck cancer, renal cell carcinoma.

The dosage of Keytruda is as follows:

1. The recommended dose of KEYTRUDA monotherapy is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as a intravenous infusion lasting 30 minutes;
2. The recommended dose of KEYTRUDA in combination therapy is 200 mg every 3 weeks, administered as an intravenous infusion over a period of 30 minutes

The most common adverse effects include weakness, pruritis, diarrhea and disorders of thyroid gland function (grade 3 and 4 — immunological pneumonia, diarrhea and colon inflammation, hypopituitarism and liver toxicity). Mortality associated with treatment is estimated to be 0.45% and is most commonly the result of immunological pneumonia, cardiotoxicity and hepatotoxicity and infections. Among rarely occurring adverse effects are neurological complications (including encephalitis, Guillian-Barre syndrome, myasthenia, uveitis, type 1 diabetes) [6–8].

Pembrolizumab dosing

Pembrolizumab dosing changed over time. Initially, the drug was registered at a dose of 2 mg/kg b.w. Q3W. Currently in all indications for adults pembrolizumab is used at a constant dose of 200 mg Q3W intravenously during a 30-minute infusion (in children the dosing is 2 mg/kg b.w.). In 2019 the European Medicines Agency (EMA) additionally registered the dosing schedule 400 mg every 6 weeks (Q6W), and the American Food and Drug Administration (FDA) accepted it in April 2020 in an accelerated mode even though it initially rejected this dosing schedule. Dosing every 6 weeks only concerns pembrolizumab in monotherapy. In combined treatment, only the dosing schedule 200 mg Q3W is accepted. This paper will present the stages of dosing evolution and the evidence justifying current pembrolizumab dosing.

Pharmacokinetics

Data concerning pharmacokinetics are derived from 5 clinical trials involving 2993 patients, which were the basis of a population pharmacokinetic model (Keynote-001, Keynote-002, Keynote-006, Kenote-010, Keynote-024). In these trials the following dosing schedules were evaluated: 2 mg/kg Q3W, 10 mg/kg Q3W and Q2W and 200 mg Q3W regardless of body mass [9, 10].

The potential of pembrolizumab activity was evaluated on the basis of the dynamics of interleukin-2 after stimulation *ex vivo* with Staphylococcus endotoxin in peripheral blood taken before and in different time intervals after pembrolizumab administration. Maximal activity measured this way was found to be reached at a minimal concentration (C_{min}) of 10 μg/ml. This is possible with dosing of at least 1 mg/kg Q3W without further advantage with doses of 3 and 10 mg/kg. During further simulations, the highest potential effect was evaluated to be with a dose of 2 mg/kg mc Q3W [11].

Pembrolizumab concentration in blood increases in a linear fashion in the dose range of 0.1–10 mg/kg. The distribution volume is about 6 liters, which means a small degree of passage into the non-vascular space. Pem-

Table 2. Exposure to pembrolizumab depending on the dosing schedule [16]

Dosing schedule (number of patients)	C_{min} [μg/mL]	AUC [μg·day/mL]	C_{max} [μg/mL]
2 mg/kg Q3W (755)	21.1 (9.18–35.7)	1316.5 (724.9–2038.5)	66.3 (48.3–88.2)
10 mg/kg Q3W (1403)	120.4 (59.8–200.2)	7436.0 (4354.0–11 172.8)	357.6 (257.7–466.8)
10 mg/kg Q2W (652)	217.8 (111.8–325.3)	11 993.5 (6834.7–16895.5)	457.7 (315.9–599.9)
200 mg Q3W (830)	27.6 14.9–46.2	1787.0 1120.6–2730.9	89.1 66.4–124.3

Values presented as median (10–90 percentile). AUC — area under the curve of change in concentration in time; C_{min} — minimal concentration; C_{max} — maximal concentration

Table 3. Effectiveness of pembrolizumab in NSCLC Keynote-001 trial [17]

Parameter	2 mg/kg Q3W n = 52	10 mg/kg Q3W n = 155	10 mg/kg Q2W n = 105
ORR, % (95%CI)	15 (7–28)	25 (8–33)	21 (14–30)
DCR, % (95% CI)	50 (36–64)	48 (40–56)	50 (40–60)

CI — confidence interval; DCR — percentage of disease control; n — number of patients analyzed; ORR — percentage of objective responses

brolizumab concentration in blood reaches a stationary state after 6–16 weeks of treatment. As pembrolizumab catabolism is via non-specific protein catabolism, the velocity of drug elimination does not significantly depend on liver and kidney function and is 195 ml/day in the stationary phase, whereas the half-life is 14–22 days [10, 12, 13]. Drug clearance is affected by body mass, albumin and bilirubin concentration, the size and type of neoplasm, the index of glomerular filtration and the sex — but the clinical significance of these factors has not been demonstrated. These factors may, however, affect the individual variation in exposure to the drug, thus they have been used in pharmacokinetic models evaluated in search for an optimal dosing schedule [12, 14]. In spite of the lack of known factors affecting pembrolizumab clearance, an unfavorable effect of rapid drug elimination in relation to overall survival has been demonstrated, but a higher dose of pembrolizumab (10 mg/kg Q3W) did not give a better prognosis [15]. This correlation may be associated with increased protein catabolism in advanced stages of the disease or in persons with severe comorbidities which would explain lack of benefits of immunotherapy in persons in a worse performance status.

Parameters used for evaluation of exposure to the drug — maximal concentration after finishing the infusion (C_{max}), the area under the curve of the change in concentration of the drug with time (AUC) and Cmin before the next infusion for particular dosing schedules are presented in Table 2.

In spite of clear differences in the extent of exposure to pembrolizumab depending on the dosing schedule, in the Keynote-001, Keynote-002, Keynote-006, Keynote-010 trials comparing dosing schedules 2 mg/kg Q3W and 10 mg/kg Q2W or Q3W [16], no significant differences were observed in the efficacy and the toxicity of the applied treatment in a direct comparison of Keynote-001 results (Tables 3 and 4) [17]. Also in the meta-analysis evaluating the frequency of adverse effects no statistically significant differences were observed between the clinical trials evaluated so far [7]. Taking into consideration data from the first three mentioned trials, Chatterjee et al. analyzed the correlation between the exposure to pembrolizumab, expressed as AUC, and the response to treatment, expressed by the degree of decrease of the dimensions of the lesions evaluated in imaging tests. In two publications concerning patients with melanoma and non-small cell lung cancer, no significant differences were found in the dynamics of the lesion sizes for individual schedules and it was concluded that dosing 2 mg/kg Q3W allows obtaining the best response to treatment [17, 18].

Dosing 200 mg every 3 weeks

Aiming at simplifying the dosage schedule and to limit errors in calculating and dispensing the dose depending on body mass, from 2016 a fixed dose of 200 mg has been used in clinical trials regardless of body mass.

Table 4. Adverse effects associated with treating patients with NSCLC in the Keynote-001 trial [17]

Adverse effects	2 mg/kg Q3W n = 61	10 mg/kg Q3W n = 287	10 mg/kg Q2W n = 202
All grades n (%)	31 (51)	201 (70)	148 (73)
Grade 3–4 n (%)	5 (8)	34 (12)	8 (4)
Mortal n (%)	1 (2)	1 (< 1)	0
Immunological n (%)	9 (15)	39 (14)	32 (16)

n — number of analyzed patients

The analysis of available data allowed a mathematical model to be created in which exposure to pembrolizumab was calculated in clinical trials in which a constant dose of 200 mg Q3W was used. The values observed in clinical trials were convergent with those estimated on the basis of the mathematical model. Moreover, on their basis, it was observed that a constant dose of 154 mg allows an AUC in the stationary phase which is the same as that with the dose of 2 mg/kg body mass, whereas the dose of 200 mg allows to reach an AUC ensuring effectiveness with acceptable toxicity, both in persons with a low body mass as well as in the subgroup of patients with body mass > 90 kg [17].

Dosing 400 mg every 6 weeks

Financial and logistic considerations were decisive in the next step in decreasing the frequency of drug administration, and thus the visits of patients in healthcare units, which is particularly desirable during the SARS-CoV-2 pandemic. During the ASCO conference in 2018, the results of mathematical analysis were presented forecasting the approximated parameters of exposure to pembrolizumab with a dose of 400 mg Q6W [19]. In a model elaborated on the basis of data from Keynote-001, Keynote-002, Keynote-006 and Keynote-010 clinical trials simulations of C_{min}, C_{max} and AUC were performed, evaluated during the first 6 weeks of treatment and the same parameters evaluated between 25 and 30 weeks of treatment (during the 5^{th} cycle). According to the performed simulations, AUC in the stationary stage between consecutive doses will be close to AUC reached with dosing 2 mg/kg Q3W and 200 mg Q2W, and the stationary state will be reached earlier than with Q3W dosing. In the context of adverse effects, the foreseen C_{max} does not exceed values reached in the cohort of patients receiving 10 mg/kg Q2W, in which the safety profile did not diverge from other dosing schedules. In turn, the simulated C_{min} will be lower than the minimal value with potential effectiveness only in approximately 0.5% of patients in a time not longer than 3 days. According to the authors of the cited work, this brief decrease in concentration does not result in a decrease of clinical effectiveness as according to the physiological model of monoclonal antibody pharmacokinetics in the stationary state the fraction of the drug bound to its receptor ensures its saturation for about 7 days (longer than the decrease in drug concentration) [17, 20].

A different position was presented in the report of the Canadian Agency for Drugs and Technologies in Health (CADTH) concerning dosing schedules in immunotherapy. According to the performed simulation, the 400 mg Q6W schedule translates into a lower saturation of target molecules, expressed as the dynamics in the changes of interleukin-2 concentration in peripheral blood and depending on the weight it is 95.88–98.16% (400 mg Q3W) as compared to the values of 98.47–99.95%, calculated for dosing 2 mg/kg body weight considered to be optimal [15]. There were, however, no data about the clinical significance of the mentioned differences.

The above reports require confirmation in trials and clinical practice. Despite that EMA registered 400 mg Q6W dosing schedule already in 2019 only on the basis of the evidence presented above. The results of a preliminary analysis of data from the Keynote-555 trial which evaluated the effectiveness and safety of the above schedule in advanced melanoma were presented during 2020 Virtual AACR meeting. Among the first 44 patients, the parameters of exposure to the drug were found to be comparable with those observed in the schedules which have been registered so far. The percentage of objective responses at this stage is 39%, grade 3 and 4 adverse effects were noted so far in 25% patients, which is comparable to data obtained in clinical conditions with different dosing schedules. The result should, however, be interpreted carefully especially in relation to adverse effects, as this is a preliminary analysis of the first group of patients with a median time of observation of 6.7 months [21].

Potential dosing schedules

Taking clinical, logistic and financial matters into consideration it seems that the recommended dosage schedule will continue to evolve. Currently, in the Keynote-555 trial (cohort B) a subcutaneous form of administering the drug is being evaluated, more com-

fortable for many patients and possible to use outside a healthcare unit.

Financial matters are also worth mentioning. Bach et al. calculated that in case of dosing depending on body mass in the USA about 16–24% of the drug is utilized which is due to the availability of vials containing 50 or 100 mg pembrolizumab. Even if the drug from an opened vial was given to the next patient (a practice not recommended by the CDC because of the risk of a blood-derived infection) the value of the unused drug was estimated close to 200 million dollars per year [22]. In order to minimize treatment costs, various dosing models were studied, allowing to ensure optimal exposure to the drug and their costs were estimated in relation to dosing 2 mg/kg b.m. The constant dose of 200 mg Q3W was found to generate costs 7% higher than the initial dosing schedule. A constant dose of 150 mg would allow savings of 25%. An intermediate form was dosing calculated on the basis of body mass ± 10% so that the dose would be a multiple of 25 mg, which would minimize the amount of the utilized drug (*dose banding*). The last strategy was based on pharmacokinetics simulations depending on the body mass and is based on adjusting the dose to the available vials (*PK-derived dose banding*). Dosing depending on the body mass interval was presented in easy to use tables which decrease the risk of an error. Economic analysis indicated the costs of both strategies were lower by 15 and 16%, respectively, in comparison to 2 mg/kg b.m. dosing [14].

A strategy taking into consideration the needs of the reduction of exposure to contact with SARS-CoV-2 and economic problems in the context of the pandemic is based on dosing 4 mg/kg Q6W to a maximal dose of 400 mg. On the basis of data from mathematical simulations such dosing will enable the maintenance of high saturation of target molecules [23], however, it differs from that obtained for dosing at 2 mg/kg Q3W. Nevertheless, in the face of the SARS-CoV-2 pandemic many international oncological societies have recommended dosing of pembrolizumab 400 mg Q6W in order to minimize the contact of patients with healthcare units.

Summary

The evolution of the pembrolizumab dosing schedules reflects the interactions between theoretical models and the results of clinical trials and everyday clinical practice. The aim to obtain a mode of drug dosing which is economical and acceptable for patients is indispensable. However only appropriately conducted clinical trials can defermine the value of a new schedule from it in all patients or can lead to determining the profile of patients who can benefit.

Conflict of interest

The authors declare no conflict of interest.

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