Treatment-induced anaemia in solid tumours with emphasis on newer anti-cancer drugs

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SUMMARY

Chemotherapy-induced anaemia is a well-known complication in cancer. With the venue of newer non-cytotoxic anti-cancer drugs, attention to anaemia and anaemia management has been shifted to the background. Nevertheless, anaemia is a frequent complication of some of these newer drugs. Mammalian target of rapamycin inhibitors, some of the antiangiogenic drugs, poly (ADP ribose) polymerases inhibitors and cyclin-dependent kinase inhibitors all can cause grade 3 or 4 anaemia. This review discusses the risks of anaemia development of anti-cancer drugs.

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INTRODUCTION

Anaemia is a well-known complication in oncology. It results from blood loss, impaired erythropoiesis due to increased apoptosis of erythroid precursor cells by cytokines or to decreased stimulation by inadequate production or efficacy of erythropoietin and to decreased availability of iron, or from a decreased life span of circulating erythrocytes. Anaemia is also a side effect of anti-cancer treatment, and chemotherapy-induced anaemia (CIA) is a recognised entity in cancer anaemia management.[1]

With the venue of newer non-cytotoxic anti-cancer drugs, including targeted agents and check point inhibitors, the attention to anaemia has shifted in the background since treatment-related anaemia in cancer is mainly considered as a side effect of chemotherapy. Nevertheless, anaemia can also be caused by these newer anti-cancer agents, but the exact pathophysiological mechanism is unknown. In this review, anaemia related to anti-cancer drug treatment is reviewed.

CHEMOTHERAPY-INDUCED ANAEMIA

Chemotherapy-induced anaemia (CIA) develops in up to 90% of patients treated with chemotherapy, and around 9-10% develop grade 3 or 4 anaemia.[2,3]

The CIA prevalence and incidence depends on the tumour type, disease stage, cytotoxic agent type or combination used, combination with radiotherapy and the duration and intensity of the cytotoxic treatment.[2-4]

During treatment, grade 3 or 4 anaemia has been more frequently reported in patients with lung, ovarian and gastric cancer compared with colorectal and breast cancer.[2]

Patients with more advanced disease stages have a higher risk of developing anaemia, increasing from 29% in stage I to 49% in stage IV disease.[2]

The incidence of CIA in relation to some treatment regimens is shown in *Table 1*. Combination regimens more frequently cause anaemia compared to single agent treatment. Platinum-based regimens induce higher rates of CIA compared with non-platinum-based regimens.[2,3]

This makes anaemia in patients treated with chemotherapy a matter of attention and its treatment with the use of erythroid stimulating agents or transfusions should be performed according to the guidelines.[1]

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TABLE 1. Grades of anaemia related to different anti-cancer drugs/treatments.

Treatment	Tumour type	Anaemia (all grades, %)	Grade 3/4 (%)
Chemotherapeutic schedules			
AC	Breast	78.9	8.1
TAC	Breast	91.1	3.5
AC followed by T	Breast	95.7	4.8
CAPOX	Colorectal	89.7	2.9
FOLFOX	Colorectal	94.6	4.6
Carbo + paclitaxel	Lung	93.1	9.2
Cis/carbo + pem	Lung	86.4	15.0
Carbo + paclitaxel	Ovarian	92.8	18.4
Angiogenesis inhibitors			
Sunitinib	Renal	60-71	4-7
Sorafenib	Renal	52	4
Pazobanib	Renal	31	2
Axitinib	Renal	35	<1
Regorafenib	Colorectal	14	5.8
Cabozantinib	Renal	33	1.3
mTOR inhibitors			
Temsirolimus	Renal	34-40	20-23
Everolimus	Renal	16-37	5-15
Immune modulatory drugs			
Nivolumab	Head and neck	5.1	3.0
Nivolumab	Lung	2	<1
Nivolumab	Renal	8	2
Nivolumab	Melanoma	4.7	0.9
Pembrolizumab	Bladder	3.4	0.8
Pembrolizumab	Lung	5.2	1.9
Pembrolizumab	Melanoma	2.2	0
Ipilimumab	Melanoma	0.4	0.4

AC: doxorubicin + cyclophosphamide, TAC: docetaxel + doxorubicin + cyclophosphamide, AC followed by T: Doxorubicin + cyclophosphamide followed by paclitaxel or docetaxel, CAPOX: capecitabine + oxaliplatin, FOLFOX: leucovorin calcium + 5-fluorouracil + oxaliplatin, pem: pemetrexed, cis: cisplatin, carbo: carboplatin.

ANGIOGENESIS TARGETING DRUGS

Several classes of drugs that target tumour angiogenesis have been developed.[5] They include monoclonal antibodies directed against vascular endothelial growth factor (VEGF; e.g., bevacizumab, aflibercept); tyrosine kinase inhibitors (e.g., sorafenib, sunitinib, pazobanib, axitinib, regorafenib, cabozantinib, vandetanib) that interfere with the VEGF receptor; mammalian target of rapamycin (mTOR) inhibitors (e.g., temsirolimus, everolimus) that block the production of hypoxia inducible factor; and inhibitors of Akt phosphory-

TABLE 2. Relative risk for anaemia development compared with standard treatment.

Agent	Tumour type	Relative risk of anaemia
Anti-angiogenic agents		
Bevacizumab	Lung, kidney, breast, pancreas, colon, gastric	0.73*
Aflibercept	Colorectal	1.36
Sunitinib	GIST, kidney, breast	1.09*
Sorafenib	Lung, melanoma, kidney	1.03
Pazobanib	Kidney, sarcoma	0.51
mTOR inhibitors		
Everolimus	Kidney, neuroendocrine	2.94
Temsirolimus	Kidney	1.08
HER signalling pathways targeting drugs		
Cetuximab	Head and neck, lung, colon, pancreas	0.98
Trastuzumab	Breast, lung, stomach	1.23*
Erlotinib	Lung	1.34*
Gefitinib	Lung, colon, breast	2.04
Cyclin-dependent kinases inhibitors		
Palbociclib + fulvestrant vs fulvestrant	Breast	2.09*
Palbociclib + letrozole vs letrozole	Breast	3.76*
PARP inhibitors		
Olaparib	Breast, ovarian, gastric	1.50
Niraparib	Ovarian	91.47*
Veliparib	Breast, ovarian, melanoma, lung	1.44

*: significant difference, GIST: gastrointestinal stromal tumour, mTOR: mammalian target of rapamycin, PARP: poly (ADP ribose) polymerases, vs: versus.

lation (e.g., thalidomide, lenalidomide), which is involved in many cell processes including angiogenesis.[6,7]

The induction of anaemia is drug specific and may be influenced by combining these drugs with other medications such as cytotoxic agents.

The addition of bevacizumab to different cytotoxic combination schedules seems to protect a patient against anaemia since it is associated with a lower risk of anaemia development compared to non-bevacizumab containing chemotherapeutic regimens (*Table 2*). This is independent of the tumour type the combinations are used for.[8] A similar effect could not be shown with aflibercept, but the addition of aflibercept to different chemotherapy regimens did not lead to a higher risk of anaemia development compared to chemotherapy alone.[9]

The induction of anaemia by tyrosine kinase inhibitors is dependent on the individual molecule.

Compared to placebo, sunitinib is more frequently inducing anaemia: 60-71% of patients of whom 4-7% develop grade 3 or 4 anaemia.[10,11]

The use of sorafenib did not lead to an increased risk of anaemia compared to placebo with rates of 52% and grade ≥3 in 4% of patients.[8,12]

Pazobanib caused less anaemia compared to sunitinib: anaemia was reported in 31% of patients of whom 2% had grade 3 or 4 anaemia while in the sunitinib arm these frequencies were 60% and 7%, respectively.[11]

Axitinib induced anaemia in 35% of patients with <1% grade ≥3 anaemia.[12] These rates were not different compared to sorafinib.[12]

Anaemia of all grades due to regorafenib was occurring in 14% of patients in the CORRECT trial; grade 3 or 4 anaemia was seen in 5.4% and 0.4% of patients, respectively.[13]

Cabozantinib induced anaemia in 33% of patients with a grade ≥3 in 1.3%, although this was not different compared to sunitinib, the comparator in this study.[14]

Anaemia has not been reported with the use of vandetinib.[15]

Anaemia is a common mTOR inhibitor complication when used as a single agent and in combination therapy with other drugs.

By itself, temsirolimus induces anaemia in 34-40% of patients of whom 20-23% develop grade 3 or 4 anaemia.[16,17] This is more compared to sorafenib alone, but similar to a treatment with interferon. When combined with interferon, grade 3 and 4 anaemia rise to 61% and 38%, respectively.[17]

Single agent everolimus induces anaemia in 16-37% of patients of whom 5-15% develop a grade 3 or higher.[18,19] In combination with exemestane, it induced anaemia more (all: 18%, grade 3 or 4: 6%) compared to exemestane alone (all: 7%, grade 3 or 4: 1%). Anaemia seemed to be more prevalent in patients older than 65 years (all: 26%, grade 3 or 4: 9%).[20]

Thalidomide and lenalidomide are mainly used in the treatment of haematological malignancies, and their activity in solid tumour types is limited. They induce anaemia grades in around 30% of patients of whom 10% develop grade 3-4 anaemia.[21]

HER SIGNALLING PATHWAYS TARGETING DRUGS

The HER signalling pathways are regulators of cell growth and survival as well as of adhesion, migration, differentiation and other cellular responses.[22] They are also involved in the carcinogenesis of many tumour types (e.g., colorectal, head and neck, lung, breast), and several drugs have been developed to interfere with their activity.

Two major classes are being used including monoclonal antibodies (e.g., cetuximab, panitumumab, trastuzumab, pertuzumab, trastuzumab emtansine) and tyrosine kinase inhibitors (e.g., gefitinib, erlotinib, afatinib).

Cetuximab, a monoclonal antibody directed against epidermal growth factor receptor (EGFR), does not increase the relative risk of anaemia compared to placebo.[8] Compared with chemotherapy alone, the addition of cetuximab was not associated with increased risks of grade ≥3 anaemia occurring in around 7% of patients except in patients with colorectal cancer in which a relative risk of 2.67 (95% CI 1.53-4.65, p=0.01; incidence, 4.0 *vs* 2.0%) to develop anaemia was observed.[23]

Panitumumab is also a monoclonal antibody directed against EGFR, and when combined with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with colorectal cancer, it did not increase the frequency of anaemia, which was observed in 16% of patients of whom 4% developed grade ≥3 anaemia.[24]

Trastuzumab, a monoclonal antibody against HER-2, showed in studies, comparing trastuzumab-containing regimens with non-trastuzumab controls, an incidence of anaemia of 42% in the trastuzumab arms with a higher risk than in the control arms for developing anaemia (relative risk 1.23, 95% CI 1.10-1.37, p=0.0003).[8]

Pertuzumab is another monoclonal antibody that targets HER2. The addition of pertuzumab to trastuzumab and docetaxel did lead to a small increase of ≥grade 3 anaemia from 19.1% to 21.9%.[25]

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate incorporating the HER2-targeted anti-tumour properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1. It induced anaemia in 10.4% with grade ≥3 in 2.7% of patients.[26]

Single agent gefitinib induces anaemia in 18% of patients with no grade 3 or 4 anaemia.[27] For erlotinib and afatinib, these rates are 7% and 3-7%, respectively.[28]

CYCLIN-DEPENDENT KINASE INHIBITORS

The cyclin-dependent kinases (CDKs) are a large family of serine-threonine kinases that play an important role in regulating cell-cycle progression. Several inhibitors have been tested in the treatment of breast cancer.

Palbociclib is an inhibitor of CDK4 and CDK6 that is combined with letrozole or fulvestrant. The combination with letrozole induced anaemia in 24.1% (grade 3-4: 5.4%) of patients compared to 9% (grade 3-4: 1.8%) for the letrozole alone arm.[29] The combination of palbociclib with fulvestrant led to anaemia in 26% (grade 3-4: 2.6%) of patients compared to 9.9% (grade 3-4: 1.7%) in patients treated with fulvestrant alone.[30]

PARP INHIBITORS

Poly (ADP ribose) polymerases (PARPs) are a family of nuclear enzymes, which play an important role in DNA repair, cell proliferation, differentiation and transformation. PARP-1, PARP-2 and PARP-3 have shown activity specific to DNA repair and genomic stability, and inhibition of the repair complex plays a role in the treatment of breast, ovarian and prostate cancer.[31]

Treatment with PARP inhibitors (e.g., olaparib, niraparib, veliparib) leads to a significant increase in the development of anaemia compared to non-PARP inhibitor containing regimens (*Table 2*). The risk of developing anaemia depends on the individual molecule used and is more frequently seen

KEY MESSAGES FOR CLINICAL PRACTICE

1. Anaemia is an important complication of anti-cancer drug treatment.
2. Chemotherapy-induced anaemia is well known and its management is guided by guidelines.
3. Anaemia is also frequently seen with selected mammalian target of rapamycin, angiogenesis, poly (ADP ribose) polymerases and cyclin-dependent kinase inhibitors.
4. Attention should be given to all drug-induced forms of anaemia and not only to chemotherapy-induced anaemia.

with niraparib compared to olaparib or veliparib.

CHECK POINT INHIBITORS

Drugs, mainly monoclonal antibodies, that interfere with the immune suppression due to cancer are being introduced in daily clinical practice. They include monoclonal antibodies against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; e.g., ipilimumab, tremelimumab), programmed cell death-1 (PD-1; e.g., nivolumab, pembrolizumab) and, most recently, programmed death ligand (PD-L1; e.g., atezolizumab, avelumab, durvalumab).[32]

These agents induce anaemia in only a minority of patients (<10%; *Table 1*), but anaemia may occur in the individual patient due to an immune phenomenon inducing haemolysis or pure red cell aplasia.

DISCUSSION

Anaemia has been linked to chemotherapy in cancer treatment with rates of 90% and grade 3-4 anaemia in around 10% of patients. Although anaemia has not been recognised as an important complication in non-cytotoxic anti-cancer treatment, it is commonly seen with the use of specific agents, either alone or in combination with cytotoxic treatments.

While for some agents (e.g., mTOR; PARP inhibitors) the complication of anaemia may be a class phenomenon, it may also be a characteristic of individual molecules (e.g., sunitinib, niraparib).

Immune therapy seems to be not a major cause of anaemia, but in individual patients, it may occur as a consequence of an immune reaction, and this should be detected and if possible treated adequately.

If anaemia in combination with symptoms occurs with the use of these newer drugs, the symptomatic treatment is by blood transfusions, while the use of erythropoietin with or without intravenous iron is not recommended.

Anaemia remains an important complication of anti-cancer treatment, even with some of the newer agents, and should be considered in daily clinical practice.

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