75.1 Definition, Epidemiology, Diagnosis, and Classification

The myelodysplastic syndrome-myeloproliferative neoplasms (MDS/MPNs) are a heterogeneous group of hematologic malignancies characterized by dysplastic and myeloproliferative clinical, laboratory, and morphological overlapping features, both in marrow and in blood. The MDS/MPN category, recently updated by the last revision to the WHO classification of myeloid neoplasms and acute leukemia (Arber et al. 2016), includes chronic myelomonocytic leukemia (CMML), atypical chronic myelogenous leukemia (aCML), juvenile myelomonocytic leukemia (JMML), MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T), as well as unclassifiable forms of mixed myelodysplastic/myeloproliferative disorders (MDS/MPN-U) (Table 75.1).

While JMML affects only children from birth up to 14 years of age (median age at diagnosis 2 years), with an estimated incidence of approximately 1.2 cases per million annually (Chang et al. 2014), adulthood MDS/MPN are typically diagnosed in elderly age with CMML being definitely the most frequent subtype (incidence of around 1 case/100,000 inhabitants per year, median age 70 years) (Solary 2014). Being very uncommon, data concerning the incidence of aCML, MDS/MPN-RS-T, and MDS/MPN-U are currently unknown.

75.2 Risk Factors and Prognostic Index

The clinical course of MDS/MPN varies from an indolent course over several years for a minor fraction of patients with CMML and MDS/MPN-RS-T to a more rapid progression with dismal prognosis and frequent transformation into secondary acute myeloid leukemia in the preponderance of patients with CMML and in the vast majority of patients with aCML and MDS/MPN-U, for whom allo-HSCT still represents the only curative option (Onida and Beran 2008; Onida 2017). Alike, long-term survival in the greater part of children with JMML may only be achieved by means of allo-HSCT.

CMML is highly heterogeneous, with clinical and hematological characteristics varying from mainly myelodysplastic to predominantly myeloproliferative. Based on marrow and peripheral blood blast percentage, the last WHO classification recognized three disease subtypes.
Atypical CML, also named as BCR-ABL-negative CML, is a rare hematologic malignancy with an overall dismal prognosis (median 24 months). Age, hemoglobin level, and leukocyte count have been identified as variables with independent prognostic significance, allowing the stratification of two groups with significantly different life expectations. Likewise, for MDS/MPN-RS-T, three risk categories of patients were recently differentiated by a Mayo Clinic prognostic model including molecular investigations (Table 75.2).

With regard to the JMML, acquisitions from modern genetic studies assign uncommon treatment indication in patients with germ line PTPN11 and CBL mutations, who frequently experience spontaneous disease regression. In contrast, patients with neurofibromatosis type 1, somatic PTPN11, KRAS, and most of those with NRAS mutations require early allo-HSCT as a result of rapidly progressive disease (Hasle 2016).

MDS/MPN-U is the most heterogeneous and the least well-characterized entity, with no currently recognized specific molecular findings. Some description of the biological and clinical characteristics have been recently reported in two series (DiNardo et al. 2014; Wang et al. 2014),
with median survival of 12.4 and 21.8 months, respectively, and possible association of thrombocytosis with a more favorable outcome.

75.3 Pretransplantation Treatment

For this rare group of diseases, there are only few prospective studies on therapy, most being either retrospective analyses or case reports, making it difficult to give recommendations. In general, because apart from allo-HSCT no therapy has been shown to modify the disease course, pre-transplantation treatments point toward symptom control rather than the achievement of disease remission (Odenike et al. 2015).

### 75.3.1 CMML

In general, treatment strategies in patients with CMML with symptomatic or progressive disease are based on the dysplastic versus proliferative features and the percentage of marrow blasts (Onida et al. 2013). In the presence of rising leukocytosis and/or organ infiltration (mostly splenomegaly) with low marrow blast percentage, hydroxyurea (HU) remains the drug of choice. Patients showing high blast percentages may be
bridged to transplant through AML-like induction chemotherapy or by means of hypomethylating agents (HMAs), with a reported 20–50% overall response rate. In a recent retrospective study including a relatively small number of patients, HMAs have been suggested to increase progression-free survival (PFS) through the reduction of post-transplantation relapse rate (Kongtim et al. 2016). Treatment strategies based on the combination of HMAs with other agents (e.g., lenalidomide) and the advent of new targeted therapies such as JAK2 inhibitors or poly(ADP-ribose) polymerase (PARP) inhibitors may further increase the response rate leading to an overall improvement of post-transplantation outcomes.

### 75.3.2 aCML

Due to its absolute rarity in patients having no age or comorbidity barrier to allo-HSCT, no consensus subsists on to whether any pretransplant treatment may have an impact on post-transplantation outcome and what kind of therapy should be best used. Control of leukocytosis is generally achieved with cytoreductive agents such as HU or IFN-α immunomodulation. Chemotherapy induction treatment is preferred when facing high blast count in advanced disease phases or in patients showing AML transformation.

Some efficacy of decitabine and of ruxolitinib single agent has also been reported, whereas a phase II trial of AZA and ruxolitinib in combination in a series of 35 MDS/MPN patients showed promising activity, with an overall response rate of 57% according to the 2015 international consortium response criteria for MDS/MPN (Savona et al. 2015), even though median survival of the few aCML included patients \( n = 4 \) was only 8 months (Assi et al. 2018). According to the most recent discovery, \( \text{SETBP1} \) and \( \text{ETNK1} \) mutations are present in 15–32% and up to 10% of aCML patients, respectively, whereas \( \text{JAK2} \) mutation is rare (0–7%), and \( \text{CSF3R} \) mutations are only occasionally observed. Even though in the near future these findings may influence therapeutic approaches by means of evolving targeted therapies, currently allo-HSCT remains the only treatment strategy with established curative potential in eligible patients (Dao et al. 2017).

### 75.3.3 JMML

For JMML patients the possible therapeutic interventions prior to transplantation are rather scarce. Different chemotherapeutic agents have been used prior to transplant, but there is no consensus on to whether there should be any pretransplant therapy and what type should be given. HMAs may have potential activity (Cseh et al. 2015), but data are too few to make any recommendation. Other potentially active agents include JAK, MEK, and SRC inhibitors, but clinical trial with these drugs is still on their way.

### 75.3.4 MDS/MPN-RS-T

MDS/MPN-RS-T generally represents the disease entity associated with the best prognosis among overlap syndromes, with a median survival of about 6 years (Broseus et al. 2012). Guidelines for disease management are not formally recognized, and treatment strategies are generally extrapolated from low-risk MDS and MPN, with adjusted individual management depending on presenting problems. While lenalidomide has been occasionally reported to reduce transfusion need, antiplatelet and cytoreductive treatments are often required due to the high risk of thrombosis. Based on the different gene mutations possibly involved (\( \text{SF3B1} \), \( \text{JAK2} \), \( \text{TET2} \), \( \text{DNMT3A} \)), attentiveness in targeted therapies is developing.

### 75.3.5 MDS/MPN-U

MDS/MPN-U is a very rare and heterogeneous disease entity, with no consensus on which therapy (if any) should be given for patients candidate to allo-HSCT. Augmented leukocyte proliferation
is generally managed by means of cytoreductive agents such as HU or through immunomodulation with IFNα, while HMAs as well as lenalidomide may represent an option in case of prevailing cytopenias. JAK inhibitors are also potential therapeutic options, either alone or in combination with HMAs (Assi et al. 2018). When patients are progressing to AML transformation, induction chemotherapy should be used as a bridge to allo-HSCT.

### 75.4 Autologous HSCT

Because the harvesting of polyclonal hematopoietic progenitor cells is not feasible through the currently available treatment options, autologous HSCT is currently not a recommended strategy in MDS/MPN.

### 75.5 Allogeneic HSCT

Currently still representing the only curative strategy, the role of allo-HSCT in adult MDS/MPN patients remains controversial mainly due to the lack of prospective studies, being therefore generally considered a possible treatment option for eligible patients with high-risk diseases.

In CMML benefits and risks of allo-HSCT have been analyzed retrospectively in various series, with different characteristics at transplant and much variable outcomes described (Table 75.3). Recent recommendations from an international expert panel agreed to limit indication for allo-HSCT in CMML patients classified in the intermediate-2 and high-risk CPSS categories (de Witte et al. 2017), representing the preferred treatment modality for younger patients with acceptable comorbidity index (Patnaik et al. 2015).

#### Table 75.3 Summary of selected studies on allo-HSCT in CMML

| Author (year)         | Pt N. | Median age (range) | Disease type/ stage | Donor type          | Conditioning (MAC vs RIC) | TRM/relapse rate | Survival outcome |
|-----------------------|-------|--------------------|---------------------|---------------------|---------------------------|------------------|------------------|
| Kröger et al. (2002)  | 50    | 44 (19–61)         | CMML-1 = 28         | MRD = 43            | MAC = 50                  | TRM = 52%        | OS (5y) = 21% DFS (5y) = 18% |
|                       |       |                    | CMML-2 = 17         | MUD = 7             | RIC = 0                   |                  |                  |
|                       |       |                    | Missing = 5         |                     |                           |                  |                  |
| Eissa et al. (2011)   | 85    | 51 (1–69)          | CMML-1 = 57         | MRD = 38            | MAC = 58                  | TRM (10y) = 35%  | OS (10y) = 40% DFS (10y) = 40% |
|                       |       |                    | CMML-2 = 26         | MUD = 47            | RIC = 27                  |                  |                  |
|                       |       |                    |                     |                     |                           |                  |                  |
| Park et al. (2013)    | 73    | 53 (27–66)         | CMML-1 = 24         | MRD = 41            | MAC = 30                  | TRM = 35%        | OS (3y) = 32% DFS (3y) = 29% |
|                       |       |                    | CMML-2 = 26         | MUD = 32            | RIC = 43                  |                  |                  |
|                       |       |                    | Missing = 23        |                     |                           |                  |                  |
| Symeonidis et al. (2015)| 513  | 53 (18–75)        | CMML-1 = 87         | MRD = 285           | MAC = 249                 | TRM (4y) = 41%   | OS (4y) = 33% DFS (4y) = 27% |
|                       |       |                    | CMML-2 = 32         | MUD = 228           | RIC = 226                 |                  |                  |
|                       |       |                    | s-AML = 95          |                     |                           |                  |                  |
|                       |       |                    | Missing = 299       |                     |                           |                  |                  |
| Kongtim et al. (2016) | 83    | 57 (18–78)        | CMML-1/2 = 47       | MRD = 30            | MAC = 64                  | TRM (3y) = 31%   | OS (3y) = 35% DFS (3y) = 34% |
|                       |       |                    | s-AML = 36          | MUD = 47            | RIC = 19                  |                  |                  |
|                       |       |                    |                     | MMR = 6             |                           |                  |                  |
| Liu et al. (2017)     | 209   | 57 (23–74)        | CMML-1 = 140        | MRD = 73            | MAC = 105                 | TRM (5y) = 28%   | OS (5y) = 30% DFS (5y) = 20% |
|                       |       |                    | CMML-2 = 52         | MUD = 127           | RIC = 99                  |                  |                  |
|                       |       |                    | Missing = 17        | MMRUD = 9           |                           |                  |                  |
| Itonaga et al. (2018) | 159   | 54 (16–75)        | Not reported        | MRD = 51            | MAC = 92                  | TRM = 28%        | OS (3y) = 33% |
|                       |       |                    |                     | MUB (BM) = 66       | RIC = 67                  |                  |                  |
|                       |       |                    |                     | Cord = 30           |                           |                  |                  |
|                       |       |                    |                     | MMR = 12            |                           |                  |                  |
As aCML is extremely rare in people younger than 65 years, outcome after allo-HSCT has been described only in small single-institution series. A 5-years OS and RFS of 51% and 36%, respectively, were recently reported by the EBMT-CMWP in a retrospective analysis of 42 patients transplanted between 1997 and 2006. With a RR of 40%, a better OS was recognized in young patients with low EBMT risk score (Onida et al. 2017).

With regard to JMML, 5-years OS and EFS out of 100 patients transplanted 1993 through 2002 within the EWOG-MDS/EBMT trial were 64% and 52%, respectively, with a 5-years TRM of 13% (Locatelli et al. 2005). Overall, younger age, male sex, low HbF, and low BM blast percentage were associated to better survival. Early disease recurrence was the major cause of treatment failure, irrespective of donor type (sibling vs unrelated vs CB). Although both acute and chronic GvHD are associated with a lower relapse risk, DLI in JMML relapse is mostly unsuccessful. In contrast, a second HSCT with the same or an alternative donor may cure about 30% of the patients (Locatelli and Niemeyer 2015).

In MDS/MPN-RS-T allo-HSCT is generally not indicated, being reserved for patients developing refractory cytopenias or accelerated/blastic transformation (Sharma et al. 2017), whereas eligible patients with MDS/MPN-U should always be considerate as potential candidate for allo-HSCT due to the general dismal prognosis.

75.6 Source of HSC

No impact of HSC source on the transplant outcome has been observed in the largest CMML series reported by the EBMT-CMWP (Symeonidis et al. 2015). This was in contrast to the CIBTMR study, in which the survival was statistically better with PBMC than with BM, with no clear explanation outside the small proportion of BM transplants (16%) (Liu et al. 2017). The source of stem cell is therefore left open, but PBSC may potentially be preferred to decrease the risk of graft failure and the relapse risk, particularly with the use of RIC.

In the pediatric population, the majority of transplantation are done with BM, mainly due to the potential of decreasing the incidence of GVHD. In the largest series of JMML patients reported, BM was the stem cell source in 79% with no significant difference on the outcome in comparison to PBSC (Locatelli et al. 2005).

For aCML, MDS/MPN-RS-T, and MDS/MPN-U, data are too scarce to make clear recommendations.

75.7 Conditioning and GvHD Prophylaxis

In MDS/MPN patients, the choice of conditioning regimen depends on many different conditions, the major ones being comorbidities, patient age, disease phase at transplant, type of donor, and HSC source. In the two largest retrospective series of CMML patients (Symeonidis et al. 2015; Liu et al. 2017), MAC and RIC were almost equal in proportion, with no outcome difference. Likewise, in the largest reported series of aCML patients, conditioning intensity had no impact on the outcome (MAC were used in 76%). Noteworthy, an improved outcome following a combined fractionated 6–8 Gray TBI/FLU conditioning regimen was recently reported in advanced CMML (Radujkovic et al. 2017).

In general, for young patients (<60 years), with a HSCT-CI (Sorror et al. 2005) less than 2, MAC regimens such as BU-CY, TT/BU/FLU (TBF), or the reduced-toxicity FLU/BUx4 (FB4) may be advisable, particularly in the proliferative variant of CMML and in other MDS/MPN with predominant proliferative features, whereas a RIC regimen such as BU/FLU or reduced TBF may be preferred for patients with older age or comorbidities and for patients undergoing transplant with disease remission following pre-transplant treatment.

Facing an aggressive disease in a very young population, MAC regimens are generally preferred in JMML. In the biggest series published, the conditioning included CT, BU and MEL (Locatelli et al. 2005), with a 5-years OS of 64%. More recently, a conditioning containing BU,
FLU, and MEL showed promising results, with more than 50% of patients in remission after alternative donor transplantation (Yabe et al. 2015). Based on those data, the recommended conditioning for JMML patients should rely on the backbone of BU and MEL with either CY or FLU.

### 75.8 Maintenance/Post transplant Strategies

As disease recurrence represents the major cause of transplant failure in MDS/MPN, there is a growing interest toward post transplant strategies, although few data are currently available in this particular setting.

Indirect evidence of a graft versus CMML by a reduced incidence of relapse in patients with GvHD has been recently reported (Itonaga et al. 2018). Some effect of DLI has also been reported in patients with relapsing CMML and low disease burden.

With more molecular markers potentially available, cell therapy-based interventions may be planned on the base of residual or increasing MRD.

Potential interest both as preemptive and as maintenance strategy derive from the use of post transplant HMAs, alone or in combination with DLI, as reported in AML and MDS.

The use of lenalidomide and checkpoint inhibitors, but also JAK2 or PARP inhibitors, alone or even in combination, together with post transplant targeted therapies represents areas of growing interest under development.

### References

Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405.

Assi R, Kantarjian HM, Garcia-Manero G, et al. A phase II trial of ruxolitinib in combination with azacitidine in myelodysplastic syndrome/myeloproliferative neoplasms. Am J Hematol. 2018;93:277–85.

Broseus J, Florensa L, Zipperer E, et al. Clinical features and course of refractory anemia with ring sideroblasts associated with marked thrombocytosis. Haematologica. 2012;97:1036–41.

Chang TY, Dvorak CC, Loh ML. Bedside to bench in juvenile myelomonocytic leukemia: insights into leukemogenesis from a rare pediatric leukemia. Blood. 2014;124:2487–97.

Cseh A, Niemeyer CM, Yoshimi A, et al. Bridging to transplant with azacitidine in juvenile myelomonocytic leukemia: a retrospective analysis of the EWOG-MDS study group. Blood. 2015;125:2311–3.

Dao KT, Tyner JW, Gotlib J. Recent Progress in chronic neutrophilic leukemia and atypical chronic myeloid leukemia, Curr Hematol Malig Rep. 2017;12:432–41.

de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood. 2017;129:1753–62.

DiNardo CD, Daver N, Jain N, et al. Myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN, U): natural history and clinical outcome by treatment strategy. Leukemia. 2014;28:958–61.

Eissa H, Gooley TA, Sorror ML, et al. Allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukemia: relapse-free survival is determined by karyotype and comorbidities. Biol Blood Marrow Transplant. 2011;17:908–15.

Elena C, Gall A, Such E, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. Blood. 2016;128:1408–17.

Hasle H. Myelodysplastic and myeloproliferative disorders of childhood. Hematology Am Soc Hematol Educ Program. 2016;1:598–604.

Itonaga H, Aoki K, Aoki J, et al. Prognostic impact of donor source on allogeneic hematopoietic stem cell transplantation outcomes in adults with chronic myelomonocytic leukemia: a Nationwide retrospective analysis in Japan. Biol Blood Marrow Transplant. 2018;24:840–8.

Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol. 2013;31:2428–36.

Kongtim P, Popat U, Jimenez A, et al. Treatment with hypomethylating agents before allogeneic stem cell transplant improves progression free survival for patients with chronic myelomonocytic leukemia. Biol Blood Marrow Transplant. 2016;22:47–53.

Kröger N, Zabelina T, Guardiola P, et al. Allogeneic stem cell transplantation of adult chronic myelomonocytic leukaemia. A report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Br J Haematol. 2002;118:67–73.

Liu HD, Ahn KW, Hu ZH, et al. Allogeneic hematopoietic cell transplantation for adult chronic myelomonocytic leukemia. Biol Blood Marrow Transplant. 2017;23:767–75.

Locatelli F, Nöllke P, Zecca M, et al. European working group on childhood MDS; European Blood and Marrow Transplantation Group. Hematopoietic
stem cell transplantation (HHSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. Blood. 2005;105:410–9.
Locatelli F, Niemeyer CM. How I treat juvenile myelomonocytic leukemia. Blood. 2015;125:1083–90.
Odenike O, Onida F, Padron E. Myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms: an update on risk stratification, molecular genetics, and therapeutic approaches including allogeneic hematopoietic stem cell transplantation. Am Soc Clin Oncol Educ Book. 2015;35:e398–412.
Onida F, Ball G, Kantarjian HM, et al. Characteristics and outcome of patients with Philadelphia chromosome negative, bcr/abl negative chronic myelogenous leukemia. Cancer. 2002;95:1673–84.
Onida F, Beran M. Diagnosis and management of chronic myelomonocytic leukemia. Curr Hematol Malig Rep. 2008;3:31–6.
Onida F, Barosi G, Leone G, et al. Management recommendations for chronic myelomonocytic leukemia: consensus statements from the SIE, SIES, GITMO groups. Haematologica. 2013;98:1344–52.
Onida F. Models of prognostication in chronic myelomonocytic leukemia. Curr Hematol Malig Rep. 2017;12:513–21.
Onida F, de Wreede LC, van Biezen A, et al. Allogeneic stem cell transplantation in patients with atypical chronic myeloid leukaemia: a retrospective study from the chronic malignancies working Party of the European Society for Blood and Marrow Transplantation. Br J Haematol. 2017;177:759–65.
Park S, Labopin M, Yanikou-Agha I, et al. Allogeneic stem cell transplantation for chronic myelomonocytic leukemia: a report from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Eur J Haematol. 2013;90:355–64.
Patnaik MM, Itzykson R, Lasho T, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. Leukemia. 2014;28:2206–12.
Patnaik MM, Lasho TL, Finke CM, et al. Predictors of survival in refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) and the role of next-generation sequencing. Am J Hematol. 2016;91:492–8.
Patnaik MM, Wassie EA, Padron E, et al. Chronic myelomonocytic leukemia in younger patients: molecular and cytogenetic predictors of survival and treatment outcome. Blood Cancer J. 2015;5:e280.
Radujkovic A, Hegenbart U, Muller-Tidow C, et al. High progression-free survival after reduced intensity total body irradiation-based conditioning in patients allografted for chronic myelomonocytic leukemia (CMML). Blood. 2017;130:4571.
Savona MR, Malcovati L, Komrokji R, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015;125:1857–65.
Sharma P, Shinde SS, Damla M, et al. Allogeneic hematopoietic stem cell transplant in adult patients with myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) overlap syndromes. Leuk Lymphoma. 2017;58:872–81.
Solary E. Chronic Myelomonocytic Leukemia (CMML). Atlas Genet Cytogenet Oncol Haematol. 2014;18:50–2.
Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (H SCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HSCT. Blood. 2005;106:2912–9.
Such E, Gerning U, Malcovati L, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood. 2013;121:3005–15.
Symeonidis A, van Biezen A, de Wreede L, et al. Achievement of complete remission predicts outcome of allogeneic haematopoietic stem cell transplantation in patients with chronic myelomonocytic leukaemia. A study of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. Br J Haematol. 2015;171:239–46.
Wang SA, Hasserjian RP, Fox PS, et al. Atypical chronic myeloid leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative neoplasms. Blood. 2014;123:2645–51.
Yabe M, Ohtsuka Y, Watanabe K, et al. Transplantation for juvenile myelomonocytic leukemia: a retrospective study of 30 children treated with a regimen of busulfan, fludarabine, and melphalan. Int J Hematol. 2015;101:184–90.

Open Access  This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.